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Efficacy of Revefenacin in Treatment of Moderate-to-Very-Severe Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a major global health issue responsible for 5% of global deaths each year, and novel treatments are at a premium. Long acting-muscarinic antagonists are a standard treatment for COPD, and the recent approval of Revefenacin, a novel, once-daily, nebulized LAMA, prompts a need for a systematic review and meta-analysis of results.

Objectives: To assess the efficacy of Revefenacin, a novel, once-daily, nebulized LAMA in the treatment of moderate to very severe COPD.

Data Sources: MEDLINE (OVID), EMBASE, and CINAHL databases, as well as grey literature sources Clinicaltrials.gov and the International Clinical Trials Registry Portal.

Eligibility Criteria for Selecting Studies: Eligibility criteria for selecting studies: Populations: No age, geographical, contextual or other restrictions were imposed on populations. All human subjects diagnosed with moderate to severe Chronic Obstructive Pulmonary Disease (COPD) were eligible. Intervention: a novel bronchodilator (Revefenacin). Comparator: Placebo. Outcomes: the efficacy of Revefenacin, measured as the endpoint change in trough FEV1 from baseline. Study design: Randomised Controlled Trials (RCTs). Only studies written in English were considered.

Study Appraisal and Synthesis Methods: 1571 records were initially screened, with 27 being eligible for full text review. Eventually, 12 articles for 7 trials were included. A random-effects meta-analysis was conducted with the primary outcome of difference in means for change in trough FEV1 from baseline to study endpoint.

Results: 1472 patients were analysed, and the overall difference in means was an increase of 119.073 mL in change in trough FEV1 from baseline to study endpoint for the Revefenacin group compared to the placebo. This result was statistically significant, with a 95% confidence interval of 102.254 mL to 135.893 mL.

Limitations: Limitations of the study include possible risk of publication bias and placebo as the only comparator, relatively few trials (7), and a low generalizability of findings due to the specific nature of RCT populations excluding multi-morbid, and other complicated patients.

Conclusions: Revefenacin is an efficacious intervention when compared to placebo in the treatment of moderate to very severe COPD. Further research is needed in order to assess its efficacy compared to current standard of care, through RCTs or network meta-analysis.

Keywords: COPD; Revefenacin; Meta-analysis; Respiratory; Lungs; Pharmaceutical; Long-acting-muscarinic antagonist

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a significant global health issue affecting an estimated 328 million people worldwide and is projected to be the leading cause of death by 2030 (1–3). COPD refers to a larger group of chronic lung diseases that cause limitations in lung airflow, and is primarily caused by smoking tobacco, indoor air pollution, outdoor air pollution, and occupational dusts and chemicals (2). These factors can contribute to cause two of the most common conditions classified under COPD: emphysema, in which the alveoli at the end of the bronchioles are destroyed, and chronic bronchitis, which is characterized by inflammation of the lining of the bronchial tubes, which are responsible for transporting air to and from the alveoli (4). They lead to the most common symptoms of COPD, namely breathlessness, excessive sputum production, and chronic cough, as well as an increased risk of cardiovascular disease, lung cancer, depression, and premature death (2,4). COPD also carries a substantial economic burden, through both healthcare costs and productivity loss, and is also associated with a reduced quality of life (5,6).

COPD consists of four stages: mild, moderate, severe, and very severe. Each stage is calculated according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Staging System. The forced expiratory volume in one second (FEV1) measurement, derived from a pulmonary function test, is used to categorize the severity (7). The forced vital capacity (FVC) test which measures the amount of air an individual can forcefully and quickly exhale after taking a deep breath, is also an important in diagnosis. FEV1 shows the amount of air a person can forcefully exhale in one second of the FVC test. Generally, lower FEV1 signals more severe COPD (8). The breakdown of COPD stages and FEV1 cut-offs is presented in Table 1.

Stage	FEV_1	GOLD	Severity
I	≥ 80%	1	Mild
II	50% - 80%	2	Moderate
III	30% - 40%	3	Severe
IV	≤ 30%	4	Very Severe

Table 1. COPD Stages

Clinical consultation is usually sought once COPD progresses to the moderate stage, and it is in this stage that physicians usually begin to prescribe bronchodilators for treatment (8). A recent study found a prevalence of 10.1% in moderate-to-severe COPD worldwide – equivalent to GOLD 2 or higher (9). COPD cannot be cured, however, treatment and effective management can provide symptom relief, improved quality of life, and reduce the risk mortality (2). Long-acting muscarinic antagonists (LAMAs), a class of bronchodilator, have been shown to be an efficacious treatment option for patients with moderate to severe COPD. These are recommended as a maintenance therapy by the GOLD, but until recently, haven't been available in a once-daily nebulized form, easing their administration for patients.

Revefenacin, a novel LAMA produced by Theravance Biopharma, has recently been approved by the Food and Drug Administration (FDA) in the US due to its efficacy, safety, and tolerability profile (10,11). It acts as a long-acting muscarinic antagonist (LAMA) and only needs to be administered once-daily via a nebulizer (12). Revefenacin prevents bronchoconstriction and allows bronchodilation by inhibiting muscarinic M3 receptors in airway smooth muscles (13). There are five muscarinic receptors – M1 to M5 – which are all expressed in the lungs. Muscarinic antagonists that target M1 to M3 are used to treat lung diseases (14). The drug, being a competitive antagonist of M3 receptors, which mediate the contraction of the airway smooth muscle, suppresses the acetylcholine-evoked calcium mobilization and contractile responses in the airway tissue in order to regulate tone and patency (14,15). Despite the current variety of bronchodilators, Revefenacin becomes innovative in that it is the first approved once-daily sprayable LAMA compatible with common nebulizers (12).

The FDA approved Revefenacin on 8th November 2018 under the drug name YulperiTM (16). The agency, moreover, approved Theravane Biopharma Inc. and Mylan N.V.'s 'New Drug Application', making these the main companies behind the inhalation solution (17). However, this recent approval prompts the need for summative information on the effectiveness of revefenacin and serves as motivation for a systematic review and meta-analysis of the data regarding its efficacy for the treatment of patients with moderate to very severe COPD.

Objective

The objective of this systematic review and meta-analysis is to determine the clinical efficacy of Revefenacin, a novel nebulized LAMA, in the treatment of patients with moderate to very severe COPD (GOLD Stages 2 through 4), and any comparator. Eligible studies can have participants of any age, gender, and in any location. The primary outcome of interest is trough change in FEV1 from baseline to study endpoint, so studies were evaluated and excluded in full text review if this outcome was not present.

Methods

Protocol and Registration

The protocol for this systematic review and meta-analysis is registered on the PROSPERO international prospective register of systematic reviews, registration identification: CRD42019131334.

Inclusion Criteria – PICOS Framework

Population: Studies involving patients with moderate to very severe COPD of all ages were included as clinical diagnosis and prescription of bronchodilators usually occurs at the moderate stage (8).

Intervention: All studies including treatment with Revefenacin alone (of any dosage or dosing regimen) were included. Revefenacin is a novel, nebulized, once-daily LAMA used in the treatment of moderate to very severe COPD. All dosage levels were included in the meta-analysis.

Comparator: Any study with Revefenacin and comparator was included in the study, but placebo was the primary comparator for analysis, as it is the standard comparator for efficacy studies (18,19).

Outcome: The primary outcome of interest was Trough FEV1 change from baseline to study endpoint in mL. Outcomes do not determine eligibility in the initial screening, yet will be considered in the full text analysis in order to determine whether the study has sufficient information for final inclusion.

Study type: Randomised controlled trials (RCTs). RCTs are the most effective and least biased study design in evaluating the efficacy of a new treatment, as they use random allocation and comparison to a control in order to account for any confounders on the outcome of interest (18). Completed studies with results in English from any year were included.

Exclusion Criteria

Studies involving treatment with Revefenacin in patients with specific comorbidities in addition to, or in place of, COPD were excluded as the results of these studies could bias efficacy measures. Studies that included patients with unspecified stages of COPD were also excluded because of possible bias, along with studies that failed to measure FEV1, due to a lack of implication in the meta-analysis.

Information Sources and Search Strategy

We searched for eligible studies up to the 24th of February 2019, using MEDLINE (OVID), EMBASE, and CINAHL databases because of their breadth covering clinical research. Search strategies for the different databases using medical subject headings (MeSH) and free text keywords including ‘Revefenacin’, ‘chronic obstructive pulmonary disease’, ‘randomised control trial’ and more, were developed and are reproduced in Appendix A. We also searched the grey literature using ClinicalTrials.Gov and the International Clinical Trials Registry Portal for relevant clinical trials. Our search was restricted to studies with results in English.

