Online Data Supplement

Use of the E-RS™: COPD as an Outcome Measure in Clinical Trials: A Rapid Systematic Review

Donald M. Bushnell[1], Rozanne Wilson[1], Florian S. Gutzwiller[2], Nancy K. Leidy[1], Carolina Hache[2], Chau Thach[2], Claus F. Vogelmeier[3]

Methods

Search Strategy and Selection Criteria

Supplemental Table E1. Summary of Concept Search Terms

Concept	Search Terms
Chronic obstructive pulmonary disease	MeSH heading: Pulmonary Disease, Chronic Obstructive MeSH terms: COAD or COPD or chronic airflow obstruction or chronic obstructive airway disease or chronic obstructive lung disease or chronic obstructive pulmonary disease Free text terms: chronic obstructive pulmonary disease, chronic bronchitis, or emphysema
Evaluating Respiratory Symptoms or EXACT-Respiratory Symptoms Scale[a]	MeSH heading: None Free text terms: Evaluating Respiratory Symptoms or EXACT-Respiratory Symptoms Scale or E-RS or E-RS™:COPD, or RS or EXACT
Randomized controlled clinical trial	MeSH heading: Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, and Controlled Clinical Trial MeSH terms: an intervention study Free text terms: randomized controlled clinical trial and non-randomized controlled clinical trial
Non-randomized controlled clinical trial	MeSH heading: None MeSH terms: None Free text terms: non-randomized controlled clinical trial and non-randomized trial
Controlled before-after study	MeSH heading: Controlled Before-After Studies MeSH terms: CBA studies Free text terms: non-randomized controlled clinical trial and non-randomized trial
SLR and Meta-analysis	MeSH heading: Systematic Review, Meta-analysis MeSH terms: None Free text terms: None

Abbreviations: CBA = controlled before-after; COAD = chronic obstructive airways disease; COPD = chronic obstructive pulmonary disease; E-RS = Evaluating Respiratory Symptoms; E-RS:COPD = Evaluating Respiratory Symptoms of Chronic Obstructive Pulmonary Disease; EXACT = EXAcerbations of Chronic pulmonary disease Tool; MeSH = medical subject heading; RS = Respiratory Symptoms; SLR = systematic literature review

[a]The EXACT was included to help identify additional studies with an E-RS:COPD endpoint. EXACT results were not extracted or synthesized.

Supplemental Table E2. Ovid Algorithm-Embase, Medline, and CENTRAL Register of Controlled Trials For Full-Text Publications

Search Number	Search Terms	Results Oct 21, 2020
1	exp Pulmonary Disease, Chronic Obstructive/ or exp chronic obstructive pulmonary disease/ or (coad or copd or chronic airflow obstruction$ or chronic obstructive airway disease$ or chronic obstructive lung disease$ or chronic obstructive pulmonary disease$ or chronic bronchitis or emphysema).ti,ab.	318,490
2	(Evaluating Respiratory Symptoms or EXACT-Respiratory Symptoms Scale or E-RS$ or ER-S$ or RS).ti,ab. or EXACT.ti.	153,796
3	1 and 2	995
4	randomized controlled trial/ or controlled clinical trial/ or exp clinical trial/ or controlled study/ or major clinical study/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or (randomized controlled trial$ or RCT$ or clinical trial$ or controlled stud$ or controlled clinical trial$ or phase 2 clinical trial$ or phase 3 clinical trial$ or phase 4 clinical trial$ or controlled before-after study or "controlled before-and-after study").tw. or (review.pt. and (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.)	12,346,497
5	3 and 4	416
6	limit 5 to (publication or publication in press) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher,CCTR; records were retained]	274
7	limit 6 to english language	268
8	limit 7 to yr="2010 -Current"	195
9	Remove duplicates from 8	167

