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The Efficacy and Safety of Biologic Drugs to Treat Severe Asthma

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This Rapid Review was conducted by the Alberta Drug and Technology Evaluation Consortium through the Post-Market Drug Evaluation CoLab Network.

Rapid Review

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Abbreviations

AEX	asthma exacerbation
BEC	blood eosinophil count
FEV_1	forced expiratory volume in 1 second
HRQoL	health-related quality of life
HTA	health technology assessment
RCT	randomized controlled trial

Key Messages

Several biologic drugs have been developed to treat severe asthma, but it is unclear how well they work across different types of asthma.

Comparing the efficacy of biologic drugs for asthma is challenging because of differing definitions of asthma severity and inconsistent application of severity criteria in randomized controlled trials.

The randomized controlled trials and systematic reviews included in this Rapid Review mainly focused on specific severe asthma subtypes (frequently, eosinophilic type 2 asthma). Recruitment and outcome reporting among different asthma subgroups was limited and varied, making it difficult to assess the efficacy of biologic drugs across the specific subgroups of severe asthma.

Determining the efficacy and safety of biologics in the pediatric population is hindered by both the lack of inclusion of children with severe asthma in clinical trials and the lack of outcome reporting specific to this population.

Further synthesis of the existing data is unlikely to provide new insights to further inform the outlined policy questions on biologics in severe asthma.

Introduction and Rationale

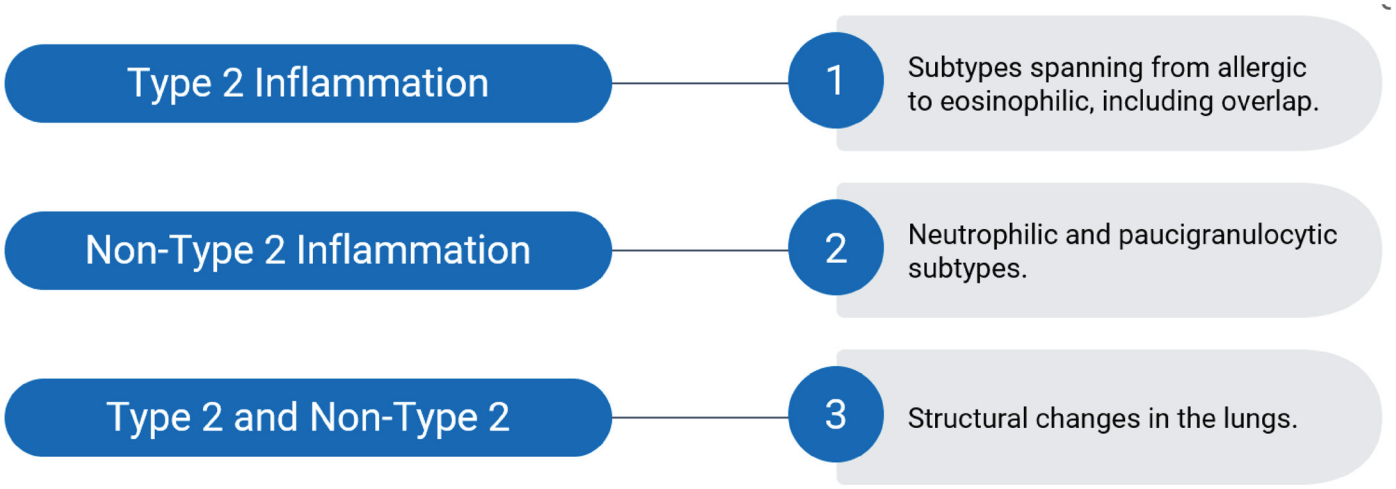
Background

Asthma is a spectrum of chronic conditions that exhibit airway inflammation and hyperreactivity.[1] Severe asthma affects approximately 5% to 10% of individuals living with asthma. It is characterized by poorly controlled symptoms despite optimal use of front-line treatments such as high-dose inhaled corticosteroids with an adjuvant controller medication and/or systemic corticosteroids.[2,3] It is estimated that as many as 250,000 people living in Canada have severe asthma. These individuals account for the majority of the morbidity and mortality related to asthma and incur most of the health care costs associated with treatment and management.[4-6] The incremental cost of severe asthma relative to no asthma in Canada is approximately $2,779 per person per year.[7]