Study Selection

Records from the search were stored using Mendeley Reference Management Software throughout the review. Titles and abstracts were initially screened by two independent reviewers to assess eligibility. Ineligible studies were then excluded, and those deemed eligible underwent full text review by two independent reviewers to determine final eligibility. Any discrepancies in eligibility determination were assessed by a third independent reviewer and discussion took place until consensus was achieved. Ineligible studies were removed and included studies entered the data collection process.

Data Collection and Items

Relevant study data was then extracted and compiled in a Microsoft Excel spreadsheet by five study team reviewers, with cross check for consensus. The form for data extraction included: authors, title, publication year, trial ID, study design, study duration, follow up duration, trial start year, country, number of participants, number of males, number of females, mean age, COPD stage (mean FEV1%), number of participants in intervention group, dosage, regimen, number of participants in control group, trough FEV1 change from baseline for placebo with standard deviation, trough FEV1 change from baseline for Revefenacin with standard deviation, and placebo-adjusted trough FEV1 change from baseline (if available) with standard deviation (Table 3). As all of the trials were multi-armed for different dosages of intervention, each dosage arm was treated as its own study and its standard error later adjusted for the unit-of analysis error and correlation between the shared placebo group using the exact adjustment method (Method 4) in Rucker et al., 2017 (See Appendix B) (20). Adjustment was performed in R statistical software, and the code can be found in Appendix C.

Risk of Bias in Individual Studies

Risk of bias in individual studies was measured at the study level by two independent reviewers with The Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials (21). This tool measures a range of sources of bias within individual studies, including: selection bias, through random sequence generation and allocation concealment; performance bias, through blinding of participants and personnel; detection bias, through blinding of outcome assessment; attrition bias, through incomplete outcome data; and reporting bias, through selective reporting (Table 2) (21). Each item in the tool was designated as low, unclear, or high risk of bias. Studies determined to have a high risk of bias will be excluded for sensitivity analysis. The risk of bias assessment within studies was created in Review Manager 5.3 (29).

No.	Bias Domain	Risk Judgment
I	Random Sequence Generation	Low
II	Allocation Concealment	
III	Blinding of Participants and Personnel	Moderate /
IV	Blinding of Outcome Assessment	Unclear
V	Incomplete Outcome Reporting	
VI	Selective Reporting	High

Table 2. Possible Biases

Principal Summary Measures

For our study, difference in means is the principal summary measure used, as measured by the change in trough FEV1 from baseline to study endpoint in mL, as this is the standard in evaluating efficacy of treatments in COPD interventions (22). Difference in means is used because of the same outcome and unit being measured in each of the included studies, as per the Cochrane Handbook (23).

Synthesis of Results

A random-effects pairwise meta-analysis was performed using Stata statistical software for a difference in means of change in trough FEV1 from baseline to study endpoint in mL between the Revefenacin intervention group and the placebo group. A random effects model was used because of the variation in dosages, study duration, and study design across the studies (24). As mentioned, adjusted standard errors were used in the pairwise meta-analysis in order to include information from multi-armed studies (20). The meta-analysis results were presented in difference in means (or mean difference) with the 95% confidence interval, and I2 was calculated as a measure of heterogeneity (25).

Risk of Bias Across Studies

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was used to evaluate risk of bias, imprecision, inconsistency, indirectness, publication bias and confidence in cumulative evidence (Table 3) (26). Funnel plots with mean difference and standard error were used to assess possible bias across studies, as well as publication bias.

No.	GRADE Factor	Consequence on Quality
I	Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
II	Inconsistency of results	↓ 1 or 2 levels
III	Indirectness of evidence	↓ 1 or 2 levels
IV	Imprecision	↓ 1 or 2 levels
V	Publication bias	↓ 1 or 2 levels
VI	Large magnitude of effect	↑ 1 or 2 levels
VII	All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
VI	Dose-response gradient	↑ 1 level

Table 3. GRADE Factors

Additional Analyses

Subgroup analysis was performed for study duration and drug dosage, which were both pre-specified, as well as study design (parallel or nonparallel), and study source (as results from the same trial are split into the different arms for analysis). Meta-regressions for drug dosage and study duration were performed for robustness. Sensitivity analysis was performed excluding studies with potential high risk of bias (27).

Results

Study Selection

We initially screened 1571 records from EMBASE, MEDLINE, and CINAHL databases, as well as 161 from the grey literature, and then removed 13 duplicates for a total of 1719 records. 27 records were assessed in full-text review, and eventually 13 full text articles containing information for 7 randomised controlled trials were included in the qualitative synthesis and meta-analysis (Figure 1). See Appendix C for full-text exclusions with reasons. Table 4 displays the authors and titles of the selected trials.

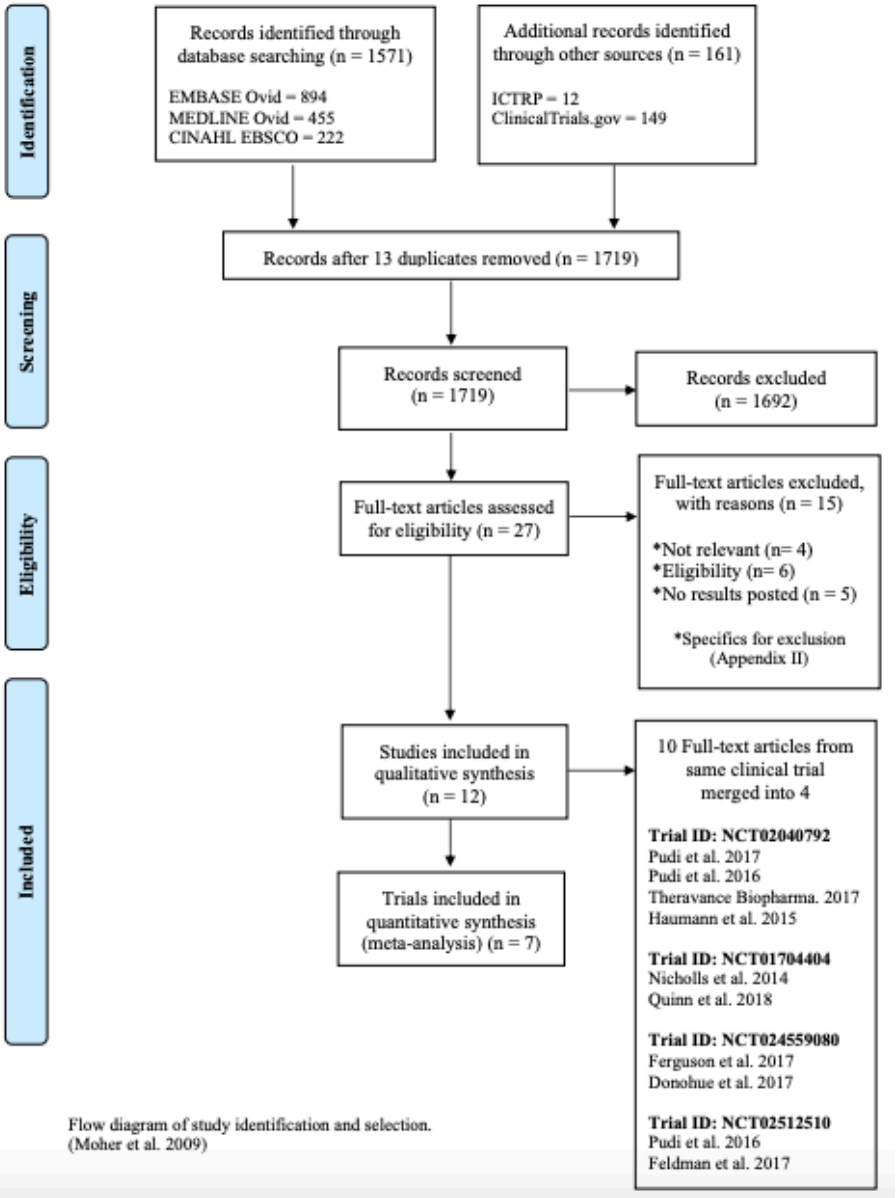

Figure 1. Study identification and selection flow diagram (28)

Author	**Title**
Pudi et al. 2017	A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized Revefenacin in patients with chronic obstructive pulmonary disease.
Nicholis et al. 2014	A Randomized, Crossover, 7-Day Study Of Once-Daily TD 4208, A Long-Acting Muscarinic Antagonist, In Subjects With COPD
Potgieter et al. 2012	A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD
Theravance Biopharma 2017	A 7-Day Cross-over Study of QD (Once Daily) and BID (Twice Daily) TD-4208 in Chronic Obstructive Pulmonary Disease (COPD)
Ferguson et al. 2017	Efficacy of Revefenacin , a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease
Pudi et al. 2016	Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD
Quinn et al. 2018	Pharmacodynamics, pharmacokinetics and safety of Revefenacin (TD- 4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies

Table 4. Selected Trials

Study Characteristics

Study characteristics in the format of the Excel spreadsheet used for data extraction are presented in Table 5. The articles which were merged for singular trials are presented in the leftmost column and only represent

Risk of bias within studies

Details of risk of bias within studies are presented in Figure 2, with a summary in Figure 3. Studies could be measured as Low risk, unclear risk, or high risk. Pudi et al. presented the only section with a high risk of bias, in random sequence generation. This was due to a lack of information detailing how patients were randomised.

