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

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ABSTRACT   Severe obstructive lung disease, which encompasses asthma, chronic obstructive pulmonary disease (COPD) or features of both, remains a considerable global health problem and burden on healthcare resources. However, the clinical definitions of severe asthma and COPD do not reflect the heterogeneity within these diagnoses or the potential for overlap between them, which may lead to inappropriate treatment decisions. Furthermore, most studies exclude patients with diagnoses of both asthma and COPD. Clinical definitions can influence clinical trial design and are both influenced by, and influence, regulatory indications and treatment recommendations. Therefore, to ensure its relevance in the era of targeted biologic therapies, the definition of severe obstructive lung disease must be updated so that it includes all patients who could benefit from novel treatments and for whom associated costs are justified. Here, we review evolving clinical definitions of severe obstructive lung disease and evaluate how these have influenced trial design by summarising eligibility criteria and primary outcomes of phase III randomised controlled trials of biologic therapies. Based on our findings, we discuss the advantages of a phenotype- and endotype-based approach to select appropriate populations for future trials that may influence regulatory approvals and clinical practice, allowing targeted biologic therapies to benefit a greater proportion and range of patients. This calls for co-ordinated efforts between investigators, pharmaceutical developers and regulators to ensure biologic therapies reach their full potential in the management of severe obstructive lung disease.

Introduction

Although asthma and chronic obstructive pulmonary disease (COPD) have historically been treated as overlapping syndromes [1, 2], the emergence of apparent mechanistic differences meant that for many years they were viewed as distinct diagnoses, with different approaches to assessment and management [3, 4]. However, the identification of multiple phenotypes of each condition (including a subset of patients with features of both, who are often excluded from studies [5, 6]), suggests that these diagnoses may more appropriately be viewed as a spectrum of conditions resulting from a range of pathobiological mechanisms [7]. Because the heterogeneity of these conditions is especially apparent at the severe end of the spectrum [8–10], a personalised healthcare approach based on analysis of phenotypes and underlying molecular endotypes could be particularly beneficial in patients with severe asthma and/or COPD. We use the term "severe obstructive lung disease" throughout this article to refer to patients with severe disease across both asthma and COPD diagnostic labels.

Despite continuous advancements in the diagnosis and treatment of obstructive lung disease, severe or uncontrolled asthma and COPD remain a considerable global health problem [11, 12]. In up to 45% of patients with asthma, symptoms and/or exacerbations remain uncontrolled [13], and severe refractory asthma (persistent symptoms and exacerbations despite adherence to high-intensity treatment [10, 14]) accounts for ~4% of the total global asthma population of 339 million people [12, 15]. Likewise, approximately half of patients with COPD receiving "triple therapy" (inhaled corticosteroid (ICS), long-acting β_2-agonist (LABA) and long-acting muscarinic antagonist (LAMA)) remain symptomatic [16, 17] and a third continue to experience exacerbations [17]. Patients with uncontrolled severe obstructive lung disease have a substantial impact on healthcare resources [18–20]. Therefore, identifying these patients and ensuring that they receive appropriate treatment to achieve and maintain control is an important goal, particularly considering the likely high cost of novel targeted biologic therapies [21]. Several such therapies (omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab) have received approval since the early 2000s for the treatment of specific subgroups of patients with severe asthma [22–30], with more in the pipeline (e.g. tezepelumab) [31, 32]. Several studies have evaluated their utility in COPD [33, 34]. Owing to recent clinical experience and a growing body of trial data for biologic therapies, the scientific community is now in a position to reassess how severe obstructive lung disease is defined in the biologic era.

Clinical definitions and regulatory perspectives influence early-phase clinical trial design, which in turn determines later-phase trial outcomes and subsequent regulatory indications, thus affecting guideline recommendations. However, the highly restrictive eligibility criteria of randomised controlled trials (RCTs) in obstructive lung disease, including trials of biologic therapies in severe disease [35], limit their generalisability to patients in real-world clinical practice [36–42]. In this article, we aim to evaluate current definitions of severe obstructive lung disease used in clinical practice, by regulators and in clinical trials of biologic therapies, in order to inform the design of future studies and the approach to regulatory approval. We review evolving definitions of severe obstructive lung disease in relation to anti-inflammatory therapy and how these have influenced the populations included in RCTs of biologic therapies. Based on this, we provide recommendations for future research, the regulatory approach to obstructive lung disease and the use of biologics in clinical practice. We discuss an approach based on phenotypes and molecularly defined endotypes, rather than existing, nonspecific diagnostic labels, to select appropriate populations for future RCTs that may influence drug approvals and clinical practice.

Current management strategies for severe obstructive lung disease

Current management strategies for asthma and COPD commonly follow a "one-size-fits-all" approach [21], mandated by existing treatment algorithms that often recommend stepwise escalation of therapy until adequate control is achieved [43–46]. This is inconsistent with the precision medicine approach that is increasingly being called for in respiratory medicine [5, 7, 21]. Of particular concern are the indiscriminate use of high-dose ICS and the widespread reliance on oral corticosteroids (OCS) as long-term anti-inflammatory maintenance treatment in patients with persistent or refractory disease [47–49] (some of whom may also be receiving topical corticosteroid treatment for comorbidities such as nasal polyposis or atopic dermatitis [50, 51]). Although ICS are an important component of asthma and COPD treatment strategies, guidelines recommend specialist referral and careful monitoring of patients requiring high-dose ICS (for asthma) and for patients with features of both asthma and COPD [14], and the use of blood eosinophil count combined with clinical assessment of exacerbation risk to guide ICS use (for COPD) [45]. Irreversible dose- and duration-dependent adverse effects of OCS are well documented (mostly for maintenance OCS, but with increasing evidence for effects of intermittent OCS treatment) [48, 52–55], and high-dose ICS has been associated with systemic adverse effects [56–58], including increased pneumonia risk (particularly in patients with COPD) [59, 60] and clinically important local adverse effects [61]. Though ICS-induced effects may be less serious than OCS-related morbidity, they should be

considered alongside the potential benefits of ICS treatment. The cost of future OCS-induced complications and/or treatment to prevent adverse effects [52, 53, 55] may offset the low purchase price for payers over the long term. Recently approved and emerging biologic therapies provide effective control [31] and reduce OCS dependence in severe or uncontrolled asthma [62–64]. Evidence supports the cost-effectiveness of biologic therapies (primarily due to improvements in symptom-related quality of life, and reductions in exacerbation-related hospitalisations and asthma-related mortality risk) if carefully targeted or with substantial discounts [65].

Thus, to minimise avoidable and potentially costly adverse effects of long-term corticosteroid treatment, and to identify patients who could benefit most from alternative treatments, it is important to accurately define and diagnose severe obstructive lung disease and determine which patients are likely to respond to standard pharmacological treatments, and which may benefit from add-on biologic therapies.

Clinical definitions of severe obstructive lung disease
To summarise current clinical definitions of severe obstructive lung disease, we reviewed recent consensus and guidelines publications on severe asthma [10, 14, 21, 66, 67], severe COPD [45] and asthma–COPD overlap [14, 68–72] (summarised in table 1).

Clinical definitions of severe asthma
All five recently proposed clinical definitions of severe asthma (table 1) [10, 14, 21, 66, 67] are partly based on the level of treatment, and most specify an ICS component and at least one additional controller (LABA, OCS or other). The World Health Organization (2010) [66] and Innovative Medicine Initiative (IMI) (2011) [67] definitions required asthma to be uncontrolled (with various thresholds for symptoms and exacerbations) on high-level treatment. The IMI definition additionally included patients dependent on OCS treatment for adequate asthma control, owing to the risk of serious adverse effects with OCS treatment [67]. However, in recognition of the potential adverse effects of high-dose ICS, the definition in the more recent European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines for severe asthma (2014) [10] and Global Initiative for Asthma (GINA) (2019) [14] also included dependence on high-dose ICS (for adults, equivalent to budesonide ⩾1600 µg per day, per ERS/ATS definition, and budesonide >800 µg per day, per GINA definition; supplementary table S1) and/or OCS for asthma control. Furthermore, GINA includes risk factors for medication side effects in its recommendation for assessing control [14].

The ERS/ATS guidelines for severe asthma recommended biologic therapy (then limited to omalizumab) for patients with severe allergic asthma [10]. These guidelines were subsequently adopted by GINA, which also recommends ICS dose escalation before considering biologic therapy [14]. Evidence shows limited or no incremental benefit at a group level for high-dose *versus* lower-dose ICS for improving airflow limitation, symptoms and health status in patients with asthma [73, 74], despite a significant dose-response for the frequency of oropharyngeal adverse effects [73]. This suggests that the current recommendation for escalating ICS dose in patients with severe asthma may only be effective in certain subgroups, such as those dependent on OCS [73]. The ERS/ATS guidelines highlight that there is individual variation in the dose-therapeutic efficacy of ICS [10], *i.e.* that limited benefit at a group level does not mean individual patients will not benefit from treatment; nevertheless, because of the risk of adverse effects, guidelines recommend only a short-term trial of high-dose ICS [14]. Otherwise, the clinical impact of adverse effects from high-dose ICS treatment [56, 57, 61] (though less severe than that of OCS-related morbidity [56]) may outweigh the limited benefit *versus* low-dose ICS, particularly in patients maintained on high-dose ICS in the long term.