Severe asthma has several typologies (Figure 1), and several biologic drugs have been developed to target inflammation in specific subtypes of severe asthma, namely type 2 eosinophilic or allergic. Type 2 inflammatory asthma is predominately caused by type 2 cytokines and lymphocytes. Subtypes include eosinophilic asthma (characterized by increased eosinophil levels in the airways and blood) and allergic asthma (characterized by elevated immunoglobulin E levels and elevated bronchial responsiveness).[8] There is overlap between the subtypes with crosstalk involving cytokine signalling so some patients may have characteristics of both eosinophilic and allergic asthma. Non–type 2 inflammatory asthma is characterized by the absence of type 2 markers with neutrophilic and paucigranulocytic airway inflammation, for which there is evidence suggesting it might respond to benralizumab and tezepelumab.[9-11] Additionally, structural changes in the lung, such as fixed airflow obstruction caused by remodelling of the airway wall, can occur

in severe asthma with or without the presence of type 2 inflammation; there are no current pharmacological treatments for targeting airway remodelling.[12]

Figure 1: Severe Asthma Typologies



Policy Issue

In Canada, reimbursement for biologics has occurred for the following drugs and indications: benralizumab and mepolizumab are indicated specifically for severe eosinophilic asthma, dupilumab is indicated for severe asthma with a type 2–eosinophilic subtype, and omalizumab is indicated for allergic asthma (Appendix 1). A Letter of Intent for tezepelumab (indicated for severe asthma) was issued by the pan-Canadian Pharmaceutical Alliance on September 15, 2023. Reslizumab is not currently covered by public drug plans in Canada and therefore was not considered in this review.[13,14] Biologics have the potential to offer more effective symptom control for 1 or more subtypes of severe asthma with fewer adverse events compared with oral corticosteroids;[13,15] however, there is some evidence of increased adverse events compared with standard care (e.g., inhaled corticosteroids, anticholinergics, and beta agonists).[16]

The available biologic therapies for severe asthma currently have disparate criteria for use due to the sequential nature of evaluation and listing, and criteria developed based on available information at the time of consideration. The efficacy of biologic drugs along the spectrum of severe asthma is unclear; similarly, the efficacy and safety in children has not been well characterized. Knowledge of the available evidence within and between biologic drugs by patient population and subtypes of severe asthma, and potential subsequent synthesis of available evidence, may inform listing criteria to optimize health and health care system sustainability.

Main Takeaway

Several biologic drugs are available for the treatment of severe asthma. These biologics are designed to target specific inflammatory subtypes of asthma, particularly type 2 eosinophilic or allergic. It is unclear how well the different drugs work across asthma subtypes, whether formulary listing criteria and prescribing practices can be streamlined, or if any of the drugs are more effective than others.

Policy Questions

1. Is there evidence of comparative efficacy and safety to support harmonization of criteria for use of biologic drugs for patients with severe asthma (compared with current biologic-specific criteria)?
    a) What is the efficacy and safety of each biologic drug by population as defined by specific asthma subtypes (i.e., eosinophilic or allergic with or without specific criteria such as immunoglobulin E levels and eosinophil counts) and age (pediatric: 6 years to 17 years; adult: ≥ 18 years)?
    b) What is the relative efficacy and safety between biologic drugs as defined by specific asthma subtypes and population age?

Objectives

The approach was to conduct the review in 2 parts. Part 1 was a Rapid Review to assess the recent body of evidence available from randomized controlled trials (RCTs) and systematic reviews to determine the feasibility of conducting a more fulsome Health Technology Assessment (HTA).

The aims of the Rapid Review (part 1) were:

- to identify and describe the research examining the comparative efficacy and safety of biologics for severe asthma using clinically important outcomes
- to characterize the patient populations studied
- to determine if further evidence synthesis (systematic review, meta-analysis, indirect treatment comparison) is feasible to address knowledge gaps for specific populations and subgroups with severe asthma.

Part 2 was to be an HTA to provide guidance about the alignment of the drug funding criteria by the public drug plans.

This report presents the findings of the part 1 Rapid Review.

Research Questions

The project identified the literature that addressed the following research questions. It determined whether recent RCTs and systematic reviews addressed these questions, and whether a future systematic review

and/or meta-analysis is feasible and needed. Details on the specific interventions and outcomes are included in Table 1.