STUDY					METHODS			PARTICIPANTS AND SETTINGS								INTERVENTION			CONTROL	OUTCOME						
																				Placebo		Intervention			Pooled	
Author	Title	Publication Year	Study ID	Trial ID	Study Design	Total Duration (days)	Follow up Duration (days)	Trial Start Year	Country	No. of participants at start	No. of participants at end	No. of males	No. of females	Mean age	COPD Stage (mean FEV1 %)	Number	Dosage	Regimen	Number	FEV1 change from baseline	SE	Related dosage	FEV1 change from baseline	SE	FEV1 Placebo adjusted change	Pooled SE
Pudi KK et al.	A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized revefenacin in patients with chronic obstructive pulmonary disease.	2017	N/A	NCT02040792	PARALLEL	28	28	2014	United States	355	354	178	176	62	44%	68	44	Once Daily	70	-32.4	25.36	44	19.4	24.61	51.8	24.98781403
Pudi KK et al.	Nebulized Revefenacin Results in a Reduction in the Daily Use of Rescue Medication: Results From a 28-Day Study in Participants With COPD	2016	N/A													71	88					88	155	24.61	187.4	24.98781403
Theravance Biopharma	A Phase 2B, 28-Day, Randomized, Double-Blind Placebo-Controlled Parallel Group	2017	(0)117													71	175					175	134.2	25.07	166.6	25.21541691
Haumann BK et al.	Dose-Ranging Study of Once-Daily TD-4208, an Inhaled Long-Acting Muscarinic Antagonist (LAMA) in Patients with Chronic Obstructive Pulmonary Disease (COPD)	2015	N/A													74	350					350	138.2	24.38	170.6	24.87482663
Nicholis AJ et al.	A Randomized, Crossover, 7-Day Study Of Once-Daily TD 4208, A Long-Acting Muscarinic Antagonist, In Subjects With COPD	2014	(00)91	NCT01704404	NONPARALLEL	112	7	2014	United Kingdom	56	37	35	27	63.9	Moderate to severe COPD	37	22	Once Daily	56	37.8	16.93	22	91.2	19.21	53.4	18.10592444
Quinn D et al.	Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies.	2018	(00)91								32					32	44					44	92.8	20.25	55	18.66396796
											35					35	88					88	113.1	19.55	75.3	18.28698171
											33					33	175					175	151.9	19.99	114.1	18.52329614
											38					38	350					350	132.2	19.02	94.4	18.00535059
											35					35	700					700	119.4	19.54	81.6	18.28163696
Potgieter P et al.	A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD	2012	N/A	N/A	NONPARALLEL	1	1	N/A	United States New Zealand	32	32	N/A	N/A	60	Moderate to severe COPD	32	350	Once Daily	32	0	31.378	350	174	31.378	174	31.378
																32	700					700	169	31.378	169	31.378
Theravance Biopharma	A 7-Day Cross-over Study of QD (Once Daily) and BID (Twice Daily) TD-4208 in Chronic Obstructive Pulmonary Disease (COPD)	2017	(0)116	NCT02109172	NONPARALLEL	7	7	2014	United States	64	57	37	27	N/A	Moderate to severe COPD	64	44	Twice Daily	64	-14.4	15.29	44	90.2	15	104.6	15.14569411
																64	175	Once Daily				175	98.5	15.03	112.9	15.16055738
Ferguson G et al.	Efficacy of Revefenacin, a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease	2017	(0)126	NCT024559080	PARALLEL	85	85	N/A	United States	619	477	317	302	64.1	54%	198	88	Once Daily	209	-19.41	16.108	88	59.81	15.095	79.22	15.60971955
Donohue J et al.	The 24-Hour Profile of FEV1 After 12-Weeks Treatment With Revefenacin, a Once Daily Long-Acting Muscarinic Receptor Antagonists for Nebulization: A Spirometry Substudy	2017	(0)126													212	175					175	126.85	15.389	146.26	15.75260272
Pudi KK et al.	Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD	2016	(0)127	NCT02512510	PARALLEL	85	85	N/A	United States	610	482	302	308	63.4	54%	205	88	Once Daily	208	-44.92	18.841	88	115.58	18.637	160.5	18.7392776
Feldman G et al.	Safety and Tolerability of Revefenacin, a Novel Once-Daily Nebulized Long-Acting Muscarinic Antagonist: Results of Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials in Participants with Moderate to Very Severe Chronic Obstructive Pulmonary Disease	2017	(0)127													197	175					175	102.9	18.542	147.82	18.69209786
Quinn D et al.	Pharmacodynamics, pharmacokinetics and safety of revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies.	2018	(00)59	U1111-1120- 8290	NONPARALLEL	N/A	1	2011	South Africa New Zealand	32	32	22	10	62	35 - 80%	32	350	Once Daily	32	1533.8	22.4	350	1636.6	22.4	102.8	22.4
																32	700					700	1670.4	22.4	136.6	22.4

Table 5. Characteristics of Individual Studies(30–43)

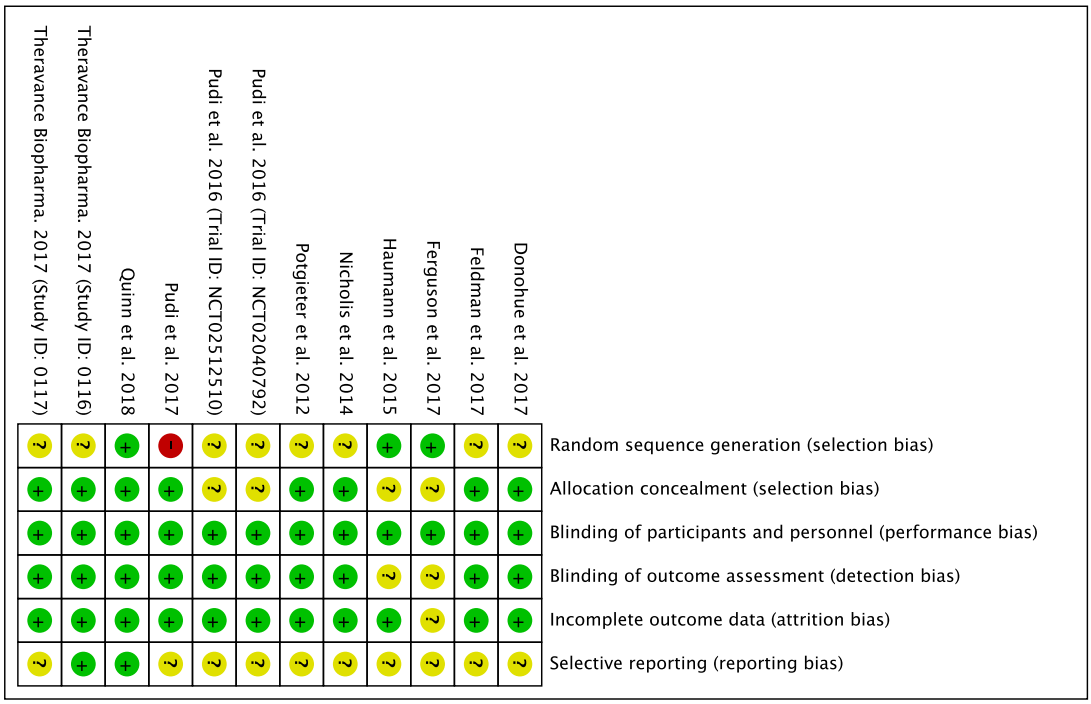

Figure 2. Risk of bias within studies

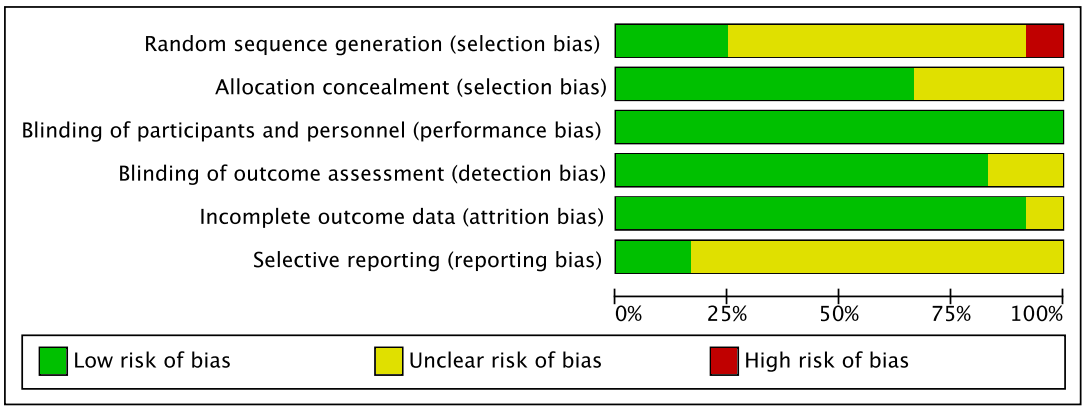

Figure 3. Summary of risk of bias within studies

Risk of Bias Across Studies

The GRADE tool was used to evaluate risk of bias, imprecision, inconsistency, indirectness, publication bias and confidence in cumulative evidence (26). The results are reproduced in the GRADE Summary of Findings (Figure 4). Funnel plots assessing possible bias across studies (Appendix E) and publication bias (Figure 5) demonstrate asymmetry and possible risk of publication bias, respectively. The possible risk of publication bias is due to all of the measured outcomes demonstrating statistical significance, as well the sponsorship by the manufacturer for all studies.