The Lancet Commission (2018) [21] addressed the concern about ICS-related adverse effects by lowering the ICS threshold in its definition of severe asthma to "moderate dose". It stipulates that patients must have impaired lung function, variable airflow obstruction or airway eosinophilia while receiving moderate-dose ICS (with or without LABA or additional controllers, depending on the specific criterion) to be classified as having severe asthma [21]. It also includes a criterion that places greater emphasis on exacerbation risk, the rationale being that exacerbations are highly responsive to better control of lower airway inflammation with either ICS [75, 76] or targeted biologics [33]; thus, identifying patients at risk of exacerbations who do not respond to ICS but may respond to targeted biologics should be a priority [21]. Predictors of exacerbation risk, such as blood eosinophil count (in isolation or combination with other characteristics) [77–79], are already used to identify patients who could benefit from biologic therapies [14, 45]. Recent evidence for alternative clinical characteristics or biomarkers that may predict treatment response independently of eosinophil count, such as nasal polyposis [80] and exhaled nitric oxide fraction (*F*eNO) [81, 82], highlight a need for further investigation [79].

TABLE 1 Recent clinical definitions of severe asthma, COPD and asthma–COPD overlap

Source	Definition	Advantages/additions to previous definitions	Disadvantages
Asthma **WHO (2010) [66]**	**Treatment-resistant severe asthma** • Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma • Asthma for which control can be maintained only with the highest level of recommended treatment o "Control" is defined based on symptoms, activity limitation, night-time awakenings and SABA use in past 2–4 weeks; lung function and the number of exacerbations per year requiring OCS	• Differentiates treatment-resistant severe asthma from untreated or difficult-to-treat severe asthma, while recognising the importance of access to effective medications	• Potential for inappropriate escalation of ICS

IMI (2011) [67]	**Severe refractory asthma**
	When the patient has been followed and reassessed for ⩾6 months:
	• Uncontrolled asthma (ACQ score ⩾1.5) and/or ⩾2 severe exacerbations per year despite:
	  o adherence to high-dose ICS (fluticasone ⩾1000 µg per day or equivalent) and/or daily OCS +LABA or another controller
	  o exclusion of alternative diagnoses and removal (if possible) of sensitising substances at work/home or drugs that may cause bronchoconstriction
	  o optimally treated comorbidities
	• Asthma that can only be controlled by the use of OCS
		• Excludes patients with alternative diagnoses that may mimic asthma and comorbidities that are untreated or inadequately treated and contribute to poor control	• Potential for inappropriate escalation of ICS dose
			• Requires ⩾2 severe exacerbations in the previous year, exposing patients to a higher risk of OCS-related adverse effects
			• Requires management of contributory factors before asthma can be classified as severe

ERS/ATS (2014) [10]	**Severe asthma** • Asthma which requires treatment with guidelines-suggested medications for GINA steps 4–5 asthma (high-dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or OCS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy o "Uncontrolled asthma" is defined as (one or more of): ACQ consistently >1.5, ACT<20 (or "not well controlled" by NAEPP/GINA guidelines); ⩾2 bursts of OCS (>3 days each) in the previous year; ⩾1 hospitalisation, ICU stay or mechanical ventilation in the previous year; or pre-bronchodilator FEV$_1$<80% predicted and FEV$_1$/FVC<LLN • Controlled asthma that worsens on tapering of these high doses of ICS or OCS (or additional biologics)	• Includes patients whose asthma is controlled but dependent on high-dose ICS/OCS (encouraging step-down to assess whether asthma becomes uncontrolled) • Provides a detailed definition of "uncontrolled", which balances symptom control with future risk • Explicitly excludes patients who present with difficult asthma, in whom appropriate diagnosis and/or treatment of confounders (*e.g.* poor adherence or comorbidities) "vastly improves" their current condition	• Potential for inappropriate escalation of ICS dose • A single pre-bronchodilator FEV$_1$<80% in the previous year is sufficient to categorise a patient as having uncontrolled severe asthma (even if they have had no exacerbations and have good symptom control) • The criterion for exacerbations requires ⩾2 bursts of OCS (of >3 days each) in the previous year, exposing patients to a higher risk of OCS adverse effects • Requires management of contributory factors before asthma can be classified as severe
Lancet Commission (2018) [21]	**Severe asthma** Asthma with any of: • ⩾1 severe attack (exacerbation or flare-up) • spirometry persistently below the normal range despite moderate-dose ICS plus one other controller	• Recognises the need to reduce the risk of attacks as a priority, including addressing poor adherence and risk factors • Avoids inappropriate escalation of ICS dose	• The first criterion may include patients with "untreated severe asthma", recognised as a separate population in the WHO definition [66], *i.e.* in a patient with one severe attack while

TABLE 1 Continued

Source	Definition	Advantages/additions to previous definitions	Disadvantages
	• persistent variable airflow obstruction despite ICS/LABA • persistent airway eosinophilia despite moderate-dose ICS • adverse behavioural/environmental factors, including unscheduled visits, failure to attend appointments, poor adherence, smoking, allergenic environment, and the three Ds – denial, depression and disorganisation		treated only with SABA, asthma may become controlled after commencing low-dose ICS
GINA (2019) [14]	**Severe asthma** Asthma that requires high-dose ICS/LABA to prevent it from becoming "uncontrolled", or asthma that remains "uncontrolled" despite this treatment (after excluding poor inhaler technique/adherence, incorrect diagnosis and comorbidities and exposure to sensitising agents/irritants) • "Uncontrolled asthma" is defined based on symptom control and future risk of adverse outcomes, as per the GINA strategy report	• Includes patients whose asthma is well controlled but dependent on high-dose ICS/OCS (encouraging step-down) • Provides a detailed definition of "uncontrolled", which includes both symptom control and future risk	• Requires management of contributory factors before asthma can be classified as severe
COPD GOLD (2019) [45]	**COPD with severe airflow limitation** Post-bronchodilator $FEV_1/FVC<0.7$ and $FEV_1<50\%$ predicted • Patients are further stratified by exacerbation history and symptoms (mMRC or CAT score) using the ABCD assessment tool to guide treatment decisions	• Partly addresses heterogeneity by basing treatment decisions on exacerbations and symptoms	• Trial eligibility is often based on airflow limitation thresholds alone, without considering the ABCD group • Excludes other important phenotypic features such as CT scan findings and low diffusion capacity
Asthma–COPD overlap			
Gibson and Simpson (2009) [68]	**Asthma and COPD overlap syndrome** Symptoms of increased variability of airflow and incompletely reversible airflow limitation, including (all of): • Symptoms of asthma and/or COPD • $FEV_1/FVC<0.7$ • $FEV_1<80\%$ predicted • Airway hyper-responsiveness[#]	• Recognises the need to identify patients with features of both asthma and COPD	• The term "syndrome" implies a single disease; does not recognise heterogeneity within the subset of patients who meet the definition • No recommendations for severity staging or treatment
CHAIN study (2012; 2016) [69, 70]	**Asthma and COPD overlap syndrome** COPD (age >40 years, with post-bronchodilator $FEV_1/FVC<0.7$ and exposure to cigarette smoke) plus at least one of: • previous history of asthma • bronchodilator response >15% and >400 mL OR two of: • IgE >100 IU • history of atopy • reversibility >12% and >200 mL on 2 separate visits • blood eosinophils >5%	• Based on precise diagnostic criteria	• Excludes certain phenotypes, such as younger patients, early-onset disease and non-smokers • The term "syndrome" implies a single disease; does not recognise heterogeneity within the subset of patients who meet the definition • No recommendations for severity staging or treatment

TABLE 1 Continued

Source	Definition	Advantages/additions to previous definitions	Disadvantages
Roundtable consensus definition (2016) [71]	**Asthma–COPD overlap syndrome** Three major criteria, including (all of): • persistent airflow limitation (FEV1/FVC<0.7 or LLN) • ≥10 pack-years' smoking history OR equivalent air pollution exposure • Documented history of asthma OR reversibility >400 mL AND at least one of: • documented history of atopy or allergic rhinitis • reversibility ≥200 mL and ≥12% on ≥2 visits¶ • blood eosinophil count of ≥300 cells per μL	• Provides a straightforward algorithm to facilitate diagnosis and research	• The term "syndrome" implies a single disease; does not recognise heterogeneity within the subset of patients who meet the definition • No attempt to classify severity and limited recommendations for treatment
GesEPOC/GEMA (2017) [72]	**Asthma–COPD overlap** Persistent airflow limitation (FEV1/FVC <0.7) in a patient ≥35 years with ≥10 pack-years' smoking history, who does not respond to ICS/LABA and/or OCS, with one of: • a diagnosis of current asthma (including history and/or symptoms in addition to objective diagnostic confirmation (reversibility ≥12% and ≥200 mL; diurnal variability in PEF ≥20%; or F_{eNO} ≥50 ppb)) • positive bronchodilator response (≥15% and ≥400 mL) AND/OR eosinophil count of ≥300 cells per μL	• Provides basic treatment recommendations	• Excludes certain phenotypes, such as younger patients, early-onset disease and non-smokers • No attempt to classify severity; treatment is based on safety considerations
GINA/GOLD (2019) [14]	**Asthma–COPD overlap** Persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD • GINA and GOLD specifically recommend against attempting to define asthma–COPD overlap, because of its obvious heterogeneous nature and different underlying mechanisms; this is a description rather than a definition • A diagnosis of asthma–COPD overlap is recommended if there are similar numbers of features of asthma and features of COPD	• Highlights that asthma–COPD overlap does not represent a single entity • Includes a wide range of potential clinical phenotypes • Provides basic treatment recommendations based on safety	• Characteristics, underlying mechanisms and treatments for different clinical phenotypes of asthma–COPD overlap are currently undetermined • No attempt to classify severity; treatment is based on safety considerations

