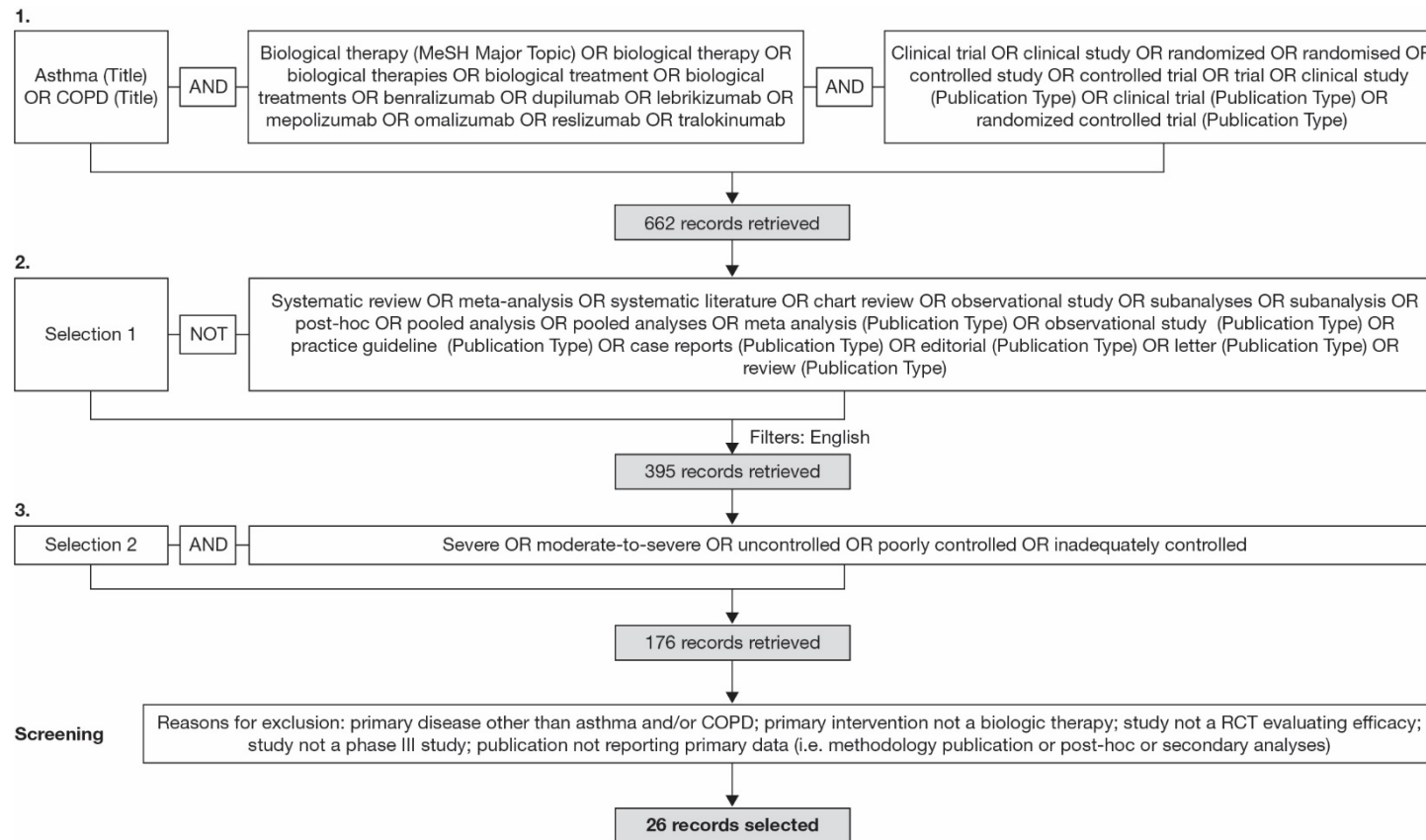


Online supplement

Defining severe obstructive lung disease in the biologic era: an endotype-based approach

SUPPLEMENTARY FIGURE S1 Search strategy to identify publications on clinical trials of biologic therapies in severe obstructive lung disease



COPD: chronic obstructive pulmonary disease; MeSH: Medical Subject Headings; RCT: randomised controlled trial.

Search conducted in PubMed for articles published through 22 May 2019. All search terms were for Title/Abstract field unless otherwise stated in parentheses. For each specific biologic therapy, search also included all experimental and brand names.