Efficacy of Revefenacin in the Treatment of Moderate to Very Severe COPD

Patient or population: the maintenance treatment of COPD
Setting: United States (n=4); United Kingdom (n=1); United States and New Zealand (n=1); South Africa and New Zealand (n=1)
Intervention: Revefenacin
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Revefenacin**				
Trough FEV1 change from baseline (0-24 hours) (FEV1) Assessed with: Spirometry Follow up range: 1 day to 85 days	N/A	N/A	**MD 119.073** (102.254 to 135.893)	1472 (7 RCTs)	⨁⨁⨁◯ MODERATE a,b,c,d,e	Revefenacin results in large increase in trough FEV1 change from baseline (0-24 hours). Note: Anticipated absolute effects of risk (95% CI) were not estimable.

*__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).
CI: Confidence interval

GRADE Working Group grades of evidence
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 substantially different
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

Explanations
a. Studies performed well in performance and attrition biases. Major unclarity has been reported for selection and reporting biases, result in a downgrading of the evidence.
b. Consistent estimates of the treatment effect across studies suggests no true differences in underlying treatment effect.
c. Head-to-head comparisons of Revefenacin and placebo.
d. 95% CI does not include null effect.
e. Visual assessment of the contour-enhanced funnel plot as an aid to differentiating asymmetry due to publication bias from that due to other factors, confirmed that all studies are plotted outside of the funnel, corresponds to p-values below 1% (p=0.01), making publication bias plausible (high risk of publication bias).

Figure 4. GRADE Summary of Findings

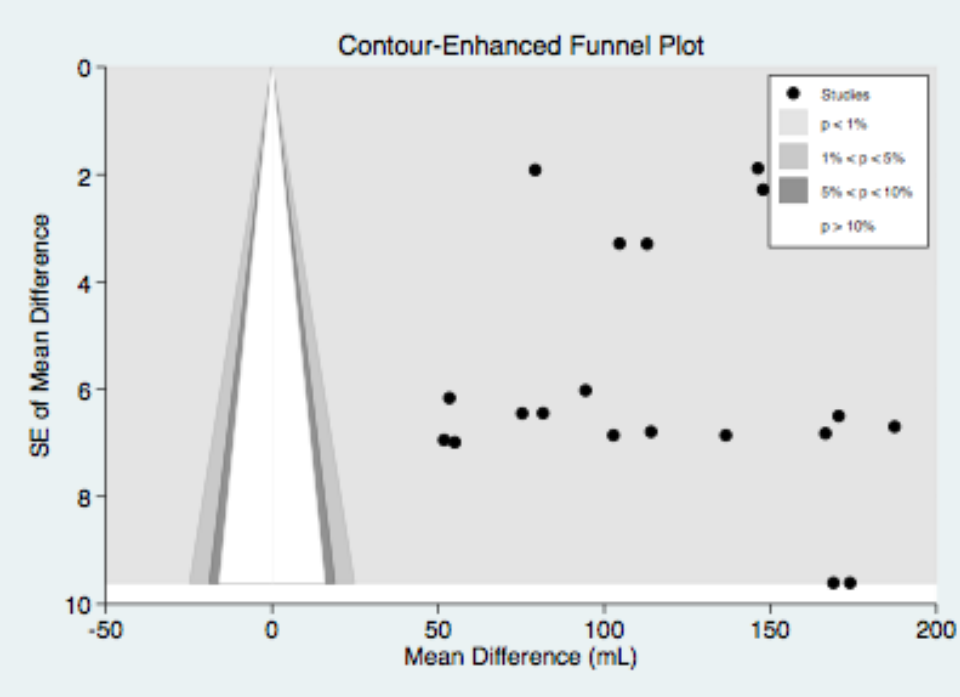

Figure 5. Contour-Enhanced Funnel Plot of Random-Effects Meta-Analysis

Results of Individual Studies

Results of individual studies and the random-effects meta-analysis are presented in Figure 6, along with the accompanying forest plot in Figure 7. For the pairwise, random-effects meta-analysis, 1472 patients were analysed, and the overall difference in means was an increase of 119.073 mL in change in trough FEV1 from baseline to study endpoint for the Revefenacin group compared to the placebo. This result was statistically significant, with a 95% confidence interval of 102.254 mL to 135.893 mL. The heterogeneity between studies was significant with a p value of 0.000, and the I2 measure of consistency was equal to 98.9%, which means that 98.9% of variation in the difference in means is attributable to heterogeneity, which can be interpreted as a high level of statistical heterogeneity.

Study	ES	[95% Conf.	Interval]	% Weight
Pudi 2017, 44{&mu}g	51.800	38.183	65.417	4.96
Pudi 2017, 88{&mu}g	187.400	174.271	200.529	4.97
Pudi 2017, 175{&mu}g	166.600	153.226	179.974	4.97
Pudi 2017, 350{&mu}g	170.600	157.860	183.340	4.98
Andrew 2014, 22{&mu}	53.400	41.317	65.483	5.00
Andrew 2014, 44{&mu}	55.000	41.304	68.696	4.96
Andrew 2014, 88{&mu}	75.300	62.656	87.944	4.99
Andrew 2014, 175{&mu	114.100	100.786	127.414	4.97
Andrew 2014, 350{&mu	94.400	82.595	106.205	5.00
Andrew 2014, 700{&mu	81.600	68.963	94.237	4.99
Potgieter 2012, 350{	174.000	155.170	192.830	4.82
Potgieter 2012, 700{	169.000	150.170	187.830	4.82
Theravance 2017, 44{	104.600	98.157	111.043	5.09
Theravance 2017, 175	112.900	106.444	119.356	5.09
Ferguson Site 1 2017	79.220	75.465	82.975	5.12
Ferguson Site 1 2017	146.260	142.560	149.960	5.12
Ferguson Site 2 2017	160.500	156.092	164.908	5.11
Ferguson Site 2 2017	147.820	143.346	152.294	5.11
Quinn 2017, 350{&mu}	102.800	89.357	116.243	4.97
Quinn 2017, 700{&mu}	136.600	123.157	150.043	4.97
D+L pooled ES	119.073	102.254	135.893	100.00

Heterogeneity chi-squared = **1808.46** (d.f. = **19**) p = **0.000**
I-squared (variation in ES attributable to heterogeneity) = **98.9%**
Estimate of between-study variance Tau-squared = **1.4e+03**

Test of ES=0 : z= **13.88** p = **0.000**

Figure 6. Results of Individual Studies and Overall Random-Effects Meta-Analysis

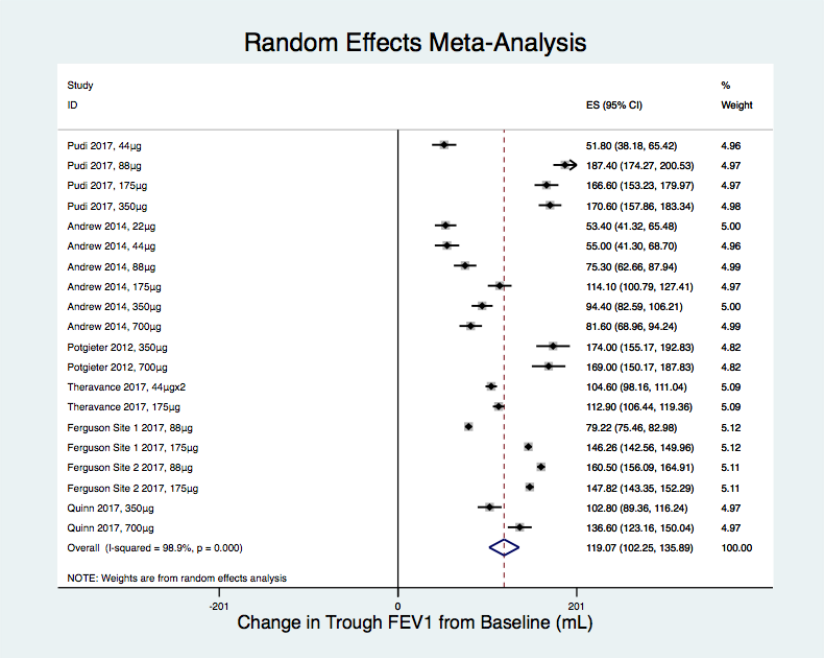

Figure 7. Forest plot of random-effects meta-analysis (Note that for Ferguson 2017 dosage was different per site)