Where publications state "systemic corticosteroid", it is assumed for the purposes of this review that they refer mostly or entirely to OCS. COPD: chronic obstructive pulmonary disease; WHO: World Health Organization; IMI: Innovative Medicine Initiative; ERS: European Respiratory Society; ATS: American Thoracic Society; GINA: Global Initiative for Asthma; GOLD: Global Initiative for Obstructive Lung Disease; CHAIN: COPD History Assessment in Spain; GesEPOC: Spanish COPD Guidelines; GEMA: Spanish Guidelines on the Management of Asthma; SABA: short-acting β_2-agonist; OCS: oral corticosteroid; ICS: inhaled corticosteroid; ACQ: Asthma Control Questionnaire; LABA: long-acting β_2-agonist; ACT: Asthma Control Test; NAEPP: National Asthma Education and Prevention Program; ICU: intensive care unit; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; mMRC: modified Medical Research Council dyspnoea scale; CAT: COPD Assessment Test; CT: computed tomography; PEF: peak expiratory flow; F_{eNO}: exhaled nitric oxide fraction. #: provocation dose of hypertonic saline that induces a 15% fall in FEV1<12 mL; ¶: response to 400 μg albuterol/salbutamol or equivalent.

Clinical definitions of severe COPD

Unlike severe asthma, clinical gradations of COPD are not based on the required level of treatment. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 report no longer defines COPD severity *per se*, but instead defines the severity of airflow limitation, requiring a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity ratio of <0.7 as part of the definition of COPD itself, and defining airflow limitation as "severe" or "very severe" if FEV_1 is <50% predicted (table 1) [45]. Although airflow limitation thresholds often determine trial eligibility, they are not intended to guide therapy. Instead, GOLD recommends basing treatment on symptom burden and exacerbation history, with combination therapy only recommended in patients meeting specific thresholds for both or with an inadequate response to initial monotherapy [45]. Evidence for predictors of frequent COPD exacerbations, including eosinophilia [83], suggests that such predictors could be used to guide treatment decisions. This is reflected in the most recent GOLD report, which recommends using blood eosinophil count to guide ICS therapy in patients with frequent exacerbations [45]. However, other characteristics that may affect prognosis and management strategies for patients with COPD in clinical practice, such as computed tomography scan findings [84, 85], are not incorporated into the GOLD assessment. These characteristics may represent particular phenotypes or comorbidities of COPD that are not necessarily correlated with lung function [85], but that nevertheless should be considered alongside other assessments as part of a more personalised treatment approach. Therefore, an improved approach to identifying patients with COPD who could benefit from modified or additional treatments, regardless of spirometric severity staging, is needed. In recent RCTs, severe COPD (in terms of eligibility for biologic add-on therapy) has been defined as COPD with two or more exacerbations in the past year despite maximal inhaled therapy (*i.e.* triple therapy with ICS, LABA and LAMA) [33], although at present this definition is not widely used in clinical practice.

Clinical definitions of severe asthma–COPD overlap

Asthma–COPD overlap refers to the heterogeneous group of patients who have features of both asthma and COPD [14]. It does not represent a single disease [14]. To date, such patients have been excluded from pharmacotherapy RCTs, and most mechanistic studies, so this population is poorly characterised. Several groups have attempted to define asthma–COPD overlap (table 1) [14, 68–72], each proposing various algorithms incorporating the evolving clinical definitions of asthma and COPD, as well as factors that may influence treatment strategies in these patients (such as allergic status and eosinophilia). However, many of these fail to recognise the heterogeneity within this group of patients. None of the definitions propose a means of assessing severity in patients with features of both asthma and COPD. This lack of clarity highlights the need to identify underlying mechanisms associated with differential long-term clinical outcomes across the whole spectrum of obstructive lung disease. Such investigations will help to clarify which features of different phenotypic groups should be considered to represent "severe" disease. This approach may also identify biomarkers that can guide targeted therapy in a manner that is not restricted by the conflicting treatment recommendations for asthma and COPD.

Current treatment guidelines for asthma and COPD, based on studies that excluded patients with features of both, have opposite recommendations regarding the use of LABA monotherapy and ICS [6, 14, 45]. Consequently, and in the absence of evidence about underlying mechanisms, treatment recommendations for patients with features of both asthma and COPD are interim and pragmatic, based primarily on safety considerations [14]: patients with COPD who also have a diagnosis of asthma are more likely to die or be hospitalised if treated with LABA only rather than with ICS/LABA [86, 87]. Guidelines do not attempt to classify asthma–COPD overlap severity; however, similar concepts for severe asthma and severe COPD are used, in terms of persistent symptoms and/or exacerbations despite maximal inhaled therapy.

The increasing recognition of asthma–COPD overlap highlights an additional consideration around the relevance of conventional criteria for the diagnosis of asthma (variable respiratory symptoms with variable airflow limitation and reversibility [14]) and COPD (respiratory symptoms with a history of risk factors and persistent airflow limitation [45]). Studies have identified populations of patients who do not meet all of these criteria and thus have non-typical phenotypes, such as asthma with non-reversible airflow limitation [9, 88, 89] and COPD with reversible airflow limitation [90]. Therefore, in defining severe asthma and COPD it is also important to consider the criteria used to diagnose each condition, and whether a more endotype-focused approach is appropriate.

Clinical trials of biologic therapies in severe obstructive lung disease

To evaluate definitions of severe obstructive lung disease used in RCTs, we performed a PubMed search to identify publications on RCTs of biologic therapies in asthma or COPD that included the terms "severe", "moderate-to-severe", "uncontrolled" or "poorly/inadequately controlled" in the title and/or abstract (articles in English, published through to 22 May 2019; supplementary figure S1). Results were manually

screened to identify primary publications from phase III RCTs in patients with a primary diagnosis of asthma and/or COPD.

The search returned 176 results, from which 26 relevant publications were identified, reporting trials of omalizumab [91–99], mepolizumab [33, 62, 100–102], reslizumab [103–105], benralizumab [34, 63, 106, 107], lebrikizumab [108], dupilumab [64, 109] and tralokinumab [110, 111]. Selected eligibility criteria and primary endpoints for each trial are summarised in table 2. Because only two publications reporting phase III COPD trials were identified, published phase II RCTs of biologic therapies in COPD are also discussed (summarised in supplementary table S2) [112–115].

Design of existing clinical trials
Target population and disease characteristics
In 24 of 26 publications identified, the trials had a target population of patients with severe and/or uncontrolled asthma [62–64, 91–111]. The remaining publications had target populations of patients with eosinophilic COPD (despite triple therapy) [33] or moderate-to-very severe COPD with a history of exacerbations [34]; the latter reporting two trials that failed to meet their primary endpoints of exacerbation reduction [34]. Four publications reporting phase II trials of patients with moderate-to-severe or very severe COPD were identified [112–115].

Most of the asthma trials required patients to have ⩾12% bronchodilator reversibility, one of several conventional asthma diagnostic criteria commonly used when the patient is first assessed [14]. Conversely, all of the phase II and phase III COPD trials required persistent, moderate-to-severe airflow limitation as per past COPD severity staging criteria [45]. Age was also consistently used to select patients with COPD, with all of the phase II and phase III COPD trials excluding patients aged <40 years (<45 years in one trial) [33, 34, 112–114].

All of the asthma trials had at least one criterion to select patients with uncontrolled disease, except SIRIUS [62], LIBERTY ASTHMA VENTURE [64] and TROPOS [111], which all required maintenance OCS use at entry and incorporated asthma control into the OCS dose-reduction criteria. Criteria for asthma control in RCTs have evolved: earlier trials enrolled patients based on symptom control [91, 92, 95] but more recently there has been increasing focus on the number and severity of exacerbations as inclusion criteria [33, 62, 63, 93, 94, 96–107, 110, 116] (except LAVOLTA I/II [108]). This was also the case in the phase II and phase III COPD trials, with all except the oldest study [112] having an inclusion criterion for exacerbations. Requiring a history of exacerbations as an inclusion criterion had the effect of enriching study populations for patients who were more likely to have an exacerbation during the study.