Supplemental Table E3. Ovid Algorithm-Embase For Conference Abstracts

Search Number	Search Terms	Results Oct 21, 2020
1	exp Pulmonary Disease, Chronic Obstructive/ or exp chronic obstructive pulmonary disease/ or (coad or copd or chronic airflow obstruction$ or chronic obstructive airway disease$ or chronic obstructive lung disease$ or chronic obstructive pulmonary disease$ or chronic bronchitis or emphysema).ti,ab.	1,905,02
2	(Evaluating Respiratory Symptoms or EXACT-Respiratory Symptoms Scale or E-RS$ or ER-S$).ti,ab. or EXACT.ti.	87,129
3	1 and 2	619
4	randomized controlled trial/ or controlled clinical trial/ or exp clinical trial/ or controlled study/ or major clinical study/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or (randomized controlled trial$ or RCT$ or clinical trial$ or controlled stud$ or controlled clinical trial$ or phase 2 clinical trial$ or phase 3 clinical trial$ or phase 4 clinical trial$ or controlled before-after study or "controlled before-and-after study").tw. or (review.pt. and (((systematic or meta) and analy$) or ((indirect or mixed) and treatment comparison)).ti,ab.)	10,619,716
5	3 and 4	349
6	european respiratory society.cf,cg.	34,927
7	american thoracic society.cf,cg.	55,224
8	5 and (6 or 7)	84
9	Limit 8 to (yr="2018-current" and English language)	44

Supplemental Table E4. Citation, Title, and Abstract Screening Tool

Question	Yes /Unclear	No
1. Does the **record** indicate publication on or after 2010 for full-text publications and 2019 for conference abstracts?	Continue screening	Stop screening Reason for exclusion: wrong year
2. Does the **title or abstract** use English?	Continue screening	Stop screening Reason for exclusion: wrong language
3. Does **the title or abstract** indicate that the record included adults with stable COPD, including: chronic bronchitis and emphysema symptomatic patients excluding: asthma	Continue screening	Stop screening Reason for exclusion: wrong population
4. Does the **title or abstract** indicate that randomized controlled trials (phases II through IV), non-randomized controlled trials, controlled before-after trials, or systematic literature review was conducted?	Continue screening	Stop screening Reason for exclusion: wrong study design
5. Does the **title or abstract** indicate any pharmacologic treatment for COPD (licensed and non-licensed) was evaluated? *Note: Non-pharmacologic studies will be explored for potential inclusion-* ***include at this point***	Continue screening	Stop screening Reason for exclusion: wrong intervention
6. Does the **title or abstract or full-text** indicate that the E-RS: COPD PRO measure was used to assess symptoms (breathlessness, cough and sputum, chest symptoms) in patients with COPD? Exclude if only symptoms reported are exacerbations (e.g., EXACT PRO) **Note**: for title/abstract screening, do not exclude records based on the outcome. Include record for full-text publications so that outcome measures can be reviewed and confirmed.	Continue screening	Stop screening Reason for exclusion: wrong outcome
Should this publication be included?	**Yes**: All 6 screening questions answered "Yes or Unclear"	**No**: at least one answer is "No"

Abbreviation: COPD = chronic obstructive pulmonary disease; E-RS:COPD = Evaluating Respiratory Symptoms of chronic obstructive pulmonary disease; EXACT = EXAcerbations of Chronic pulmonary disease Tool; PRO = patient-reported outcome

Supplemental Table E5. Eligibility Criteria Based on the Population, Setting, Intervention, and Comparator [PICOS] Framework

PICOS	Inclusion Description and Rationale	Exclusion Criteria
Population	• Adults diagnosed with clinically stable COPD (all severity levels) including patients with chronic bronchitis, emphysema, as well as symptomatic patients **Rationale**: population of interest	Non-COPD patients Patients with asthma
Intervention/ Comparator	• Any treatment for COPD (licensed and non-licensed), with pharmacologic studies primary focus **Rationale**: interventions of interest *Note:* Non-pharmacologic studies were explored for potential inclusion	Non-treatment intervention
Outcomes	• Evaluating Respiratory Symptoms of Chronic Obstructive Pulmonary Disease (E-RS™:COPD) (exploratory, secondary, primary endpoints) **Rationale**: PRO measure of interest	The study did not include the E-RS:COPD
Study Design	• Randomized controlled trials (phases II through IV) • Non-randomized controlled trials • Controlled before-after trials • Systematic literature reviews **Rationale**: Studies specified as phase I are not deemed appropriate for this review because they are focused on drug safety and side effects and include healthy volunteers and not treatment effectiveness in patients *Note*: SLRs and meta-analyses were included to identify relevant studies that may have included the E-RS: COPD	Cohort studies; observational studies; non-human studies; basic science studies; case reports, case series, non-controlled before and after studies; qualitative studies, discussion papers; editorials; non-systematic reviews
Other	**Inclusion Description and Rationale**	**Exclusion Criteria**
Publication Date	• Full-text publications: 2010 to October 2020 • Meeting abstracts: 2019 to current **Rationale**: The E:RS: COPD was qualified in 2014, thus expanding the time point to 2010 would capture all relevant literature related to the use of the E-RS in clinical trials	Full-text articles published before 2010; conference abstracts published before 2019
Geographical Regions	• Any **Rationale**: no reason for limiting geographical region	Not applicable
Language	• English **Rationale**: Medical research work is often presented in English; translation service is not considered for this project	Non-English publications