Additional Analysis

Subgroup analysis

Subgroup analysis was performed for study duration (Figure 8), demonstrating significant difference for difference in means for 1 day versus 7 days only, as the 95% confidence interval for 1 day was higher and did not overlap with that of 7 days. There were non-significant differences amongst the rest of the groups by study duration. Subgroup analysis was also performed for dosage (Figure 9), yielding the highest overall difference in change in trough FEV1 from baseline to study endpoint for 175 μg, significantly higher than that of 22 and 44 μg. A dosage of 22 μg yielded a significantly lower difference than all but a dosage of 44 μg, with non-significant differences amongst the groupings of 44, 88, 350, and 700 μg, as well as 88, 175, 350, and 700 μg. Subgroup analysis of study design yielded no significant difference between parallel and nonparallel studies. Overall study is included to demonstrate the additive study effects if results were pooled, as the arms of each different study were split for analysis (Appendix F).

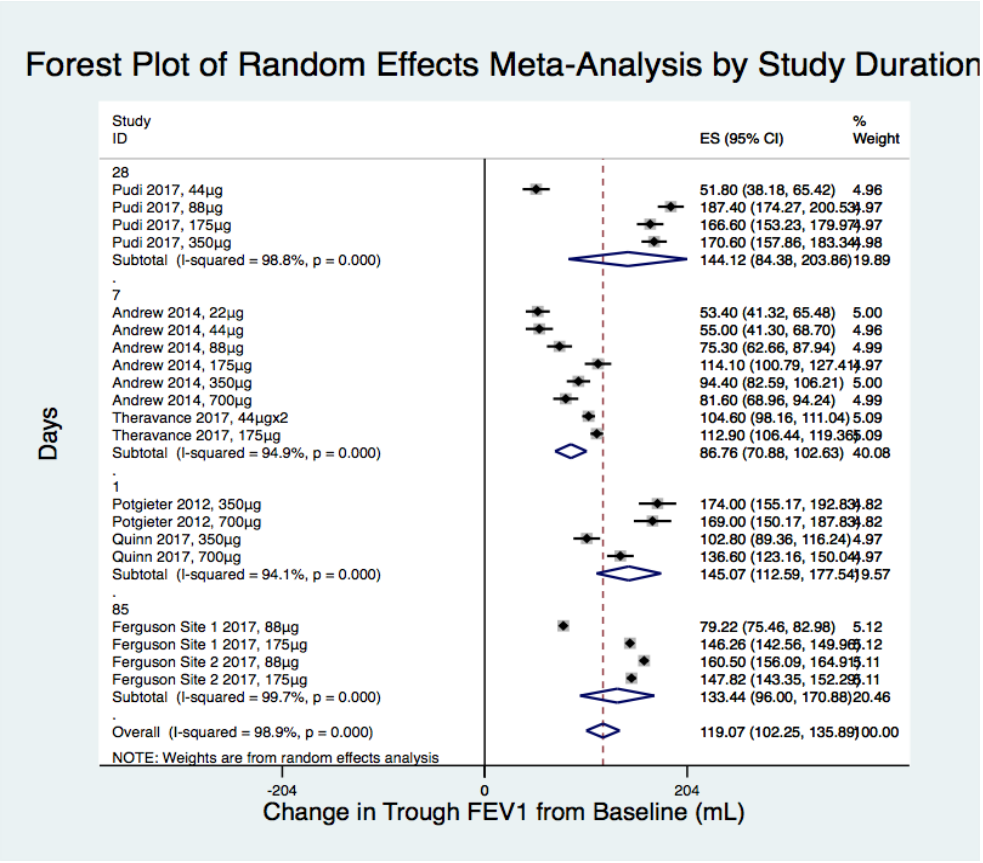

Figure 8. Random Effects Model Meta-analysis by Days

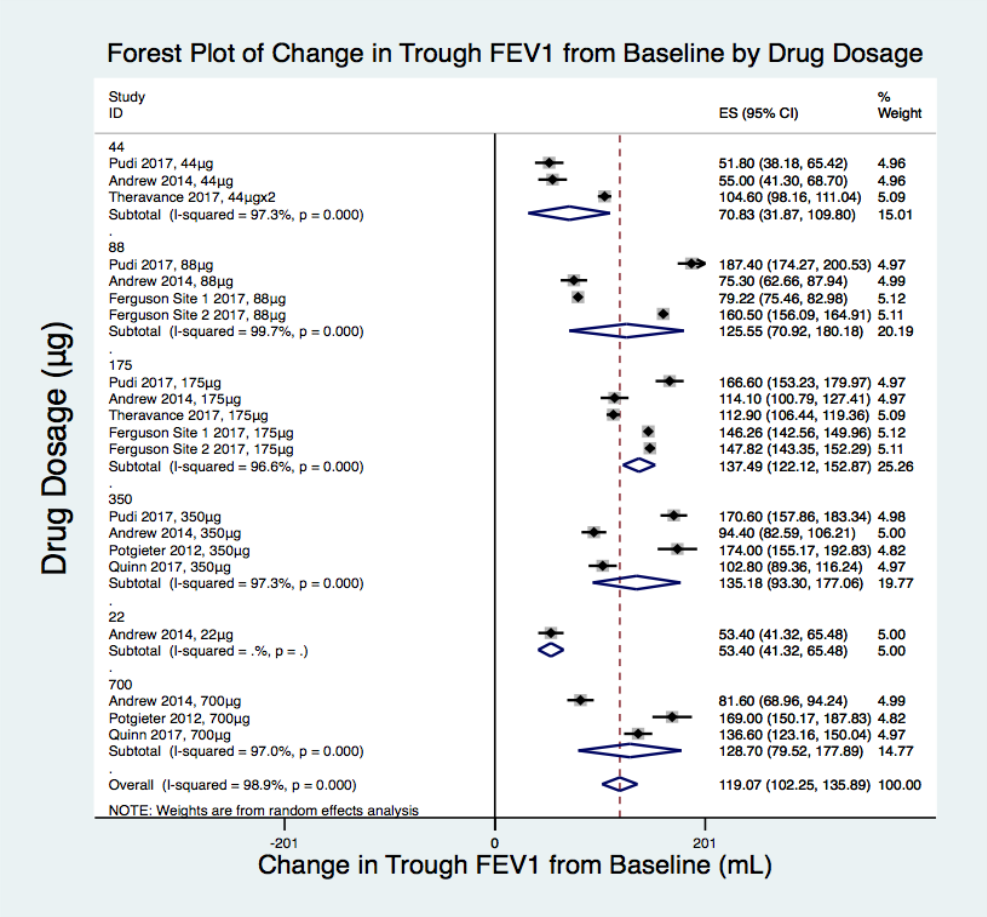

Figure 9. Random Effects Model Meta-analysis by Dosage

Meta-Regression

Meta-regression was performed for both study duration and dosages, yielding no significant correlation for either. Whilst meta-regression analysis for < 10 trials is not recommended, the precedent was unclear as we split the 7 trials into 20 intervention arms. Hence meta-regression was chosen to be robust (results in Appendix G).

Sensitivity Analysis

Sensitivity analysis included removing Pudi et al. from the analysis because of the high risk of bias in sequence of randomisation, resulting in a non-significant difference in difference in means before and after removal. The results of the sensitivity analysis are presented in Appendix H.