Current treatment
In line with the clinical definitions discussed above, all of the phase III trials included one or more criteria for current treatment. All of the asthma trials specified either medium- to high-dose or high-dose ICS according to GINA definitions (GINA definitions of low-, medium- and high-dose ICS are shown in supplementary table S1). The majority also specified LABA and/or additional controllers. The phase III COPD trials required either triple therapy with high-dose ICS, LABA and LAMA [33], or double or triple therapy with LABA plus LAMA and/or ICS [34]. Many asthma trials explicitly allowed OCS use in their inclusion criteria, but only SIRIUS [62], ZONDA [63], LIBERTY ASTHMA VENTURE [64] and TROPOS [111] (all designed to evaluate OCS sparing) mandated it. Eight asthma studies excluded patients with chronic or maintenance OCS use at baseline, either at all or at various dose thresholds [92–95, 104, 105, 108, 110].

Phenotype
Most of the trials were restricted to a specific phenotype appropriate to the molecular target of the treatment. Thus, all trials of omalizumab (anti-IgE) only enrolled patients with evidence of IgE-mediated allergic asthma [91–99], whereas trials of mepolizumab or reslizumab (anti-interleukin (IL)-5) or benralizumab (anti-IL-5 receptor) enrolled or performed primary analyses on patients with sputum or blood eosinophil counts above a specific threshold [33, 34, 62, 63, 100–104, 106, 107, 113] (with the exception of CORREN et al. [105]). Only the DREAM trial of mepolizumab (a goal of which was to identify characteristics, including biomarkers, that predicted response) had an inclusion criterion for F_{ENO} [100]. The LAVOLTA trials of lebrikizumab (anti-IL-13) performed primary analyses on patients with a "biomarker-high" phenotype of higher concentrations of the Type 2 (T2) inflammatory marker periostin and/or blood eosinophilia [108]. The two trials of dupilumab (which blocks IL-4 and IL-13 signalling via the IL-4 receptor) did not restrict eligibility based on T2 inflammatory markers [64, 109]. The STRATOS 2 trial of tralokinumab (anti-IL-13) specified a primary analysis population of patients with F_{ENO} ⩾37 ppb, which was identified as the preferred "biomarker-high" population in the all-comers trial, STRATOS 1 [110].

TABLE 2 Design of existing phase III RCTs of biologic therapies in severe obstructive lung disease

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	F_{eNO} requirement	Allergy/atopy requirement	Notable exclusions	Primary endpoint
Target population: patients with asthma									
Busse et al. [91] (omalizumab)	Severe allergic asthma	Symptomatic (total daily symptom score ⩾3)	ICS 420–840 µg per day (BDP or equivalent)#	⩾12%	n/a	n/a	Positive skin-prick, IgE 30–700 IU·mL⁻¹	n/a	Number of exacerbations (during ICS stable and ICS reduction phases)
Solèr et al. [92] (omalizumab)	Allergic asthma	Symptomatic (total daily symptom score ⩾3)	Medium- to high-dose ICS (BDP 500–1200 µg per day or equivalent) +β₂-agonist as needed for maintenance	⩾12%	n/a	n/a	Positive skin-prick, IgE 30–700 IU·mL⁻¹	Maintenance OCS use	Number of exacerbations (during ICS stable and ICS reduction phases)
SOLAR [93] (omalizumab)	Concomitant allergic asthma and PAR	Concomitant moderate-to-severe PAR ⩾2 years; AQLQ total score >64 and RQLQ total score >54; ⩾2 unscheduled visits for asthma in the past year or ⩾3 in past 2 years	Medium- to high-dose ICS (budesonide ⩾400 µg per day)	⩾12%	n/a	n/a	Positive skin-prick, IgE 30–1300 IU·mL⁻¹	OCS use	(Co-primary) Number of exacerbations and proportion of patients with improvement in both asthma and rhinitis quality-of-life scores
INNOVATE [94] (omalizumab)	Severe persistent asthma	Daytime or night-time symptoms; ⩾2 exacerbations requiring OCS in the past year or ⩾1 severe exacerbation requiring hospitalisation or ER treatment in the past year	High-dose ICS (BDP >1000 µg per day or equivalent)+LABA ±OCS or other controllers	⩾12%	n/a	n/a	Positive skin-prick, IgE 30–700 IU·mL⁻¹	Maintenance OCS use >20 mg per day, (⩽20 mg per day was permitted providing ⩾1 exacerbation in the past year occurred on this therapy); smokers or former smokers with ⩾10 pack-years	Rate of clinically significant asthma exacerbations
Ohta et al. [95] (omalizumab) NCT00232050	Moderate-to-severe persistent asthma	Moderate-to-severe asthma as per GINA 2002; daytime and/or night-time symptoms	Medium- to high-dose ICS (BDP ⩾800 µg per day or equivalent)+ ⩾1 LABA, OCS or other controllers	n/a	n/a	n/a	Positive skin-prick or in vitro reactivity, IgE 30–700 IU·mL⁻¹	Maintenance OCS use (>10 mg·day); complicated pulmonary disease considered to interfere with evaluation	Change from baseline in morning PEF
Lanier et al. [96] (omalizumab) NCT00079937	Moderate-to-severe, uncontrolled allergic asthma (children)	Daytime or night-time symptoms; ⩾2 exacerbations in the past year or ⩾3 in past 2 years or ⩾1 severe exacerbation requiring hospitalisation in the past year	Medium- to high-dose ICS (FP ⩾200 µg per day or equivalent)	⩾12%	n/a	n/a	Positive skin-prick, IgE 30–1300 IU·mL⁻¹	OCS use for reasons other than asthma	Rate of clinically significant asthma exacerbations

Continued

TABLE 2 Continued

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	F_{eNO} requirement	Allergy/atopy requirement	Notable exclusions	Primary endpoint
EXTRA [97] (omalizumab) NCT00314574	Severe, uncontrolled allergic asthma	Daytime and night-time symptoms requiring SABA; ⩾1 exacerbation in the past year	High-dose ICS (fluticasone ⩾500 µg twice daily or equivalent) +LABA±OCS or other controllers	n/a	n/a	n/a	Positive skin-prick or *in vitro* reactivity, IgE 30–700 IU·mL^{-1}	Exacerbation requiring OCS or increase in baseline OCS in ⩽30 days prior to screening; smokers or former smokers with ⩾10 pack-years; active lung disease other than asthma	Rate of exacerbations
Garcia et al. [98] (omalizumab) NCT01007149	Severe, persistent, uncontrolled, non-atopic asthma	Severe uncontrolled asthma as per GINA 2006; ⩾2 exacerbations per year and/or ⩾1 exacerbation requiring hospitalisation or ER treatment in the past year	High-dose ICS (BDP >1000 µg per day or equivalent) +LABA±OCS	n/a	n/a	n/a	Negative Phadiatop, radioallergosorbent and skin-prick tests; IgE 30–700 IU·mL^{-1}	Smokers or former smokers with ⩾10 pack-years; uncontrolled other chronic diseases	Change from baseline high-affinity IgE receptor (FcεRI) expression on basophils and plasmacytoid dendritic cells
Li et al. [99] (omalizumab) NCT01202903	Moderate-to-severe allergic asthma	Moderate-to-severe asthma as per GINA 2014; ⩾2 exacerbations in the past year or ⩾3 in past 2 years	Medium- to high-dose ICS (per GINA 2014)+LABA	⩾12%	n/a	n/a	A positive reaction to ⩾1 perennial aeroallergen, IgE 30–700 IU·mL^{-1}	Active lung disease other than allergic asthma	Mean change from baseline in morning PEF
DREAM [100] (mepolizumab) NCT01000506	Severe eosinophilic asthma	Refractory asthma per ERS/ATS definition; one of ⩾2 exacerbations in the past year, prompt deterioration of asthma control after ⩽25% reduction in maintenance ICS or OCS, eosinophilia, or elevated F_{eNO}	High-dose ICS (FP ⩾880 µg per day or equivalent)±OCS +additional controllers	>12% and 200 mL	Any indicator of eosinophilic inflammation, including sputum eosinophil count of ⩾3% or asthma-related blood eosinophil count of ⩾300 cells per µL	Any indicator of eosinophilic inflammation, including F_{eNO}⩾50 ppb	Positive radioallergosorbent test	Smokers or former smokers with ⩾10 pack-years; substantial uncontrolled comorbidity	Rate of clinically significant asthma exacerbations
MENSA [101] (mepolizumab) NCT01691521	Severe eosinophilic asthma	⩾2 exacerbations requiring OCS or ⩾2-fold increase in usual OCS dose in the past year	High-dose ICS (FP ⩾880 µg per day or equivalent)+an additional controller	⩾12%¶	Blood eosinophil count of ⩾300 cells per µL during the previous year or of ⩾150 cells per µL during the optimisation phase	n/a	n/a	Smokers or former smokers with ⩾10 pack-years; clinically important lung condition other than asthma (including COPD)	Rate of clinically significant asthma exacerbations