SUPPLEMENTARY TABLE S1 GINA-defined low, medium and high daily doses of inhaled corticosteroids

Low dose ICS provides most of the clinical benefit for most patients. However, ICS responsiveness varies between patients, so some patients may need **medium dose ICS** if asthma is uncontrolled despite good adherence and correct inhaler technique with low dose ICS. **High dose ICS** is needed by very few patients, and its long-term use is associated with an increased risk of local and systemic side-effects.

This is not a table of equivalence, but estimated clinical comparability, based on available studies and product information.

Inhaled corticosteroid	Adults and adolescents		
	Low	Medium	High
Beclomethasone dipropionate (CFC) [#]	200–500	>500–1000	>1000
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n/a	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000
Inhaled corticosteroid	Children 6–11 years		
	Low	Medium	High
Beclomethasone dipropionate (CFC) [#]	100–200	>200–400	>400
Beclomethasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Ciclesonide (HFA)	80	>80–160	>160
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220–<440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

Doses are in µg. CFC: chlorofluorocarbon propellant; DPI: dry-powder inhaler; GINA: Global Initiative for Asthma; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; n/a: not applicable.

[#]Included for comparison with older literature.

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SUPPLEMENTARY TABLE S2 Design of phase II RCTs of biologic therapies in severe COPD

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	FeNO requirement	Allergy/atopy requirement	Notable exclusions	Primary end-point
Rennard et al [4] (infliximab [anti-TNF])	Moderate-to-severe COPD	Post-bronchodilator FEV ₁ ≥30% and <80% predicted (GOLD 2007 criteria [5]); ≥1 episode of COPD-related symptoms in past 2 months; CRQ score <120	n/a	<20% [#]	n/a	n/a	n/a	OCS use within 2 weeks of screening; smoking history <10 pack-years; asthma as the main component of obstructive airway disease; age <40 years	Change from baseline in CRQ total score
Brightling et al [6] (benralizumab) NCT01227278	Moderate-to-severe COPD with sputum eosinophilia	Post-bronchodilator FEV ₁ ≥30% and <80% predicted (GOLD 2014 criteria [7]); ≥1 exacerbation requiring OCS, antibiotics or hospitalisation in past year	n/a	n/a	Sputum eosinophil count of ≥3%	n/a	n/a	Smoking history <10 pack-years; additional clinically significant pulmonary disease or asthma; age <40 years	Moderate/severe AER

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	FeNO requirement	Allergy/atopy requirement	Notable exclusions	Primary end-point
Calverley et al [8] (MEDI8968 [anti-IL-1R]) NCT01448850	Moderate-to-very severe COPD	Post-bronchodilator FEV ₁ <80% predicted (GOLD 2011 criteria); ≥2 exacerbations requiring OCS, antibiotics, ER visit or hospitalisation in the past year; EXACT score ≥2 for 7 of the past 14 days	Standard maintenance therapy	n/a	n/a	n/a	n/a	Smoking history <10 pack-years; other significant pulmonary disease as primary diagnosis; current diagnosis of asthma; age <45 years	Moderate/severe AER
Eich et al [9] (CNT0 6785 [anti-IL-17A]) NCT01966549	Symptomatic moderate-to-severe COPD	Post-bronchodilator FEV ₁ ≥40% and <80% predicted; ≥2 exacerbations requiring OCS or antibiotics in past 2 years; persistent COPD symptoms requiring repeated rescue medication; chronic bronchitis	LABA and/or LAMA ± ICS	n/a	n/a	n/a	n/a	Other pulmonary disease such as asthma; age <40 years	Change from baseline in pre-bronchodilator FEV ₁

Published phase II RCTs were identified from PubMed.

AER: annual exacerbation rate; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; EXACT: EXAcerbations of Chronic pulmonary disease Tool; FeNO: fractional exhaled nitric oxide; FEV₁: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; IgE: immunoglobulin E; IL-17A: interleukin-17A; IL-1R: interleukin-1 receptor; n/a: not applicable (not mentioned in inclusion/exclusion criteria); LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnoea scale; OCS: oral corticosteroid; RCT, randomised controlled trial; TNF: tumour necrosis factor inhibitor.

#: <20% reversibility and FEV₁ variability ≤20% between screening and baseline visits.

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