Discussion

Overall, through a systematic review and random-effects meta-analysis, 1472 patients were analysed from 7 RCTs. The difference in means in change in trough FEV1 from baseline to study endpoint between the Revefenacin intervention and the placebo comparator was significant, at an increase of 119.07 mL (95% CI 102.25, 135.89) demonstrating that Revefenacin is significantly more efficacious in treatment for moderate to very severe COPD compared to placebo. Subgroup analysis demonstrated 175 μg to potentially be the most efficacious dosage, in line with recommendations from the FDA.(44) Heterogeneity was detected across studies, but the I2 statistic must be interpreted cautiously as the seven individual studies were split into twenty intervention arms for analysis, inflating the heterogeneity between the arms as all studies used multiple dosages. The contour-enhanced funnel plot demonstrated high risk of publication bias, which could be due to industry sponsorship (funding bias), or comparison to placebo, so this must be taken into account with interpretation. It has been demonstrated that industry sponsored studies more frequently result in favourable efficacy outcomes, possibly hampering the validity of our own selected studies.(45) GRADE assessment concludes that Revefenacin results in a significant, large increase in change in trough FEV1 from baseline to study endpoint when compared to placebo, with moderate certainty of evidence. The results are also consistent with the 'time lag bias' in which simultaneous studies with negative results are published years after those with positive ones, which also must be taken into consideration.(21)

Implications of this meta-analysis include supporting evidence in approval of Revefenacin as a LAMA treatment for COPD, but further research into drug combinations with long-acting beta agonists and comparison to other LAMAs and COPD interventions is necessary to test its relative efficacy.(46) This study also used a recently developed method for including multi-armed trials in pairwise meta-analysis, allowing for dosage-specific subgroup analysis within the meta-analysis itself, a technique that will be useful in future drug intervention meta-analyses.(20) Some limitations of the study are that the main comparison was placebo, due to the lack of available studies with comparators. To address this, further research in clinical trials and a network meta-analysis of moderate to very severe COPD interventions including Revefenacin should be conducted. The study is also limited by a low number of RCTs (7), and an update as Revefenacin is compared to other interventions should occur sometime in the near future. Furthermore, the generalizability of the study is limited due to the nature of RCTs and their controlling for other factors affecting outcome, such as multimorbidities. Moreover, a geographical bias might be present with the majority of trials being performed in the US (n=4). This adds to the low number of studies which could severely impact the generalisability of results. Furthermore, despite proving that Revefenacin is efficacious against placebo, it is important to point out this systematic review and meta-analysis does not take into account safety and tolerability of the drug, which will need to be further assessed.

Conclusion

This paper's aim was to determine the clinical efficacy of Revefenacin in patients with moderate to severe COPD. Revefenacin has been determined to be an efficacious treatment for moderate to very severe COPD in comparison to placebo. Further research into whether it is efficacious in comparison to the current standard of care, through RCTs or network meta-analysis for the network of interventions to treat moderate to very severe COPD, is needed. This systematic-review and meta-analysis was limited by a small number of RCTs (n=7), and a larger body of evidence could provide further information on dosage gradients and duration of use. Moreover, being all the selected studies funded by Revefenacin 's manufacturer poses an important risk of publication bias which needs to be considered. There is also a need for further research into efficacy of Revefenacin in multi-morbid and other trial-excluded patient groups. However, this systematic review and meta-analysis provides a summary of the current evidence and demonstrates the efficacy of Revefenacin in comparison to placebo in its current setting.

References

1. Quaderi SA, Hurst JR. The unmet global burden of COPD. Glob Heal Epidemiol genomics [Internet]. 2018 [cited 2019 Feb 24];3:e4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29868229
2. World Health Organization. Chronic obstructive pulmonary disease (COPD) [Internet]. 2017. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
3. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. Samet J, editor. PLoS Med [Internet]. 2006 Nov 28 [cited 2019 Feb 24];3(11):e442. Available from: https://dx.plos.org/10.1371/journal.pmed.0030442
4. Mayo Clinic. COPD - Symptoms and causes - Mayo Clinic [Internet]. 2017 [cited 2019 Apr 30]. Available from: https://www.mayoclinic.org/diseases-conditions/copd/symptoms-causes/syc-20353679
5. May SM, Li JTC. Burden of chronic obstructive pulmonary disease: healthcare costs and beyond. Allergy asthma Proc [Internet]. 2015 [cited 2019 Feb 24];36(1):4–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25562549
6. Erdal M, Johannessen A, Askildsen JE, Eagan T, Gulsvik A, Grønseth R. Productivity losses in chronic obstructive pulmonary disease: a population-based survey. BMJ Open Respir Res [Internet]. 2014 Dec 1 [cited 2019 Feb 24];1(1):e000049. Available from: http://bmjopenrespres.bmj.com/lookup/doi/10.1136/bmjresp-2014-000049
7. BMJ Best Practice. Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [Internet]. BMJ Publ. Group; 2018 [cited 2019 Apr 30]. Available from: https://bestpractice.bmj.com/topics/en-gb/7/criteria
8. Lung Institute. Stages of COPD: Mild through End-Stage COPD | Lung Institute [Internet]. 2018 [cited 2019 Apr 30]. Available from: https://lunginstitute.com/blog/stages-of-copd-mild-through-end-stage/

9. Doucet M, Rochette L, Hamel D. Incidence, Prevalence, and Mortality Trends in Chronic Obstructive Pulmonary Disease over 2001 to 2011: A Public Health Point of View of the Burden. Can Respir J [Internet]. 2016 [cited 2019 Feb 24];2016:7518287. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27478397
10. AJMC. FDA Approves Revefenacin , a Once-a-Day Nebulized LAMA, for COPD [Internet]. 2018 [cited 2019 Feb 25]. Available from: https://www.ajmc.com/newsroom/fda-approves-Revefenacin -a-onceaday-nebulized-lama-for-copd
11. K. P, C. B, E. M, B. H. Nebulized Revefenacin results in a reduction in the daily use of rescue medication: Results from a 28-day study in participants with COPD. Chest [Internet]. 2016;150(4 Supplement 1):828A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=613468950
12. Melao A. Revefenacin , Marketed as Yupelri, Approved by FDA to Treat COPD [Internet]. COPD News Today. [cited 2019 Jul 6]. Available from: https://copdnewstoday.com/2018/11/13/Revefenacin -marketed-as-yupelri-approved-by-fda-for-copd/
13. Heo Y-A. Revefenacin : First Global Approval. Drugs [Internet]. 2019 Jan 17 [cited 2019 Jul 6];79(1):85–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30560478
14. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. Handb Exp Pharmacol [Internet]. 2012 [cited 2019 Jul 6];(208):317–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22222705
15. Hegde SS, Pulido-Rios MT, Luttmann MA, Foley JJ, Hunsberger GE, Steinfeld T, et al. Pharmacological properties of Revefenacin (TD-4208), a novel, nebulized long-acting, and lung selective muscarinic antagonist, at human recombinant muscarinic receptors and in rat, guinea pig, and human isolated airway tissues. Pharmacol Res Perspect [Internet]. 2018 [cited 2019 Jul 6];6(3):e00400. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29736245
16. FDA - US Food and Drug Administration. Novel Drug Approvals for 2018 | FDA [Internet]. [cited 2019 Jul 6]. Available from: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2018
17. Theravance Biopharma. Theravance Biopharma and Mylan Receive FDA Approval for YUPELRI™ (Revefenacin) in Adults with Chronic Obstructive Pulmonary Disease | Theravance Biopharma, Inc. [Internet]. 2018 [cited 2019 Jul 6]. Available from: https://investor.theravance.com/news-releases/news-release-details/theravance-biopharma-and-mylan-receive-fda-approval-yupelritm
18. Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized controlled trials: part 17 of a series on evaluation of scientific publications. Dtsch Arztebl Int [Internet]. 2011 Sep [cited 2019 Apr 30];108(39):663–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22013494
19. Sibbald B, Roland M. Understanding controlled trials: Why are randomised controlled trials important? BMJ [Internet]. 1998 Jan 17 [cited 2019 Apr 26];316(7126):201. Available from: https://www.bmj.com/content/316/7126/201
20. Rücker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm

trials in pairwise meta-analysis. Res Synth Methods [Internet]. 2017 Dec [cited 2019 Apr 24];8(4):392–403. Available from: http://doi.wiley.com/10.1002/jrsm.1259
21. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2011 Oct 18 [cited 2019 Feb 25];343:d5928. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22008217
22. Glaab T, Vogelmeier C, Buhl R. Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations. Respir Res [Internet]. 2010 Dec 17 [cited 2019 Feb 25];11(1):79. Available from: http://respiratory-research.biomedcentral.com/articles/10.1186/1465-9921-11-79
23. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 2011 [cited 2019 May 1]. Available from: https://handbook-5-1.cochrane.org/front_page.htm
24. Borenstein M, Hedges L V., Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods [Internet]. 2010 Apr 1 [cited 2019 May 1];1(2):97–111. Available from: http://doi.wiley.com/10.1002/jrsm.12
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med [Internet]. 2002 Jun 15 [cited 2019 May 1];21(11):1539–58. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12111919
26. Siemieniuk R, Guyatt G. What is GRADE? | BMJ Best Practice [Internet]. [cited 2019 Feb 25]. Available from: https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/
27. Bown MJ, Sutton AJ. Quality Control in Systematic Reviews and Meta-analyses. Eur J Vasc Endovasc Surg [Internet]. 2010 Nov [cited 2019 May 1];40(5):669–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20732826
28. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med [Internet]. 2009 Jul 21 [cited 2019 May 1];6(7):e1000097. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19621072
29. The Cochrane Collaboration. Review Manager (RevMan) Version 5.3 [Internet]. 2014 [cited 2019 May 1]. Available from: https://community.cochrane.org/help/tools-and-software/revman-5
30. Ferguson G, Pudi KK, Feldman G, Pendyala S, Barnes CN, Moran EJ, et al. Efficacy and safety of Revefenacin (REV), a long-acting muscarinic antagonist for nebulization: Results of replicate randomized, double-blind, placebo-controlled, parallelgroup phase 3 trials in participants with moderate to very severe COPD. Eur Respir J [Internet]. 2017;50(Supplement 61):PA1812. Available from: http://erj.ersjournals.com/content/50/suppl_61/PA1812
31. Haumann BK, Nicholls AJ, Barnes C, Bourdet DL. Dose-ranging study of once-daily TD-4208, an inhaled long-acting muscarinic antagonist (LAMA) in patients with chronic obstructive pulmonary disease (COPD). Am J Respir Crit Care Med [Internet]. 2015;191(MeetingAbstracts):A5750. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A5750