1. What is the comparative efficacy of biologic drugs for patients with severe asthma by specific population?
   a) Population defined by severe asthma:
      - Type 2 asthma
        - allergic and/or eosinophilic asthma
        - specific criteria for allergic or eosinophilic asthma (e.g., immunoglobulin E level, bronchial responsiveness, sputum or blood eosinophil count)
   b) Population defined by age:
      - pediatric (6 years to 17 years); adult (≥ 18 years)
2. What is the safety of biologic drugs for pediatric populations with severe asthma?

Methods

To inform the conduct of this focused Rapid Review, a review of the existing literature, including RCTs and systematic reviews, was performed. The part 1 study used the CADTH Rapid Review *Summary with Critical Appraisal and Peer Review* process, with modifications:

- The selection of studies and data extraction were conducted by 2 reviewers.
- The literature search included additional databases and sources, and the literature search strategy was peer reviewed.
- Because it was subsequently decided that part 2 (the HTA) was not required, a decision was made to post the part 1 draft science report for stakeholder feedback.

Literature Search Methods

The literature searches were developed by an experienced librarian with systematic searching experience. A Peer Review of Electronic Search Strategies (PRESS) was performed by a second librarian to optimize the search. Searches were last conducted or updated in May 2023.

The search was restricted to articles published in the past 5 years (2018 onward) and only included those published in English. The search was restricted to RCTs, systematic reviews, meta-analyses, and network meta-analyses conducted using the Ovid interface, and included the following databases and registers: MEDLINE All (1946 to present) via Ovid, Embase (1974 to present) via Ovid, PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials via Wiley Cochrane Library, preprints via EuropePMC.org, ClinicalTrials.gov, WHO ICTRP, Health Canada's Clinical Trials Database, EU Clinical Trials Register, International Traditional Medicine Clinical Trial Registry, and PROSPERO. The detailed search strategies are presented in Appendix 2.

Table 1: Selection Criteria

Criteria	Description
Population	Adults (≥ 18 years) and children (6 to 17 years) with severe asthma and subtypes of severe asthma (type 2, including eosinophilic and allergic, and non–type 2)
Interventions	• Dupilumab • Omalizumab • Benralizumab • Mepolizumab • Tezepelumab
Comparators	• Oral corticosteroids plus standard of care • Placebo plus standard of care

Outcomes	• Safety
	• Efficacy
	  ◦ Hospitalizations
	  ◦ Acute asthma exacerbations
	  ◦ Mortality
	  ◦ Change in forced expiratory volume (pre-bronchodilators)
	  ◦ Health-related quality of life
	  ▪ Asthma Control Questionnaire
	  ▪ Asthma Control Test
	  ▪ Asthma Quality of Life Questionnaire

Study designs	Randomized controlled trials, systematic reviews, meta-analyses, and network meta-analyses published in 2018 or later
Subgroup analyses	• Subtypes of severe asthma (type 2 eosinophilic and/or allergic, and non–type 2) • Age 6 to 17 years; ≥ 18 years

Selection Criteria and Methods

Study Selection

Two reviewers independently screened titles and abstracts for relevance to the clinical research questions. The full text of potentially relevant articles was retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). The 2 reviewers then compared their chosen included and excluded studies; disagreements were discussed until consensus was reached. Both the abstract screening and the full-text screening were pilot tested by 2 reviewers with nonconsensus resolved by third reviewer; clarification of inclusion and exclusion criteria was done as required through pilot testing and calibration.

Exclusion Criteria

Articles were excluded if they did not meet selection criteria outlined in Table 1, were duplicate publications, reported duplicate data on the outcomes of interest, or were published before 2018. Studies that focused on niche subpopulations not identified a priori (e.g., severe asthma with nasal polyps or rhinosinusitis),

or study populations of asthma with other conditions (e.g., chronic obstructive pulmonary disorder), were excluded. Post hoc analyses of RCTs were included provided that they added new data relevant to the research and policy questions, and reviewers were confident that the new analysis met the inclusion criteria (e.g., population, intervention, comparator, and outcome [PICO] criteria were clearly met after changes to population via filtering). Systematic reviews, meta-analyses, and network meta-analysis were excluded if they contained data from nonrandomized or observational studies.