Abbreviations: COPD = chronic obstructive pulmonary disease; E-RS:COPD = Evaluating Respiratory Symptoms of Chronic Obstructive Pulmonary Disease; PICOS = population, intervention/comparator, outcomes, study design; PRO = patient-reported outcome; SLR = systematic literature review

Data Extraction

Supplemental Table E6. Extracted Data Elements Included in the Rapid Review based on the Population, Setting, Intervention, and Comparator [PICOS] Framework

PICOS Concept	Data Elements
Population and setting	• Population description from which the study was drawn • Sample size • Participant baseline characteristics: sex, age distribution, race, ethnicity, symptom severity, history of exacerbation, background medications allowed during the study treatment period (e.g., LABA, LAMA, ICS), and GOLD criteria for COPD • Total number of randomized participants • Withdrawals and exclusions • Comorbidities • Other treatments received • Country/geographic location • Recruitment and sampling methods • Study inclusion/exclusion criteria
Intervention	• Types of intervention (definition and identification) • Number of exposed subjects and any exclusions • Treatment/dosing regimen • Assessment time points
Comparator	• Comparators' identification and definition of unexposed individuals • Number of unexposed subjects and any exclusions
Outcome	• Respiratory symptom severity, measured by the E-RS:COPD and: o Primary, co-primary, secondary, or exploratory endpoint description, o E-RS:COPD results: E-RS:COPD mean score change (baseline to follow-up), reported significant treatment effects, and E-RS:COPD responder analysis. • 0ther relevant outcomes shown to correspond with respiratory symptoms, including lung function (FEV1), other symptom measures (BDI-TDI), health-related quality of life (SGRQ; CAT), number of exacerbations, and rescue medication use.
Study/Trial characteristics and design	• General information: title, first author, publication year, publication type, funding source • Type of study (RCTs, NRCTs, CBA trials) • Trial number • Trial name • Trial phase • Methods: study design, objectives, duration

Abbreviations: BDI = Baseline Dyspnea Index; CAT = COPD Assessment Test; CBA = controlled before-after; COPD = chronic obstructive pulmonary disease; E-RS:COPD = Evaluating Respiratory Symptoms of Chronic Obstructive Pulmonary Disease; FEV1 = forced expiratory volume in one second; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; NRCT =non-randomized controlled trial; PICOS = population, intervention/comparator, outcomes and study design; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; TDI = Transition Dyspnea Index

Results

Summary of Included Publications (n=28)

This section summarizes study characteristics from all full-text publications included in the review (n=28).

Supplemental Table E7. Characteristics of Publications Reporting use of The Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS:COPD) in Clinical Trials (N=28)

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
<u>Publications of unique trial data (n=17)</u>										
E-RS:COPD as the primary endpoint (n = 2)										
Lazaar 2020[1]	NCT03034967 Not reported GlaxoSmithKline	RCT: parallel-group Phase IIb Double-blind 5 groups	Multi-center 64 sites Multi-country: 9 countries (location not reported)	614	Moderate to severe	24 weeks	CXC chemokine receptor 2 antagonist (CRXC2)	E-RS:COPD (dose-response) vs. placebo Safety vs. placebo	Co-Primary	No
Smith 2019[2]	NCT02375724 Not reported AstraZeneca and Berlin Chemie	RCT: parallel-group Phase IV Double-blind 1 group	Multi-center 30 sites Multi-country: 5 European countries (location not reported)	269	Moderate	8 weeks	LAMA	E-RS:COPD	Primary Secondary Exploratory	Yes (total score)
E-RS:COPD as a secondary endpoint (n = 4)										
Ferguson 2018[3]	NCT02497001 KRONOS AstraZeneca	RCT: parallel-group Phase II Double-blind 4 groups	Multi-center 215 sites Multi-continental: Canada, China, Japan, the United States	1902	Moderate to very severe	24 weeks	ICS/LAMA/LABA	FEV1	Secondary	Yes (not all groups)
Lee 2017[4]	NCT02164539 Not reported GlaxoSmithKline	RCT: parallel-group Phase II Double-blind 6 groups	Multi-center 55 sites Multi-continental: Argentina, Germany, Poland, Romania, Russia, Ukraine, and the US	338	Not reported	6 weeks	ICS/LAMA	FEV1	Secondary	Yes (total score and all domains)