Continued

TABLE 2 Continued

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	F_{eNO} requirement	Allergy/atopy requirement	Notable exclusions	Primary endpoint
SIRIUS [62] (mepolizumab) NCT01691508	Severe eosinophilic asthma	n/a	High-dose ICS (FP ≥880 µg per day or equivalent)+an additional controller (for ≥3 months in previous 12 months)+OCS (equivalent to prednisone 5–35 mg per day, for past 6 months)	≥12% and 200 mL[+]	Blood eosinophil count of ≥300 cells per µL within 1 year of screening or of ≥150 cells per µL at screening	n/a	n/a	Smokers or former smokers with ≥10 pack-years; clinically important lung condition other than asthma (including COPD)	% reduction in daily OCS dose from optimised dose to weeks 20–24[§]
MUSCA [102] (mepolizumab) NCT02281318	Severe eosinophilic asthma	Severe uncontrolled asthma per ERS/ATS definition; ≥2 exacerbations requiring OCS or ≥2× increase in usual OCS dose in the past year	High-dose ICS+ ≥1 additional controller	n/a	Blood eosinophil count of ≥300 cells per µL within 1 year of screening or of ≥150 cells per µL at screening	n/a	n/a	Smokers or former smokers with ≥10 pack-years; concurrent respiratory disease	Mean change from baseline in SGRQ total score
Castro et al. Study 1, Study 2 [103] (reslizumab) NCT01287039, NCT01285323	Inadequately controlled, moderate-to-severe eosinophilic asthma	ACQ-7 score ≥1.5; ≥1 exacerbation requiring OCS in the past year	Medium- to high-dose ICS (FP ≥440 µg per day or equivalent)±an additional controller (including OCS)	≥12%	Blood eosinophil count of ≥400 cells per µL	n/a	n/a	Current smokers; another confounding underlying lung disorder (including COPD)	Rate of clinically significant asthma exacerbations
Bjermer et al. [104] (reslizumab) NCT01270464	Inadequately controlled asthma with elevated blood eosinophils	ACQ-7 score ≥1.5	Medium- to high-dose ICS (FP ≥440 µg per day or equivalent)±an additional controller	≥12%	Blood eosinophil count of ≥400 cells per µL	n/a	n/a	Maintenance OCS use; current smokers; other confounding lung disorders or pulmonary conditions	Change from baseline in pre-bronchodilator FEV$_1$
Corren et al. [105] (reslizumab) NCT01508936	Poorly controlled asthma	ACQ-7 score ≥1.5	Medium- to high-dose ICS (FP ≥440 µg·day or equivalent)±an additional controller	≥12%	n/a	n/a	n/a	Maintenance OCS use; current smokers; underlying lung disorders or pulmonary conditions	Change from baseline in FEV$_1$
CALIMA [106] (benralizumab) NCT01914757	Severe, uncontrolled eosinophilic asthma	ACQ-6 score ≥1.5; ≥2 exacerbations requiring OCS or increase in usual OCS dose in the past year	High-dose ICS (FP ≥500 µg per day or equivalent)+LABA ±OCS and additional controllers	≥12% and 200 mL	Blood eosinophil count of <300 cells per µL or of ≥300 cells per µL (≥300 cells per µL in primary analysis population)	n/a	n/a	Clinically important pulmonary or eosinophilic disease other than asthma (including COPD)	AER ratio versus placebo for patients receiving fluticasone ≥500 µg or equivalent plus LABA with baseline blood eosinophils ≥300 cells per µL

Continued

TABLE 2 Continued

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	F_{eNO} requirement	Allergy/atopy requirement	Notable exclusions	Primary endpoint
SIROCCO [107] (benralizumab) NCT01928771	Severe, uncontrolled eosinophilic asthma	ACQ-6 score ⩾1; ⩾2 exacerbations requiring OCS or increase in usual OCS dose in the past year	High-dose ICS (FP ⩾500 µg per day or equivalent)+LABA ±OCS and additional controller	⩾12% and 200 mL	Blood eosinophil count of <300 cells per µL or of ⩾300 cells per µL (⩾300 cells per µL in primary analysis population)	n/a	n/a	Clinically important pulmonary or eosinophilic disease other than asthma (including COPD)	AER ratio *versus* placebo for patients with baseline blood eosinophils ⩾300 cells per µL
ZONDA [63] (benralizumab) NCT02075255	Severe eosinophilic asthma requiring OCS	⩾1 exacerbations in the past year	High-dose ICS (fluticasone >500 µg per day or equivalent)+LABA +OCS (equivalent to prednisone 7.5–40 mg per day, for past 6 months)	⩾12% and 200 mL¶ or documented reversibility during past 2 years	Blood eosinophil count of ⩾150 cells per µL	n/a	n/a	Clinically important pulmonary or eosinophilic disease other than asthma (including COPD)	% reduction in daily OCS dose from baseline to end of maintenance phase while maintaining asthma control[f]
LAVOLTA I, LAVOLTA II [108] (lebrikizumab) NCT01867125, NCT01868061	Uncontrolled asthma	ACQ-5 score ⩾1.5; at least one of symptoms ⩾2 days/ week, night-time awakenings ⩾1 night per week, SABA ⩾2 days per week or interference with daily activities	High-dose ICS (FP 500–2000 µg per day or equivalent) +⩾1 additional controller	⩾12%	Blood eosinophil count of <300 cells per µL or of ⩾300 cells per µL (⩾300 cells per µL and/or periostin ⩾50 ng·mL⁻¹ in primary analysis population)	n/a	n/a	Maintenance OCS use within past 3 months; smokers or former smokers with ⩾10 pack-years; clinically significant lung disease other than asthma	AER in "biomarker-high" patients (periostin ⩾50 ng·mL and/or blood eosinophils ⩾300 cells per µL)
LIBERTY ASTHMA QUEST [109] (dupilumab) NCT02414854	Moderate-to-severe, uncontrolled asthma	ACQ-5 score ⩾1.5; ⩾1 exacerbation in past year requiring hospitalisation, emergency medical care or OCS for ⩾3 days	High-dose ICS (FP ⩾500 µg per day or equivalent)+up to 2 additional controllers	⩾12% and 200 mL	n/a	n/a	n/a	Current smokers, or former smokers with >10 pack-years; COPD or other lung disease that may impair lung function	(Co-primary) Severe AER and change from baseline in pre-bronchodilator FEV$_1$
LIBERTY ASTHMA VENTURE [64] (dupilumab) NCT02528214	Glucocorticoid-dependent severe asthma	n/a	High-dose ICS (FP >500 µg per day or equivalent)+up to 2 additional controllers +maintenance OCS (equivalent to prednisone 5–35 mg per day)	⩾12% and 200 mL, or airway hyper-responsiveness	n/a	n/a	n/a	Current smokers, or former smokers with >10 pack-years; COPD or other lung disease that may impair lung function; clinically significant lung disease other than asthma	% reduction in OCS dose while maintaining asthma control[##]
STRATOS 1, STRATOS 2 [110] (tralokinumab) NCT02161757, NCT02194699	Severe, uncontrolled asthma	ACQ-6 score ⩾1.5; ⩾2 exacerbations requiring OCS in the past year [116]	High-dose ICS (FP ⩾500 µg per day or equivalent)+LABA ±additional controllers excluding OCS	⩾12% and ⩾200 mL	n/a	⩾37 ppb in STRATOS 2 primary analysis population	n/a	Regular OCS use within past 3 months; current smokers, or former smokers with ⩾10 pack-years; clinically important pulmonary disease other than asthma [116]	AER in all-comers (STRATOS 1) or patients with F_{eNO} ⩾37 ppb (STRATOS 2)

Continued

TABLE 2 Continued

Trial (treatment)	Authors' description of target population	Severity/control	Current treatment	Bronchodilator reversibility requirement (see footnotes)	Eosinophilic status	F_{eNO} requirement	Allergy/atopy requirement	Notable exclusions	Primary endpoint
TROPOS [111] (tralokinumab) NCT02281357	Severe, uncontrolled asthma	Severe, uncontrolled asthma requiring maintenance OCS treatment plus ICS/LABAs	Medium- to high-dose ICS (FP ⩾500 µg per day or equivalent)+LABA +maintenance OCS (equivalent to prednisone 7.5–30 mg per day)	⩾12% or documented reversibility in the past 6 months	n/a	n/a	n/a	Current smokers, or former smokers with ⩾10 pack-years; clinically important pulmonary disease other than asthma (including COPD)	% reduction in OCS dose while maintaining asthma control¶¶
Target population: patients with COPD									
METREX, METREO [33] (mepolizumab) NCT02105948, NCT02105961	Eosinophilic COPD	FEV₁/FVC<0.7 and post-bronchodilator FEV₁ >20% and ⩽80% predicted; ⩾2 moderate or ⩾1 severe exacerbations in past year	High-dose ICS (FP ⩾500 µg per day or equivalent)+LABA +LAMA	n/a	METREX: no blood eosinophil threshold METREO: blood eosinophil count of ⩾300 cells per µL in previous 12 months or of ⩾150 cells per µL at screening	n/a	n/a	Current diagnosis of asthma; any history of asthma in never smokers; age <40 years	Moderate/severe AER In METREX, all patients and eosinophilic (⩾300 cells per µL in previous 12 months or ⩾150 cells per µL at screening) patients were analysed as separate groups
GALATHEA, TERRANOVA [34] (benralizumab) NCT02155660, NCT02138916	Moderate-to-very severe COPD with exacerbation history	Post-bronchodilator FEV₁ >20% and ⩽65% predicted; ⩾2 exacerbations requiring OCS or antibiotics or ⩾1 requiring hospitalisation in the past year; mMRC score ⩾1	LABA+LAMA and/or ICS	n/a	No blood eosinophil threshold, but enrolment stratified/capped by blood eosinophil count (⩾220 cells per µL in primary analysis population)	n/a	n/a	Non-smokers or smoking history <10 pack-years; clinically important pulmonary disease other than COPD; asthma as a primary or main diagnosis; age <40 years	AER in patients with baseline blood eosinophils ⩾220 cells per µL