Data Extraction and Critical Appraisal

Data Extraction

Information from each article was extracted using a standardized data extraction form. Extracted information encompassed characteristics of the study (year of publication, study design, sample size, and general statistics), trial participants (including characteristics that defined asthma subtype and age groups), inclusion and exclusion criteria, type of intervention(s) or control (including dose, duration, and co-medication), relevant outcomes, and broad results of the clinical efficacy or effectiveness and safety. Specific extracted outcomes included hospitalization, mortality, asthma exacerbations (AEXs), changes in force expiratory volume in 1 second (FEV_1), and health-related quality of life (HRQoL). HRQoL was measured using 3 validated questionnaires: the Asthma Control Questionnaire, the Asthma Control Test, and the Asthma Quality of Life Questionnaire.

All data were extracted by 1 reviewer and checked for accuracy by a second independent reviewer. The presence of publications reporting on specific combinations of medications, subgroups, and outcomes was also abstracted. If a recent systematic review or meta-analysis had been conducted for each combination was also captured. Country of origin for each article was not extracted because some studies were conducted across numerous countries to recruit an adequately large sample of participants with severe asthma.

Multiple publications for a unique trial (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study) were handled by extracting the most recently adjudicated data for each outcome specified a priori. Results were presented from the original trial if multiple articles were published based on the same clinical sample and provided unique data relevant to the study question.

Quality Assessment

Risk of bias assessments were conducted on the included RCTs using the second version of the Cochrane Risk of Bias,[17] and the systematic reviews using A Measurement Tool to Assess Systematic Reviews second version (AMSTAR 2).[18]

Data Analysis and Synthesis

Extracted data were summarized heuristically; no meta-analysis or new data analysis was conducted. Statistical significance of results were reported as they were described in the included articles, without attempting any adjustment for multiple comparisons. Outcomes such as HRQoL were generally

secondary outcomes in these trials and may be more susceptible to bias from multiple testing. Post hoc analyses reported in the articles are reported in this report without any controlling for potential bias from multiple testing.

Operational definitions for subtypes of severe inflammatory asthma, for which biologics have been developed to target, was determined based on available literature and clinical expert opinion (Table 2).[19] Severe inflammatory asthma was characterized as type 2 that was further classified (subtype) based on the presence of eosinophilic and/or allergic markers, or non–type 2. Due to possibility of overlap between type 2 eosinophilic and allergic asthma, characterization by both an eosinophilic and allergic subtype was also included.

Table 2: Operational Definitions for Severe Inflammatory Asthma Subgroups

Criteria	Description
Severe asthma	Asthma categorized on severity alone, without specifying underlying type(s). Severe asthma is defined as either: • controlled asthma that worsens on tapering of medium- to high-dose inhaled corticosteroid(s) or systemic corticosteroids (or additional biologics) • symptoms that remain uncontrolled with the use of high-dose inhaled corticosteroid(s) plus a second controller (and/or systemic corticosteroids).
Non–type 2	Asthma without type 2 inflammation or markers of eosinophilic or allergic asthma subtypes.
Type 2	Asthma involving type 2 inflammation. Allergic and eosinophilic are nonexclusive subtypes.
Allergic	Subtype of type 2 asthma identified using immunoglobulin E, and allergen sensitivity as markers. Eosinophilic asthma status is unspecified.
Eosinophilic	Subtype of type 2 asthma normally identified using blood eosinophil count as the marker. Allergic asthma status is unspecified.
Nonallergic	Subgroup without allergic markers and eosinophilic asthma status is unspecified.
Noneosinophilic	Subgroup without eosinophilic markers and allergic asthma status is unspecified.
Allergic and noneosinophilic	Subgroup with allergic markers but not markers for eosinophilic asthma.
Eosinophilic and nonallergic	Subgroup with eosinophilic markers but not allergic markers.
Eosinophilic and allergic	Subgroup with markers for both eosinophilic and allergic asthma.

Eosinophilic status was determined by blood eosinophil count (BEC) (cells/μL of blood). For this review, the criterion for eosinophilic asthma was set at a BEC of 150 cells/μL or higher at enrolment or a history of BEC 300 cells/μL or higher. The criteria for noneosinophilic asthma was set at a BEC less than 150 cells/μL with no previous history of BEC 300 cells/μL or higher. In some trials, cut-offs of BEC 300 cells/μL or higher and less than 300 cells/μL at enrolment were used to define eosinophilic and noneosinophilic asthma, respectively. Trials investigating tezepelumab also assessed enrolled participants with severe asthma by fractional exhaled nitric oxide levels (trials used several cut-offs methods including less than 25 parts per billion and 25 or more parts per billion, 25 parts per billion to 50 parts per billion, and less than 50 parts per billion and greater than or equal to 50 parts per billion).