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
Papi 2017[5]	EudraCT 2012–004162–17 Not reported Mundipharma	RCT: parallel-group Phase III Double-blind 3 groups	Multi-center 223 sites Multi-continental: Bulgaria, Czech Republic, Germany, Hungary, Latvia, Lithuania, Republic of Macedonia, Poland, Romania, Russian Federation, Slovakia, South Africa, South Korea, Spain, Ukraine, and the UK	1,765	Moderate to severe	52 weeks	ICS/LABA	Number of exacerbations	Secondary	Yes (total score)
Singh 2020[6]	NCT03443414; EudraCT 2016–005205-40 Not reported Verona	RCT: parallel-group Phase IIb Double-blind 4 groups	Multi-center 47 sites Multi-country: Bulgaria, Czech Republic, Germany, Poland, Romania, and UK	405	Moderate to severe	4 weeks	PDE 3 and 4 inhibitors	FEV1	Secondary	Yes (total score)
E-RS:COPD as an exploratory endpoint (n = 11)										
Beier 2013[7]	NCT01462929 Not reported Almirall and Forest Laboratories	RCT Phase IIIb Double-blind 2 groups	Multi-center 41 sites Multi-country: Czech Republic, Germany, Hungary, and Poland	414	Moderate to severe	6 weeks	LAMA	FEV1	Exploratory	Yes (significant improvement in total score)
D'Urzo 2014[8]	NCT01437397 AUGMENT COPD Not Reported	RCT Phase III Double-blind 4 groups	Multi-center 222 sites Multi-continental: North America, Australia, and New Zealand	1,692	Moderate to severe	24 weeks	LAMA/LABA	FEV1	Exploratory	Yes

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
Kerwin 2017[9]	NCT02347761; NCT02347774 GOLDEN 3; GOLDEN 4 Sunovion	RCT Phase III (all) GOLDEN 3 and GOLDEN 4: Double-blind 4 groups (all)	Multi-center Not reported Single-country: US	GOLDEN 3: 653 GOLDEN 4: 641 *(1,294 across all trials)*	Moderate to very severe	12 weeks	LAMA	FEV1	Exploratory	Yes (total score relative to placebo for GOLDEN 3 and GOLDEN 4)
Kerwin 2018[10]	NCT02347761; NCT02347774; NCT02276222 GOLDEN 3; GOLDEN 4; GOLDEN 5 Sunovion	RCT Phase III (all) GOLDEN 3 and GOLDEN 4: Double-blind blind; GOLDEN 5: open-label 2 groups (all)	Multi-center Not reported Single-country: US	2,379	Moderate to very severe	GOLDEN 3/GOLDEN 4: 12 weeks GOLDEN 5: 48 weeks	LAMA/LABA	FEV1	Exploratory	Yes (12-week placebo-controlled studies only)
Maltais 2019[11]	NCT03034915 Not reported GlaxoSmithKline	RCT: parallel-group Phase IV Double-blind 3 groups	Multi-center 213 sites Multi-continental: Germany, United states, Argentina, Sweden, Canada, Italy, South Africa, Netherlands, Spain, Australia, France, and Mexico	2,431	Moderate to severe	24 weeks	LAMA/LABA	FEV1	Exploratory	Yes (total score)
McGarvey 2016[12]	NCT00891462; NCT01001494; NCT01462929 ACCORD COPD I; ATTAIN; Not reported Almirall and Forest Laboratories	RCT Phase 3 (ACCORD COPD I & ATTAIN); Phase IIIb (active-comparator study) Double-blind (all) 4 groups	Multi-center Not reported Single-country: US	ACCORD COPD 1: 375 ATTAIN: 542 Active-comparator: 414 *(1,331 across all trials)*	Moderate to severe	NCT00891462: 12 weeks NCT01001494: 24 weeks NCT01462929: 6 weeks	LAMA	Not specified	Exploratory	Yes (total score and cough and sputum domain)