Where publications state "systemic corticosteroid", it is assumed for the purposes of this review that they refer mostly or entirely to patients receiving OCS. RCT: randomised controlled trial; F_{eNO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroid; BDP: beclomethasone dipropionate; n/a: not applicable (not mentioned in inclusion/exclusion criteria); OCS: oral corticosteroid; PAR: persistent allergic rhinitis; AQLQ: Asthma Quality of Life Questionnaire; RQLQ: Rhinitis Quality of Life Questionnaire; ER: emergency room; GINA: Global Initiative for Asthma; PEF: peak expiratory flow; LABA: long-acting β₂-agonist; FP: fluticasone propionate; SABA: short-acting β₂-agonist; ERS: European Respiratory Society; ATS: American Thoracic Society; SGRQ: St George's Respiratory Questionnaire; COPD: chronic obstructive pulmonary disease; ACQ-n: n-item Asthma Control Questionnaire; AER: annual exacerbation rate; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; LAMA: long-acting muscarinic antagonist; mMRC: modified Medical Research Council dyspnoea scale. #: published information does not state whether the dose range given for current treatment inclusion criterion was metered or delivered dose [91]; ¶: one of ⩾12% reversibility, positive results on methacholine or mannitol challenge, or FEV₁ variability (⩾20%) between two visits [63, 101]; +: one of ⩾12% and 200 mL reversibility, positive results on methacholine or mannitol challenge, FEV₁ variability (⩾20%) between two visits, or >20% diurnal variability in peak flow [67]; §: dose reduction was mandatory unless patients had an exacerbation, met any criteria for loss of asthma control (PEF, night-time awakenings, rescue medication use and ACQ-5 score) or had symptoms of adrenal insufficiency [62]; ƒ: dose reduction was mandatory unless patients had worsening of asthma symptoms (new or increased asthma symptoms or clinical signs that were troubling to the patient or were related to an electronic Asthma Daily Diary alert upon reduction) or did not meet reduction criteria (pre-bronchodilator FEV₁, PEF, night-time awakenings and rescue medication use); ##: defined as the lowest dose that a patient could receive without having an increase in ACQ-5 score of ⩾0.5, a severe exacerbation or any clinically significant event leading to an upward adjustment in the oral glucocorticoid dose [64]; ¶¶: defined as the lowest dose that a patient could receive while meeting all reduction criteria (pre-bronchodilator FEV₁, PEF, night-time awakenings, rescue medication use, no exacerbations requiring OCS and investigator judgement of asthma control) [111].

Comorbidities

Most of the asthma trials excluded patients with lung disease other than asthma, including COPD; this was most consistent among the more recent trials [62–64, 99, 101–111]. Additionally, most studies excluded patients with features more characteristic of COPD [14], such as a history of smoking [62, 94, 98, 100–102, 110, 111] or lack of bronchodilator reversibility [62–64, 91–94, 96, 99–101, 103–111]. Conversely, all of the COPD trials excluded patients with a current or primary diagnosis of asthma, and most excluded non-smokers or patients with <10 pack-years [34, 112–114].

Primary endpoints

Primary endpoints varied between trials. The majority of trials specified exacerbation reduction as a primary endpoint. Six trials evaluated lung function (one as a co-primary endpoint with exacerbation reduction) [95, 99, 104, 105, 109, 115], two evaluated quality of life (one as a co-primary endpoint with exacerbation reduction) [93, 102], four evaluated OCS sparing [62–64, 111] and one evaluated target-specific biomarker expression [98].

Biomarkers for predicting response to biologic therapy

In addition to their primary analyses, several of the phase III trials included pre-specified or *post hoc* sub-analyses that identified biomarkers that predicted treatment response [33, 64, 82, 100, 102, 105–111, 117, 118] (summarised in table 3). In a *post hoc* analysis of INNOVATE for omalizumab, higher baseline IgE predicted a greater reduction in clinically significant exacerbations than in patients with lower baseline IgE [117], but this was not confirmed in a separate analysis [119]. A pre-specified *post hoc* analysis of T2 biomarkers in EXTRA found that higher F_{eNO}, blood eosinophil count and periostin all predicted a greater exacerbation rate reduction with omalizumab than their respective low-biomarker subgroups [82], although potential suppression of eosinophils by corticosteroids [76] suggests that eosinophil count should be assessed in light of OCS and ICS exposure. In patients with asthma taking high-dose ICS, blood eosinophil count predicted response to mepolizumab for several endpoints based on exploratory modelling in DREAM [100] and MUSCA [102] and a pooled *post hoc* analysis of DREAM and MENSA [118], and blood eosinophil count similarly predicted response to mepolizumab in patients with COPD in a meta-analysis of METREX and METREO [33]. Likewise, blood eosinophil count predicted responses to reslizumab [105] and benralizumab [106, 107] in patients with asthma, except for exacerbation rate in CALIMA, potentially due to a large "placebo" response that may have resulted from background ICS being supplied to patients [106]. However, pre-specified subgroup analyses of the GALATHEA and TERRANOVA trials showed no association between blood eosinophil count and response to benralizumab in patients with COPD [34]. In the LAVOLTA trials for lebrikizumab, both eosinophil-high patients and a biomarker-high group with eosinophilia and high periostin showed greater exacerbation reduction than the respective "low" groups, while stratifying by eosinophilia alone showed the greatest difference in exacerbation rate [108]. In LIBERTY ASTHMA VENTURE [64] and LIBERTY ASTHMA QUEST [109], dupilumab efficacy for exacerbation reduction, FEV_1 improvement or OCS sparing was greatest in patients with higher baseline blood eosinophil counts and/or F_{eNO}. Similarly, higher F_{eNO} predicted significant exacerbation reduction with tralokinumab in STRATOS 1, although this was not replicated in STRATOS 2 [110] and there was no difference in OCS sparing based on F_{eNO} levels in TROPOS [111]. Though not a complete review of biomarker studies in the biologic era, the findings described above suggest that several biomarkers specific to T2 inflammation mechanisms can predict response to biologic therapies that target components of the T2 pathway. Although the most appropriate cut-off points are yet to be determined, this supports the concept that establishing molecularly defined endotypes will enable better characterisation of patients with severe obstructive lung disease to inform treatment decisions.

Limitations of the current approach to trial design

Our review of phase III RCTs of biologic therapies demonstrates that these trials have narrow and sometimes conflicting eligibility criteria that exclude certain phenotypes of interest (summarised in box 1). For example, most required bronchodilator reversibility at screening, despite this being more difficult to demonstrate once patients are taking maintenance treatment [14]. Such a requirement is illogical, because it requires patients with long-standing, chronic disease to continue to satisfy criteria by which the disease is diagnosed at the time of initial presentation. Many severe asthma trials excluded patients with another pulmonary disease (such as COPD), even though patients with asthma–COPD overlap comprise 15%–30% of patients with chronic airways disease [5, 120]. Asthma trials also excluded current smokers and patients with ⩾10 pack-years' smoking history, who represent approximately 26%–32% of the severe asthma population [35, 121], whereas most COPD trials (including all of the phase II trials identified) excluded patients with <10 pack-years [34, 112–114]. Some patients with COPD display T2-high and/or eosinophilic phenotypes [122, 123], and those with eosinophilic COPD have been shown to respond to mepolizumab for moderate-to-severe exacerbations [33], albeit to a lesser extent than patients with

TABLE 3 Biomarkers that predicted treatment response in phase III RCTs of biologic therapies in severe obstructive lung disease