32. Potgieter P, Hopkins A, Liu P, Quinn D, Amburgey C. A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD. Eur Respir J [Internet]. 2012;40(SUPPL. 56):P2878. Available from: http://erj.ersjournals.com/content/40/Suppl_56/P2878.abstract?sid=fb221b1f-d72c-4ed1-bb7f-0ad2d9c4d084
33. Kerwin EM, Donohue JF, Sethi S, Haumann B, Pendyala S, Dean L, et al. Revefenacin , a once-daily, long-acting muscarinic antagonist for nebulized therapy of chronic obstructive pulmonary disease (COPD): Results of a 52-week safety and tolerability phase 3 trial in participants with moderate to very severe COPD. Am J Respir Crit Care Med [Internet]. 2018;197(MeetingAbstracts):A4239. Available from: http://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A4239
34. Ferguson G, Barnes C, Pendyala S, Crater G. Efficacy and safety of Revefenacin , a long-acting muscarinic antagonist for nebulization from phase 3 trials in patients with moderate to very severe chronic obstructive pulmonary disease. JACCP J Am Coll Clin Pharm [Internet]. 2018;1(2):341. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexb&NEWS=N&AN=625879660
35. Quinn D, Barnes CN, Yates W, Bourdet DL, Moran EJ, Potgieter P, et al. Pharmacodynamics, pharmacokinetics and safety of Revefenacin (TD-4208), a long-acting muscarinic antagonist, in patients with chronic obstructive pulmonary disease (COPD): Results of two randomized, double-blind, phase 2 studies. Pulm Pharmacol Ther [Internet]. 2018;48:71–9. Available from: http://www.elsevier.com/inca/publications/store/6/2/2/9/3/6/index.htt
36. Pudi K, Barnes C, Moran E, Haumann B. Nebulized Revefenacin results in a reduction in the daily use of rescue medication: Results from a 28-day study in participants with COPD. Chest [Internet]. 2016;150(4 Supplement 1):828A. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed17&NEWS=N&AN=613468950
37. Cazzola M, Rogliani P, Segreti A, Matera MG. An update on bronchodilators in Phase I and II clinical trials. Expert Opin Investig Drugs [Internet]. 2012;21(10):1489–501. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med8&NEWS=N&AN=22916733
38. Ferguson G, Barnes C, Pendyala S. Efficacy and safety of Revefenacin , a long-acting muscarinic antagonist for nebulization from phase 3 trials in patients with moderate to very severe chronic obstructive pulmonary disease. Consult Pharm [Internet]. 2018;33(10):600. Available from: c
39. Pudi KK, Barnes CN, Moran EJ, Haumann B, Kerwin E. A 28-day, randomized, double-blind, placebo-controlled, parallel group study of nebulized Revefenacin in patients with chronic obstructive pulmonary disease. Respir Res [Internet]. 2017;18(1):182. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med13&NEWS=N&AN=29096627
40. Ferguson GT, Pudi KK, Pendyala S, Barnes CN, Moran EJ, Haumann B. Efficacy of

Revefenacin , a novel once-daily nebulized long-acting muscarinic antagonist: Results of two randomized, double-blind, placebo-controlled, parallel-group phase 3 trials in participants with moderate to very severe chronic obstructive pulmonary. Am J Respir Crit Care Med [Internet]. 2017;195:A5474. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5474

41. Donohue J, Pendyala S, Barnes C, Moran E. The 24-hour profile of FEV1 after 12-weeks treatment with Revefenacin , a once daily long-acting muscarinic receptor antagonists for nebulization: A spirometry substudy. Chest [Internet]. 2017;152(4 Supplement 1):A770. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed18&NEWS=N&AN=619296687
42. Nicholls AJ, Barnes C, Yates W, Moran EJ. A randomized, crossover, 7-day study of once-daily TD 4208, a long-acting muscarinic antagonist, in subjects with COPD. Am J Respir Crit Care Med [Internet]. 2014;189(MeetingAbstracts):A6003. Available from: http://www.atsjournals.org/doi/pdf/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A6003
43. Pudi K, Pendyala S, Barnes C, Moran E, Haumann B, Kerwin E. Trials in Progress: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trials of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With Moderate to Very Severe COPD. [Internet]. Vol. 150, Chest. Upstate Pharmaceutical Research, Greenville, SC: American College of Chest Physicians; 2016. p. 825A-825A. Available from: http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=118540780&site=ehost-live
44. Li F, Yang J. Revefenacin for the treatment of chronic obstructive pulmonary disease. Expert Rev Clin Pharmacol [Internet]. 2019 Apr 3 [cited 2019 May 1];12(4):293–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30803279
45. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev [Internet]. 2017 Feb 16 [cited 2019 May 1];(2). Available from: http://doi.wiley.com/10.1002/14651858.MR000033.pub3

Appendix A: Search Strategies

MEDLINE (Ovid) - final ver.

1. lung diseases, obstructive/
2. exp pulmonary disease, chronic obstructive/
3. (copd or coad or cobd or aecb).tw.
4. emphysema*.tw.
5. (chronic* adj4 bronch*).tw.
6. (chronic* adj3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) adj3 obstruct*).tw.
7. (pulmonum adj4 (volumen or pneumatosis)).tw.
8. Pneumonectasia.tw.
9. *Dyspnea/
10. (chronic* adj3 (breath* or respirat*) adj3 (difficult* or labor* or labour* or problem* or short*)).tw.
11. (chronic* adj3 (dyspnea* or dyspnoea* or dyspneic or breathless*)).tw.
12. or/1-11
13. Muscarinic Antagonists/
14. (long act* adj4 muscarinic*).tw.
15. (muscarinic* adj1 antagonist*).tw.
16. LAMA*.tw.
17. Revefenacin .tw.
18. TD?4208.tw.
19. or/13-18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomi#ed.ab.
23. placebo.ab.
24. randomly.ab.
25. clinical trials as topic.sh.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. 12 and 19 and 28

Clinicaltrials.gov final search

149 Results

Relevant RCTs will be searched using the following search strategy:

ClinicalTrials.Gov Advanced Search

- Condition or disease: Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis
- Study Type: Interventional Studies (Clinical Trials)
- Study Results: All Studies
- Status: Recruitment: Completed
- Sex: All
- Eligibility Criteria: Intervention/treatment: Muscarinic Antagonist OR TD-4208 OR Revefenacin OR LAMA

International Clinical Trials Registry Platform final search

8 results

RCTs searched in ICTRP

Look for trials with the exact phrase or contains:

- In the Title: (Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis) AND (Revefenacin OR TD-4208 OR LAMA OR Muscarinic Antagonist)
- In the Condition: Chronic Obstructive Pulmonary Disease OR Emphysema OR respiratory tract disease OR Bronchitis
- In the Intervention: Revefenacin OR TD-4208 OR LAMA OR Muscarinic Antagonist
- Recruitment Status: ALL
- In the Title AND In the Condition AND in the Intervention

CINHAL (EBSCO)
222 results

1. (MH "Lung Diseases, Obstructive+")
2. TX (copd or coad or cobd or aecb)
3. TX emphysema*
4. TX (chronic* N4 bronch*)
5. TX (chronic* N3 (airflow* or airway* or bronch* or lung* or respirat* or pulmonary) N3 obstruct*)
6. TX (pulmonum N4 (volumen or pneumatosis))
7. TX Pneumonectasia
8. (MH “Respiratory Tract Diseases+”)
9. TX (chronic* N3 (breath* or respirat*) N3 (difficult* or labor* or labour* or problem* or short*))
10. TX (chronic* N3 (dyspnea* or dyspnoea* or dyspneic or breathless*))
11. Or/S1-S10
12. (MH "Muscarinic Antagonists+")
13. TX (“long act*” N4 muscarinic*)
14. TX (muscarinic* N1 antagonist*)
15. TX LAMA*
16. TX Revefenacin
17. TX “TD#4208”
18. Or/S12-S17
19. (pt "clinical trial") or (pt "randomized controlled trial")
20. ti (placebo* or random*) or ab (placebo* or random*)
21. ti (“single blind*” or “double blind*” or “treble blind*” or mask* or dummy* or singleblind* or doubleblind* or trebleblind*) or ab (“single blind*” or “double blind*” or “treble blind*” or mask* or dummy* or singleblind* or doubleblind* or trebleblind*)
22. ti (crossover or “cross over”) or ab (crossover or “cross over”)
23. ti clinical n2 trial* or ab clinical n2 trial*
24. (mh "crossover design") or (mh "placebos") or (mh "random assignment") or (mh "random sample")
25. (mh "clinical trials+")
26. Or/S19-25
27. S11 and S18 and S26

EMBASE (Ovid)
894 results
1. exp chronic obstructive lung disease/
2. (copd or coad or cobd or aecb).tw.