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
Murray 2018[13]	NCT00949975; NCT01023516 Not reported AstraZeneca	RCT Phase II Double-blind 2 groups	Multi-center Not reported Single-country: US	340	All severity	12 weeks for both trials	Neutrophil elastase inhibitor	Exacerbation recovery	Post-hoc endpoint	Yes
Naya 2018[14]	NCT02345161 FULFIL GlaxoSmithKline	RCT: parallel-group Phase III Double-blind 4 groups (ITT and EXT)	Multi-center Not reported Not reported	ITT population: 1810 *EXT sub-population: 430*	Severe to very severe	24 weeks (ITT pop) 52 weeks (EXT sub-set population)	ICS/LAMA/LABA	Clinically important deterioration	Post-hoc endpoint	Not reported
Rennard 2016[15]	NCT01443845 Not reported AstraZeneca and Forest Laboratories	RCT: parallel-group Phase IV Double-blind 1 group	Multi-center Not reported Multi-country: 17 countries (location not reported)	2,354	Moderate to severe	52 weeks	PDE 4 inhibitor added to ICS/LABA	Number of exacerbations	Exploratory	Not reported (sample results only)
Sethi 2019[16]	NCT02796677 AMPLIFY AstraZeneca	RCT: parallel-group Phase III Double-blind 4 groups	Multi-center Not reported Multi-continental: Bulgaria, Czech Republic, Germany, Hungary, Israel, Poland, Russia, Spain, Ukraine, UK, and UUS	1,594	Moderate to very severe	24 weeks	LAMA/LABA	FEV1	Exploratory	Not reported
Singh 2014[17]	NCT01462942 ACLIFORM-COPD Almirall and Forest Laboratories	RCT: parallel-group Phase III Double-blind 4 groups	Multi-center 193 sites Multi-continental: 22 countries Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the	1,729	Moderate to severe	24 weeks	LAMA/LABA	FEV1	Exploratory	Yes

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
			Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, Ukraine, UK, South Africa and South Korea							
<u>Publications reporting additional results based on the unique trials (listed above) included in the review (n=11)</u>										
E-RS:COPD as a secondary and exploratory endpoint (n=3)										
Bateman 2015[18]	NCT01462942; NCT01437397 ACLIFORM; AUGMENT Almirall and Forest Laboratories	RCT: parallel-group Phase III Double-blind 3 groups	Multi-center 415 sites Multi-continental: South Africa, South Korea, 20 countries in Europe, Australia, Canada, New Zealand and UUS	3,421	Moderate to severe	24 weeks	LAMA/LABA	Not specified	Exploratory	Yes
Ichinose 2019[19]	NCT02497001 KRONOS AstraZeneca	RCT: parallel-group Phase III Double-blind 4 groups	Multi-center Not reported Multi-continental: Canada, Japan, China, and US	416	Moderate to very severe	24 weeks	ICS/LAMA/LABA	FEV1	Exploratory	Yes
Tabberer 2018[20]	NCT02345161 FULFIL GlaxoSmithKline	RCT: parallel-group Phase III Double-blind 4 groups (ITT and EXT)	Multi-center Not reported Not reported	1,810	All severity	24 weeks (ITT pop) 52 weeks (EXT sub-set population)	ICS/LAMA/LABA	FEV1 SGRQ	Secondary	Yes (total score and all sub-domains)
E-RS:COPD as a post-hoc endpoint (n = 8)										
Beier 2017[21]	NCT01462929 Not reported Almirall	RCT Phase IIIb Double-blind 2 groups	Multi-center Not reported Not reported	414	Moderate to severe	6 weeks	LAMA	FEV1	Post-hoc endpoint	Yes (total score and all sub-domains)