Cut-off (greater response *versus* lesser/no response)	Outcome(s)	Trial (treatment)
Phase III RCTs in patients with severe asthma		
IgE		
$\geqslant$274 IU·mL^{-1}, 148–273 IU·mL^{-1} and 76–147 IU·mL^{-1} *versus* 0–75 IU·mL^{-1}	Exacerbation rate Emergency visits FEV$_1$ AQLQ score	INNOVATE [117] (omalizumab)
Blood eosinophil count		
$\geqslant$260 cells per µL *versus* <260 cells per µL	Exacerbation rate	EXTRA [82] (omalizumab)
Continuous modelling (higher blood eosinophil count = greater response)	Exacerbation rate	DREAM [100] (mepolizumab)
Continuous modelling (higher blood eosinophil count = greater response); identified a cut-off of $\geqslant$150 cells per µL *versus* <150 cells per µL	Exacerbation rate Trends also noted for: FEV$_1$ SGRQ score ACQ-5 score	DREAM/MENSA [118] (mepolizumab)
Continuous modelling (higher blood eosinophil count = greater response)	Exacerbation rate FEV$_1$ ACQ-5 score	MUSCA [102] (mepolizumab)
$\geqslant$400 cells per µL *versus* <400 cells per µL	FEV$_1$	Corren *et al.* [105] (reslizumab)
$\geqslant$300 cells per µL *versus* <300 cells per µL	Exacerbation rate	LAVOLTA I and LAVOLTA II [108] (lebrikizumab)
$\geqslant$300 cells per µL *versus* <300 cells per µL	FEV$_1$	CALIMA [106] (benralizumab)
$\geqslant$300 cells per µL *versus* <300 cells per µL	Exacerbation rate FEV$_1$	SIROCCO [107] (benralizumab)
$\geqslant$300 cells per µL and $\geqslant$150–<300 cells per µL *versus* <150 cells per µL	FEV$_1$	LIBERTY ASTHMA QUEST [109] (dupilumab)
$\geqslant$300 cells per µL *versus* <300 cells per µL	OCS dose Exacerbation rate FEV$_1$	LIBERTY ASTHMA VENTURE [64] (dupilumab)
F_{eNO}		
$\geqslant$19.5 ppb *versus* <19.5 ppb	Exacerbation rate	EXTRA [82] (omalizumab)
$\geqslant$50 ppb and $\geqslant$25–<50 ppb *versus* <25 ppb	FEV$_1$	LIBERTY ASTHMA QUEST [109] (dupilumab)
$\geqslant$50 ppb and $\geqslant$25–50 ppb *versus* <25 ppb	OCS dose Exacerbation rate FEV$_1$	LIBERTY ASTHMA VENTURE [64] (dupilumab)
$\geqslant$37 ppb *versus* <37 ppb or all patients	Exacerbation rate FEV$_1$ AQLQ score ACQ-6 score Total asthma symptom score	STRATOS 1 [110] (tralokinumab)
Periostin		
$\geqslant$50 ng·mL^{-1} *versus* <50 ng·mL^{-1}	Exacerbation rate	EXTRA [82] (omalizumab)
Combined blood eosinophil count+periostin		
$\geqslant$300 cells per µL or $\geqslant$50 ng·mL^{-1} *versus* <300 cells per µL or <50 ng·mL^{-1}	Exacerbation rate	LAVOLTA I and LAVOLTA II [108] (lebrikizumab)
Phase III RCTs in patients with severe COPD		
Blood eosinophil count		
$\geqslant$500 cells per µL, $\geqslant$300–<500 cells per µL and $\geqslant$150–<300 cells per µL *versus* >150 cells per µL	Exacerbation rate	METREX/ METREO [33] (mepolizumab)

RCT: randomised controlled trial; FEV$_1$: forced expiratory volume in 1 s; AQLQ: Asthma Quality of Life Questionnaire; F_{eNO}: exhaled nitric oxide fraction; COPD: chronic obstructive pulmonary disease; SGRQ: St George's Respiratory Questionnaire; ACQ-n: n-item Asthma Control Questionnaire; OCS: oral corticosteroid.

BOX 1 Eligibility criteria that may exclude populations of interest from phase III randomised controlled trials of biologic therapies in severe obstructive lung disease

Bronchodilator reversibility
- May exclude patients in whom reversible airflow limitation is no longer apparent due to treatment
- Inappropriately requires patients with chronic disease to continue to satisfy criteria for initial diagnosis
- May exclude patients with asthma–chronic obstructive pulmonary disease (COPD) overlap, including patients with asthma and non-reversible airflow limitation or COPD and reversible airflow limitation

Comorbidities (respiratory and/or non-respiratory)
- Excludes patients with asthma–COPD overlap
- Excludes patients with persistent airway infection or other lung diseases
- Precludes research to identify endotypes in patients with multi-morbidity

Smoking history
- Excludes smokers with asthma and patients with COPD who have limited/no smoking history
- May exclude patients with asthma–COPD overlap
- Excludes patients with COPD with a phenotype/endotype that is relevant to a specific mechanism of action (*e.g.* eosinophilic phenotype)

Disease severity/control
- Precludes investigation of the potential benefits of earlier intervention or treatment of milder disease
- Excludes patients whose obstructive lung disease appears less severe, but who depend on high-dose inhaled corticosteroids or maintenance oral corticosteroids for adequate control

eosinophilic asthma [118]. This suggests that significant subsets of patients with severe obstructive lung disease, who could potentially benefit from biologic therapies, are excluded from trials that inform regulatory decisions and thus influence treatment options in clinical practice. A recent analysis of patients with severe asthma found that only 3.5%–17.5% would have been eligible for enrolment in 14 phase III trials of biologic therapies in severe asthma [35]. Furthermore, comorbidity is an important contributor to disease burden in both asthma [124] and COPD [125, 126], and excluding patients with comorbidities from RCTs limits the evidence available to support treatment approaches that target multi-morbidity *via* underlying mechanisms. Additionally, although patients with severe, uncontrolled disease are the focus of most RCTs to date, evidence of benralizumab efficacy for pre-bronchodilator FEV_1 in a short-term study in patients with milder but persistent asthma [127] suggests that earlier intervention with biologic therapy may prevent the early structural damage that contributes to the development of severe disease in some patients [127, 128].

Recommendations for future research and regulatory indications of biologic therapies

The importance of accurately defining severe obstructive lung disease

Given that long-term treatment with OCS or high-dose ICS can have potentially costly long-term adverse effects [52, 53, 55–57, 59], treatment with alternative controllers and/or targeted biologics (despite high acquisition costs) may be the preferred approach in patients with asthma who fail to achieve control with lower doses [21]. This is reflected in more recent clinical definitions of severe asthma, which include patients dependent on medium- to high-dose ICS/LABA with or without OCS to maintain control (*i.e.* asthma is uncontrolled on a medium dose) (table 1). However, most RCTs of biologic therapies in severe obstructive lung disease enrol patients whose asthma is uncontrolled on medium- to high-dose ICS, with or without additional controllers (table 2). This, together with the high acquisition costs [21], has led some regulators and payers to restrict the approved indications of such medications to patients whose asthma is inadequately controlled despite high-dose ICS plus LABA or additional controllers [22, 25, 27], thereby missing the opportunity to reduce long-term high-dose ICS and maintenance OCS use in patients who have achieved control with such treatment.

An endotype-based approach to future RCTs

The use of highly specific eligibility criteria in existing RCTs of biologic therapies in severe obstructive lung disease may exclude patients with clinically relevant phenotypes (box 1), thereby limiting the generalisability of such trials to patients in clinical practice. In countries with fewer restrictions for prescribing biologic therapies for obstructive lung disease, real-world studies may reveal the extent to which RCT findings can be generalised to patients who do not fulfil typical inclusion criteria. To aid exploratory analyses and identify additional potentially responsive populations, we believe that trial populations (particularly for earlier phase studies) should include groups that are currently excluded, such

as patients with persistent or latent airway infection or other lung diseases (*e.g.* bronchiectasis), patients with asthma and non-reversible airflow limitation, patients with cardiovascular and other comorbidities, and patients who have normal interval lung function but nonetheless experience symptoms and exacerbations. Also, trials should include assessments that may help to elucidate responsive phenotypes or endotypes, such as bronchoscopic evaluation. There is increasing interest in breathomics, which in a recent validation study identified clusters of patients with asthma/COPD that differed by ethnicity, systemic eosinophilia and neutrophilia, F_{eNO}, body mass index, atopy and exacerbation rate, regardless of the diagnostic label [129]. In addition to identifying molecular biomarkers for targeted biologic therapies, such an approach could also be applied to RCTs of emerging non-pharmacological treatments, such as bronchoscopic lung reduction in patients with emphysema-predominant COPD [45] and bronchial thermoplasty in patients with severe asthma [14]. For example, although the mechanism of clinical benefit from bronchial thermoplasty is currently not well defined, it has been suggested that structural features measured by high resolution imaging, *e.g.* airway smooth muscle mass, could be used to characterise severe asthma phenotypes and predict response [130]. Future studies to identify biological predictors of response to such treatments could enable a wider array of treatment options to be included in the personalised healthcare repertoire for severe obstructive lung disease. Ultimately, for the maximum number of patients to gain access to the most appropriate treatment, a paradigm shift is likely to be required in patient selection for trials, moving away from conventional diagnostic labels and control criteria (clinical approach) towards recruitment and stratification of clinically broader populations predicted to respond based on an underlying, biologically defined disease mechanism (endotype-based approach).