3. emphysema$.tw.
4. exp bronchitis/
5. (chronic$ adj4 bronch$).tw.
6. (chronic$ adj3 (airflow$ or airway$ or bronch$ or lung$ or respirat$ or pulmonary) adj3 obstruc$*).tw.
7. (pulmonum adj4 (volumen or pneumatosis)).tw.
8. pneumonectasia.tw.
9. dyspnea/
10. (chronic$ adj3 (breath$ or respirat$) adj3 (difficult$ or labor$ or labour$ or problem$ or short$)).tw.
11. (chronic$ adj3 (dyspnea$ or dyspnoea$ or dyspneic or breathless$)).tw.
12. Or/1-11
13. exp Revefenacin /
14. muscarinic receptor blocking agent/
15. (long act$ adj4 muscarinic$).tw.
16. (muscarinic$ adj1 antagonist$).tw.
17. LAMA*.tw.
18. Revefenacin .tw.
19. TD?4208.tw.
20. Or/13-19
21. randomized controlled trial/
22. controlled clinical trial/
23. randomi$ed.ab.
24. placebo.ab.
25. randomly.ab.
26. clinical trials as topic.sh.
27. trial.ab.
28. groups.ab.
29. Or/21-28
30. 12 and 20 and 29

Appendix B: *Exact adjustment method with R code*

This method of standard error adjustment to avoid unit of analysis error and account for correlation between groups using the same placebo comes from a paper titled *Methods for including information from multi-arm trials in pairwise meta-analysis*.(20) This method (Method 4) adjusts the standard errors within a study by exact inflation factors using a method similar to that of network meta-analysis, which also allows for multi-armed studies and accounts for the unit of analysis error and correlation between groups. The R code used for exact adjustment in our study is reproduced below.

Line	Code
1	pudi <- data.frame(study=rep("Pudi 2017", 5), id=c(1,2,3,4,5), treatment=c("placebo", "44", "88", "175", "350"), n=c(70,68,71,71,74), mean=c(-32.4,19.4,155,134.2,138.2), sd=c(25.36,24.98,24.61,25.07,24.38))
2	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=pudi, studlab=study)
3	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
4	as.data.frame(nm)[,1:6]
5	andrew <- data.frame(study=rep("Andrew", 7), id=c(1,2,3,4,5,6,7), treatment=c("placebo", "22", "44", "88", "175", "350", "700"), n=c(56,37,32,35,33,38,35), mean=c(37.8,91.2,92.8,113.1,151.9,132.2,119.4), sd=c(16.93,19.21,20.25,19.55,19.99,19.02,19.54))
6	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=andrew, studlab=study)
7	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
8	as.data.frame(nm)[,1:6]
9	potgieter <- data.frame(study=rep("Potgieter", 3), id=c(1,2,3), treatment=c("placebo", "350", "700"), n=c(32,32,32), mean=c(0,174,169), sd=c(31.378,31.378,31.378))
10	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=potgieter, studlab=study)
11	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
12	as.data.frame(nm)[,1:6]
13	theravance <- data.frame(study=rep("Theravance", 3), id=c(1,2,3), treatment=c("placebo", "44x2", "175"), n=c(64,64,64), mean=c(-14.4,90.2,98.5), sd=c(15.29,15,15.03))
14	p1 <- pairwise(treat=treatment, n=n, mean=mean, sd=sd, , data=theravance, studlab=study)
15	nm <- netmeta(TE, seTE, treat1, treat2, studlab, data=p1)
16	as.data.frame(nm)[,1:6]

Appendix C: Full-Text Excluded Studies with Reason for Exclusion

Authors	Title	Date	Reason for exclusion
Fura, A.,Obermeier, M., Tino, J., Burke, J., Marathe, P., Yang, Z.	Abstracts for the 9th American Conference on Pharmacometrics, ACoP	2018	Only pharmokinetics of the drug, not relevant
Donohue J., Pendyala, J., Barnes, C., Moran, E.	Improvements in health status with Revefenacin , a once-daily long-acting muscarinic antagonist for nebulization: Changes in St George's respiratory questionnaire and COPD assessment test in replicate 3-month studies	2017	Self-assessment and looks at qualitative aspects, not relevant for this research
Harris, E.	Industry update: What is new in the field of therapeutic delivery?	2018	Business focus with no clinical-relevant data
Mahler, D.A., Pendyala, S., Barnes, C.N.	Prevalence and characteristics of patients with COPD and low peak inspiratory flow rate recruited in a phase 3 development program for Revefenacin , a nebulized once-daily long-acting muscarinic antagonist	2017	No Revefenacin in the study
Borin, M., Barners, C., Darpo, B., Pendyala, S.	Revefenacin , a long-acting muscarinic antagonist (LAMA), does not prolong qt interval in healthy subjects: Results of a placebo-and positive-controlled thorough QT study	2018	Doesn't meet the elegibility criteria (healthy patinets for the RCT)
Baldwin, M., McConn, D., Potgieter, P., Steinfeld, T., Quinn, D.	Single-dose pharmacokinetics of TD-4208, a novel long-acting muscarinic antagonist, in patients with COPD	2013	Only pharmokinetics of the drug, not relevant
DeLaCruz, L., Pendyala, S., Barnes, C., Moran, E., Haumann, B., Feldman, G.	Trial in Progress: A 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial to Evaluate the Safety and Tolerability of a Nebulized Long-Acting Muscarinic Antagonist (Revefenacin) in Study Participants With COPD.	2016	There is another treatment on the side. Moreover, only an update on an ongoing trial with no useable data
Theravance Biopharma	Revefenacin Peak Inspiratory Flow Rate (PIFR) Study in COPD	2018	Does not meet the eligibility criteria of moderate to severe COPD patients

Kerwin,E.M. , Donohue, J.F., Sethi, S., Haumann, B., Pendyala, S., Dean, L., Barnes, C.N., Moran, E.J., Crater, G.D.	Revefenacin , a Once-Daily, Long-Acting Muscarinic Antagonist for Nebulized Therapy of Chronic Obstructive Pulmonary Disease (COPD): Results of a 52-Week Safety and Tolerability Phase 3 Trial in Participants with Moderate to Very Severe COPD	2018	No results posted
Theravance Biopharma	Effects of TD-4208 on FEV1 in Subjects With Chronic Obstructive Pulmonary Disease (COPD)	2017	No results posted
Theravance Biopharma	A 52-Week Parallel Group Safety Study of TD-4208 in Chronic	2018	Does not meet the eligibility criteria of moderate to severe COPD patients
Theravance Biopharma	7 Days of TD−4208 in Subjects With Chronic Obstructive Pulmonary Disease	2017	Does not meet the eligibility criteria of moderate to severe COPD patients - has all levels of COPD patients
Theravance Biopharma	A 42-day Parallel Group Safety Study of Revefenacin and Formoterol, Administered in Sequence and as a Combination, in Subjects With COPD	2018	No results posted
Theravance Biopharma	A 42-day parallel group safety study of Revefenacin and formoterol, administered in sequence and as a combination, in subjects with COPD	2018	No results posted
Cazzola, M., Rogliani, P., Segreti, A., Matera, M. G.	An update on bronchodilators in Phase I and II clinical trials.	2012	No results in the text, this is an informative update
Feldman G., Barnes CN.., Moran E.J., et al.	Safety and tolerability of Revefenacin , a novel once-daily nebulized long-acting muscarinic antagonist: Results of two 12-week, randomized, double-blind, placebo-controlled, parallel-group phase 3 trials in participants with moderate to very severe COPD	2017	Looks only at saftey and tollerability

Appendix D: Risk of bias and interpretation

Risk of Bias	Interpretation	Within a Study	Across Studies
Low	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains **Quinn et al. 2018**	Most information is from studies at low risk of bias
Unclear	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains **Donohue et al. 2017** **Feldman et al. 2017** **Ferguson et al. 2017** **Haumann et al. 2015** **Nicholis et al. 2014** **Potgieter et al. 2012** **Pudi et al. 2016** **Pudi et al. 2016** **Theravance Biopharma. 2017** **Theravance Biopharma. 2017**	Most information is from studies at low or unclear risk of bias
High	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains **Pudi et al. 2017**	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results