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
Carlin 2020[22]	NCT02347761; NCT02347774 GOLDEN 3; GOLDEN 4 Sunovion	RCT Phase III (all) GOLDEN 3 and GOLDEN 4: Double-blind 2 groups	Not reported Not reported Not reported	1,293	Moderate to very severe	12 weeks	LAMA	Not specified	Post-hoc endpoint	Yes
Donohue 2020[23]	NCT02347761; NCT02347774 GOLDEN 3; GOLDEN 4 Sunovion	RCT Phase III Double-blind 4 groups	Multi-center Not reported Single-country: US	781	Moderate to very severe	12 weeks for both trials	LAMA	Not specified	Post-hoc endpoint	Yes (significant only in the Q1 baseline rescue medication subgroup)
Jones 2016[24]	NCT01001494; NCT01437397 ATTAIN; AUGMENT COPD I Almirall	RCT: parallel-group Phase III Double-blind 1 group	Multi-center Not reported Single-country (locations not reported)	1,161	Moderate to severe	24 weeks	LAMA	E-RS:COPD	Post-hoc endpoint	Yes (total score and all sub-domains)
Kerwin 2020[25]	NCT03034915 EMAX GlaxoSmithKline	RCT: parallel-group Phase III Double-blind 3 groups	Multi-center Not reported Not reported	2,425	Moderate to severe	24 weeks	LAMA/LABA	E-RS:COPD and Rescue salbutamol use	Post-hoc endpoint	Yes (total score)
Miravitlles 2016[26]	NCT01462942; NCT01437397 ACLIFORM; AUGMENT Almirall	RCT: parallel-group Phase III Double-blind 3 groups	Multi-center Not reported Not reported	3,394	Moderate to severe	24 weeks	LAMA/LABA	E-RS:COPD	Post-hoc endpoint	Yes (total score in more symptomatic patients)
Ohar 2020[27]	NCT02347761; NCT02347774 GOLDEN 3; GOLDEN 4 Sunovion	RCT Phase III Double-blind 2 groups	Multi-center Not reported Not reported	861	Moderate to very severe	12 weeks for both trials	LAMA	Not specified	Post-hoc endpoint	Yes

First Author, Year	Clinical Trial Number Trial Name Funding Source	Trial Design Trail Phase Blinding Number Treatment Groups	Setting Number of Sites Location	Total Number of Randomized Participants	Severity of Airflow Limitation	Treatment Period (weeks)	Treatment Intervention Drug Class	Study Primary/Co-Primary Outcome Measure	E-RS:COPD Endpoint Position	Reported Treatment Effects for E-RS:COPD (yes/no)
Watz 2020[28]	NCT03443414; EudraCT2016-005205-40 Not reported Verona	RCT: parallel-group Phase IIb Double-blind 4 groups	Not reported Not reported Single-country: US	405	Moderate to severe	4 weeks	PDE 3 and 4 inhibitors	FEV	Post-hoc endpoint	Yes (total score and all subscales)

Abbreviations: COPD = chronic obstructive pulmonary disease; E-RS = Evaluating Respiratory Symptoms; EXT = extension; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; ITT = intention to treat; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; PDE3 = phosphodiesterase-3; PDE4 = phosphodiesterase-4; RCT = randomized controlled trial; SGRQ = St. George's Respiratory Questionnaire; UK = United Kingdom; US = United States.

References:

1. Lazaar AL, Miller BE, Donald AC, et al. CXCR2 antagonist for patients with chronic obstructive pulmonary disease with chronic mucus hypersecretion: a phase 2b trial. *Respir Res*. Jun 12 2020;21(1):149. doi:10.1186/s12931-020-01401-4

2. Smith JA, McGarvey L, Morice AH, et al. The Effect of Aclidinium on Symptoms Including Cough in Chronic Obstructive Pulmonary Disease: A Phase 4, Double-Blind, Placebo-controlled, Parallel-Group Study. *Am J Respir Crit Care Med*. Sep 1 2019;200(5):642-645. doi:10.1164/rccm.201901-0048LE

3. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med*. Oct 2018;6(10):747-758. doi:10.1016/S2213-2600(18)30327-8

4. Lee L, Kerwin E, Collison K, et al. The effect of umeclidinium on lung function and symptoms in patients with fixed airflow obstruction and reversibility to salbutamol: A randomised, 3-phase study. *Respir Med*. Oct 2017;131:148-157. doi:10.1016/j.rmed.2017.08.013

5. Papi A, Dokic D, Tzimas W, et al. Fluticasone propionate/formoterol for COPD management: a randomized controlled trial. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1961-1971. doi:10.2147/COPD.S136527

6. Singh D, Martinez FJ, Watz H, Bengtsson T, Maurer BT. A dose-ranging study of the inhaled dual phosphodiesterase 3 and 4 inhibitor ensifentrine in COPD. *Respir Res*. Feb 10 2020;21(1):47. doi:10.1186/s12931-020-1307-4

7. Beier J, Kirsten AM, Mroz R, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. *COPD*. Aug 2013;10(4):511-22. doi:10.3109/15412555.2013.814626

8. D'Urzo AD, Rennard SI, Kerwin EM, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res*. Oct 14 2014;15:123. doi:10.1186/s12931-014-0123-0