This endotype-based approach is not yet recognised by regulators, and the consequent risk to pharmaceutical developers of failing to satisfy current approval requirements may deter them from conducting studies in this way. However, if there is sound scientific rationale underpinning the decision to target a specific population, based on endotype and drug mechanism of action rather than conventional labels (supported by robust early-phase clinical development), it seems reasonable to predict that the probability of achieving successful treatment outcomes in phase III RCTs would be high. An additional benefit of this exploratory approach is the potential to identify reliable, lower-cost surrogates for exacerbations as the primary outcome. In our opinion, pharmaceutical developers should be able to adopt this endotype-based approach when defining eligibility criteria for future RCTs, to support regulatory approval and to provide evidence for clinical practice guidelines. This requires recognition of the value of such an approach by regulators so that more exploratory studies can meet approval requirements. Therefore, co-ordinated partnerships between investigators, pharmaceutical developers and regulators are necessary to make meaningful change and provide more patients with targeted treatment options.

In addition to this shift towards endotype-based enrolment, standardisation of eligibility criteria and outcome measures will be important in evaluating the therapeutic benefit of new biologics in the appropriate populations. To ensure the clinical benefit of such biologics, the targeted molecular endotype should manifest as a clinically important outcome, such as exacerbations. Developing a core outcome set could help to improve comparability between trials and ensure clinical relevance of trial data [131].

Identifying novel endotypes in severe obstructive lung disease

Existing treatments for severe obstructive lung disease, especially corticosteroids, inhibit inflammation *via* multiple targets and may have unwanted additional anti-inflammatory effects. There is now extensive evidence that molecularly targeted biologic therapies improve outcomes in patients with T2-high, inflammatory asthma that is inadequately controlled by medium- to high-dose ICS [62, 63, 91–104, 106, 107, 132]. However, not all targets evaluated in phase III trials have proven effective. For example, results for therapies targeting IL-13 have been mixed. Lebrikizumab significantly reduced exacerbation rate among "biomarker-high" patients with uncontrolled asthma in LAVOLTA I, but efficacy did not reach significance in LAVOLTA II [108].

In contrast, tralokinumab failed to significantly reduce exacerbation rate either in all-comers with severe asthma in STRATOS 1 [110] and TROPOS [111] or among F_{eNO}-high patients in STRATOS 2 [110]; by contrast, in a recent phase II trial it significantly reduced F_{eNO} and IgE levels, but not eosinophil counts, suggesting a non-eosinophil-mediated mechanism of action [133]. The anti-IL-5 receptor therapy benralizumab has shown efficacy in severe eosinophilic asthma [63, 106, 107], but did not significantly reduce exacerbations in patients with eosinophilic COPD [34]. The failure of these phase III trials suggests that further research is needed to link phenotypes with molecularly defined, targetable endotypes, particularly in severe COPD and asthma–COPD overlap, where few data are available.

Despite mixed results for some therapies, trial success in patients with severe, T2-high asthma demonstrates that targeting specific endotypes could improve outcomes in other, less well-studied

populations, such as patients with T2-low disease. Currently, all approved biologic therapies for severe obstructive lung disease target severe or moderate-to-severe asthma with T2 inflammation (either IgE-mediated, eosinophilic or OCS-dependent asthma) [22–30]. However, these patients may have one or more of various T2-high phenotypes, which may or may not include blood and/or airway eosinophilia [134, 135]. Furthermore, up to 50% of patients with severe asthma lack T2 inflammation [121, 136, 137], *i.e.* they have a T2-low phenotype (or their T2 inflammation is controlled by anti-inflammatory medication(s) [138]). Additionally, patients with lung disease other than asthma (*e.g.* COPD or asthma–COPD overlap) can also have uncontrolled disease despite high-level treatment [139–141]. This heterogeneity results in an unmet need for targeted therapies that address the underlying causes of disease for patients with T2-low severe asthma or other phenotypes of severe obstructive lung disease not currently catered for by available biologics. Although our literature review focused on phase III trials, several non-T2-targeted biologic therapies have been investigated in earlier phases of clinical development. For example, a phase II trial of the anti-IL-17 receptor therapy brodalumab, which used similar eligibility criteria to most of the asthma studies listed in table 2 but did not differentiate patients based on inflammatory phenotype, failed to meet its primary endpoint of clinically meaningful improvement in Asthma Control Questionnaire total score (although a pre-specified subgroup analysis found a significant improvement among patients with high reversibility) [142]. Earlier trials of the anti-tumour necrosis factor-α therapies golimumab and etanercept were similarly unsuccessful [143, 144], but imatinib, an inhibitor of the stem cell factor receptor KIT, has shown promise in an early, placebo-controlled, proof-of-principle trial [145]. One therapy currently in development for the treatment of uncontrolled asthma, tezepelumab, may also be effective in T2-low disease. Tezepelumab is a thymic stromal lymphopoietin-targeted therapy that demonstrated efficacy regardless of blood eosinophil count (<250 cells per μL *versus* ⩾250 cells per μL) in a phase IIb severe asthma trial [146], leading to it being granted Breakthrough Therapy Designation by the US Food and Drug Administration [32]. Defining severe obstructive lung disease and designing future trials in a way that maximises the potential therapeutic impact of existing and future biologic therapies will be key to finding more therapies that fulfil this need. Furthermore, identifying novel endotypes of obstructive lung disease, including those not involving T2 inflammation, should be a key goal of future research.

The current high cost of biologic therapies (*versus* the relatively low cost of OCS/ICS) makes accurate prediction and monitoring of response necessary. Previous research shows that endotype-specific biomarkers of T2 inflammation can predict a patient's response to biologic therapies that target these particular mechanisms. Future biomarkers identified and utilised for this purpose should, therefore, be appropriate to the endotype being treated, as recommended by previous cost-effectiveness studies [65]; however, substantial price discounts may be needed to achieve acceptable cost-effectiveness, even within biomarker-targeted populations [65].

To better understand the mechanisms underlying obstructive lung disease and to identify specific endotypes that may be carried forward into interventional studies, large-scale studies in broad, real-world populations with standardised outcome measures are needed. Studies such as U-BIOPRED [47] in asthma and ECLIPSE [147], SPIROMICS [148] and COPDGene [149] in COPD have yielded important insights in their respective populations [150–154], with the caveat that these cohorts each focus primarily on a single diagnostic label (U-BIOPRED did not exclude patients with COPD, but required an asthma diagnosis and excluded patients with a primary diagnosis of severe emphysema or bronchiectasis [47]). NOVELTY (a NOVEL observational longiTudinal studY in patients with a diagnosis or suspected diagnosis of asthma and/or COPD) is an ongoing study that includes approximately 12 000 patients across the spectrum of obstructive lung disease, with broad inclusion criteria and very few exclusion criteria to capture a broad patient population [155]. In NOVELTY, patients are required to have a diagnosis or clinically suspected diagnosis of asthma and/or COPD (according to the treating physician), be aged ⩾12 years and be able to provide informed consent. The only exclusion criteria are participation in an interventional respiratory clinical trial in the previous 12 months, low likelihood of completing 3 years of follow-up and a primary respiratory diagnosis other than asthma or COPD (though co-diagnoses of other respiratory diseases are allowed) [155]. NOVELTY is prospectively collecting data on a wide range of diagnosis-agnostic variables, with the aim of identifying phenotypes and endotypes through detailed clinical and biomarker characterisation [155]. Such large observational studies will complement the RCT evidence base and may help to identify novel endotypes that can inform the development and use of future targeted therapies.

Conclusions

Current treatment recommendations for severe obstructive lung disease, based on high-dose ICS with one or more add-on therapies, are inadequate in some patients and can have long-term adverse effects. OCS, previously the mainstay of severe asthma treatment and still used in frequent pulses for the treatment of

severe exacerbations, has for some time been recognised as having serious, often permanent, adverse effects. Alternative, biologic therapies are currently only available for patients with T2-high phenotypes. Additionally, the narrow eligibility criteria used in existing RCTs of these therapies mean that their generalisability is limited to patients with specific clinical phenotypes, leading to limited therapeutic reach owing to regulatory restrictions. An unmet need, therefore, remains in two areas:

1) Studies of existing biologics in patients typically excluded from RCTs, including those whose asthma is well controlled on high-dose ICS and those with overlapping diagnostic labels (*e.g.* asthma and COPD), to provide evidence to support regulatory approval and reimbursement in such populations.
2) Targeted biologic therapies (and biomarkers to predict response) for patients with severe obstructive lung disease that is not, or is only partially, driven by T2 inflammation.

We therefore recommend a phenotype- and endotype-focused approach to future research on severe obstructive lung disease, in both clinical trials and exploratory studies, to identify novel biomarkers and potential targets. The success of this approach will depend on co-ordinated efforts between investigators, pharmaceutical developers and regulators to ensure biologic therapies reach their full potential in the treatment of patients with severe obstructive lung disease, irrespective of conventional diagnostic labels.

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