9. Kerwin E, Donohue JF, Goodin T, Tosiello R, Wheeler A, Ferguson GT. Efficacy and safety of glycopyrrolate/eFlow((R)) CS (nebulized glycopyrrolate) in moderate-to-very-severe COPD: Results from the glycopyrrolate for obstructive lung disease via electronic nebulizer (GOLDEN) 3 and 4 randomized controlled trials. *Respir Med*. Nov 2017;132:238-250. doi:10.1016/j.rmed.2017.07.011

10. Kerwin EM, Tosiello R, Price B, Sanjar S, Goodin T. Effect of background long-acting beta2-agonist therapy on the efficacy and safety of a novel, nebulized glycopyrrolate in subjects with moderate-to-very-severe COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2917-2929. doi:10.2147/COPD.S172408

11. Maltais F, Bjermer L, Kerwin EM, et al. Efficacy of umeclidinium/vilanterol versus umeclidinium and salmeterol monotherapies in symptomatic patients with COPD not receiving

inhaled corticosteroids: the EMAX randomised trial. *Respir Res*. Oct 30 2019;20(1):238. doi:10.1186/s12931-019-1193-9

12. McGarvey L, Morice AH, Smith JA, et al. Effect of aclidinium bromide on cough and sputum symptoms in moderate-to-severe COPD in three phase III trials. *BMJ Open Respir Res*. 2016;3(1):e000148. doi:10.1136/bmjresp-2016-000148

13. Murray LT, Leidy NK. The Short-term Impact of Symptom-defined COPD Exacerbation Recovery on Health Status and Lung Function. *Chronic Obstr Pulm Dis*. Jan 24 2018;5(1):27-37. doi:10.15326/jcopdf.5.1.2017.0166

14. Naya I, Compton C, Ismaila AS, et al. Preventing clinically important deterioration with single-inhaler triple therapy in COPD. *ERJ Open Res*. Oct 2018;4(4)doi:10.1183/23120541.00047-2018

15. Rennard SI, Martinez FJ, Rabe KF, et al. Effects of roflumilast in COPD patients receiving inhaled corticosteroid/long-acting beta2-agonist fixed-dose combination: RE(2)SPOND rationale and study design. *Int J Chron Obstruct Pulmon Dis*. 2016;11:1921-8. doi:10.2147/COPD.S109661

16. Sethi S, Kerwin E, Watz H, et al. AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:667-682. doi:10.2147/COPD.S189138

17. Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components

and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. Nov 18 2014;14:178. doi:10.1186/1471-2466-14-178

18. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res*. Aug 2 2015;16:92. doi:10.1186/s12931-015-0250-2

19. Ichinose M, Fukushima Y, Inoue Y, et al. Efficacy and Safety of Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Formulated Using Co-Suspension Delivery Technology in Japanese Patients with COPD: A Subgroup Analysis of the KRONOS Study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2979-2991. doi:10.2147/COPD.S220850

20. Tabberer M, Lomas DA, Birk R, et al. Once-Daily Triple Therapy in Patients with COPD: Patient-Reported Symptoms and Quality of Life. *Adv Ther*. Jan 2018;35(1):56-71. doi:10.1007/s12325-017-0650-4

21. Beier J, Mroz R, Kirsten AM, Chuecos F, Gil EG. Improvement in 24-hour bronchodilation and symptom control with aclidinium bromide versus tiotropium and placebo in symptomatic patients with COPD: post hoc analysis of a Phase IIIb study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:1731-1740. doi:10.2147/COPD.S121723

22. Carlin B, Ferguson GT, Ozol-Godfrey A, Goodin T, Sanjar S. The Effect of Metabolic Syndrome Status on Lung Function and Patient-reported Outcomes in Patients with COPD Receiving Nebulized Glycopyrrolate. *Chronic Obstr Pulm Dis*. Oct 2020;7(4):315-326. doi:10.15326/jcopdf.7.4.2020.0145

23. Donohue JF, Ozol-Godfrey A, Goodin T, Sanjar S. The Effect of Baseline Rescue Medication Use on Efficacy and Safety of Nebulized Glycopyrrolate Treatment in Patients with COPD from the GOLDEN 3 and 4 Studies. *Int J Chron Obstruct Pulmon Dis*. 2020;15:745-754. doi:10.2147/COPD.S242767

24. Jones PW, Leidy NK, Hareendran A, Lamarca R, Chuecos F, Garcia Gil E. The effect of aclidinium bromide on daily respiratory symptoms of COPD, measured using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) diary: pooled analysis of two 6-month Phase III studies. *Respir Res*. May 23 2016;17(1):61. doi:10.1186/s12931-016-0372-1

25. Kerwin EM, Boucot IH, Vogelmeier CF, et al. Early and sustained symptom improvement with umeclidinium/vilanterol versus monotherapy in COPD: a post hoc analysis of the EMAX randomised controlled trial. *Ther Adv Respir Dis*. Jan-Dec 2020;14:1753466620926949. doi:10.1177/1753466620926949

26. Miravitlles M, Chapman KR, Chuecos F, Ribera A, Gil EG. The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2041-53. doi:10.2147/COPD.S114566

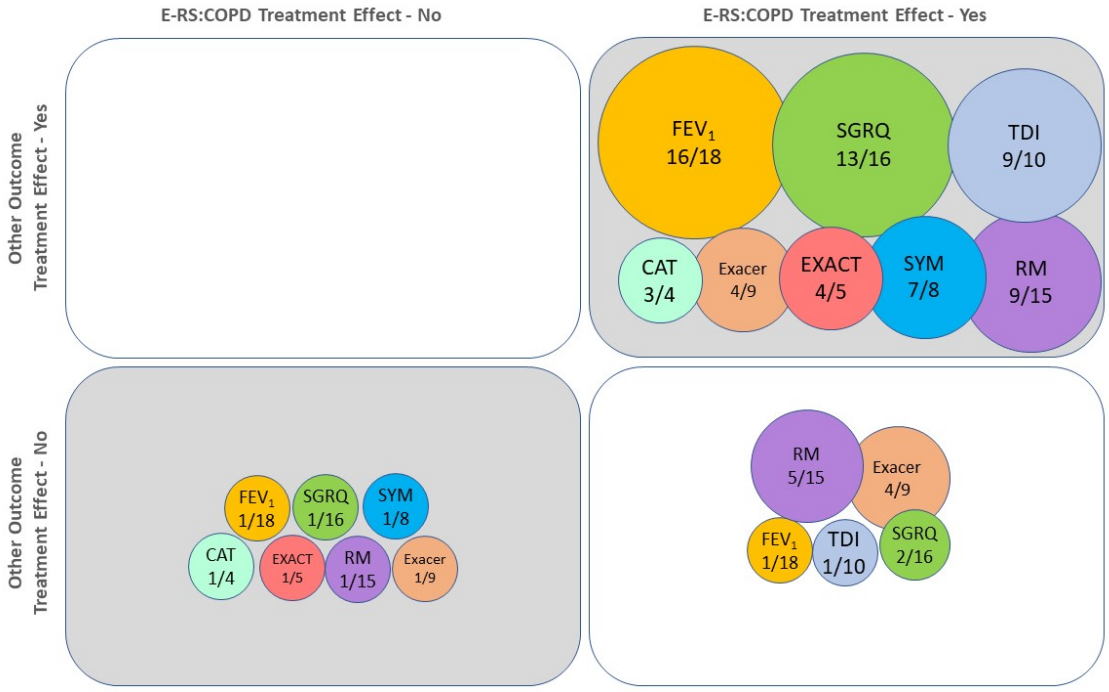
27. Ohar JA, Ozol-Godfrey A, Goodin T, Sanjar S. Effect of Gender on Lung Function and Patient-Reported Outcomes in Patients with COPD Receiving Nebulized Glycopyrrolate. *Int J Chron Obstruct Pulmon Dis*. 2020;15:995-1004. doi:10.2147/COPD.S240303

28. Watz H, Rickard K, Rheault T, Bengtsson T, Singh D. Symptom Improvement Following Treatment with the Inhaled Dual Phosphodiesterase 3 and 4 Inhibitor Ensifentrine in Patients

with Moderate to Severe COPD - A Detailed Analysis. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2199-2206. doi:10.2147/COPD.S263025

Supplement Figure title and Legend

Supplemental Figure E1. Distribution of E-RS: COPD treatment effects and other outcome measure treatment effect included in all full-text publications (n=28)



Note: The bubble size is based on the numerator reported in the figure.

Abbreviations: CAT = COPD Assessment Test; E-RS:COPD = Evaluating Respiratory Symptoms of Chronic Obstructive Pulmonary Disease; Exacer = exacerbation; EXACT = EXAcerbations of Chronic pulmonary disease Tool; FEV1 = forced expiratory volume in one second; RM = rescue medication; SGRQ = St. George's Respiratory Questionnaire; Sym = early morning (n=4)/daytime (n=1) symptoms of COPD and nighttime symptoms o