Trials were heterogeneous in definition of allergic status, and included thresholds based on immunoglobulin E level, radioallergosorbent test, skin prick test, fluoroenzyme immunoassay, and/or other allergy measures. Given this heterogeneity, we assumed trial-specific criteria used to characterize type 2 allergic asthma were appropriate to define this severe asthma subtype. Although the variation in clinical testing used to establish allergic status was considerable, we relied on these trial-based criteria to define this status in the interest of feasibility. We recognize the variation in the underlying condition across studies resulting from this heterogeneity is a limitation of this Rapid Review but is not a major limitation in the context of assessing the breadth of subgroup analysis in recent publications.

Feasibility of a future meta-analysis or network meta-analysis was determined based on assessment of published literature and availability of data to examine efficacy and safety by specific subgroups with severe asthma.

Summary of Evidence

Quantity of Research Available

Summary

From a total of 1,014 identified articles published in the last 5 years, 47 were included in this focused Rapid Review: 26 publications from 13 RCTs (a total sample population of 7,773 people, primarily adults) and 21 systematic reviews.

Of the 1,014 identified articles, 233 underwent full-text screening. Of these, 47 articles were included in this review that consisted of 26 publications from 13 RCTs[9,11,20-43] (2 sets of trials were pooled: MENSA and MUSCA as well as SIROCCO and CALIMA]) and 21 systematic reviews[15,16,44-62] (3 systematic reviews without meta-analyses, 8 meta-analyses, 6 network meta-analyses, and 4 indirect treatment comparisons including matching-adjusted indirect comparisons). Details on study selection and included studies are in Appendix 3 and Appendix 4.

Although most data in the included systematic reviews were from RCTs that met the inclusion criteria for this review, some were from trials published before 2018 (e.g., DREAM for mepolizumab). In addition, 19[15,16,44-49,51,52,54-62] systematic reviews included in this study contained trials that were outside of the selection criteria (13 included at least 1 trial with moderate to severe asthma[16,44-48,54,55,57-59,61,62] and others included trials that administered biologics intravenously or studied other biologics). However, these systematic reviews were included based on the following: more than 75% of the trials included in the systematic review only had participants with severe asthma and it provided relevant data and reported results in a manner that allowed for the abstraction of pertinent information. Appendix 5 shows the RCTs included in the systematic reviews.

Supplemental information: A total of 37 articles were excluded because they contained populations with moderate to severe (versus severe only) asthma, of which a number investigated efficacy and safety

of biologic drugs for pediatric populations. These studies are listed in Appendix 6 to facilitate future consideration of nonexclusively severe asthma populations. A list of RCTs of biologics for the treatment of asthma comprising the 13 trials included in this review, relevant trials within included SRs, and additional known major trials (compiled with the assistance of a clinical expert) is found in Appendix 7.

Study Characteristics

Patient Population

The population of interest was individuals identified as living with severe asthma.

There are 2 commonly used definitions of severe asthma: the Global Initiative for Asthma definition and the European Respiratory Society and American Thoracic Society definition, with the latter considered the definitive definition by asthma experts.[63,64] These definitions have undergone modifications over the past decade, which introduces the potential for inconsistencies in populations that meet the criteria for severe asthma over time. In general, the trials included in this focused rapid systematic review used the European Respiratory Society and American Thoracic Society definition, which considers a person to have severe asthma if either:

- their controlled asthma worsens on tapering of medium- to high-dose inhaled corticosteroid(s) or systemic corticosteroids (or additional biologics)
- symptoms remain uncontrolled with the use of high-dose inhaled corticosteroid(s) plus a second controller (and/or systemic corticosteroids).

Uncontrolled asthma is defined as at least 1 of the following: at least 1 AEX requiring hospitalization, intensive care unit stay, or mechanical ventilation in the past year; 2 or more short courses of systemic corticosteroids in the past year; reduced lung functioning (FEV_1 < 80% predicted) after appropriate bronchodilator treatment; or an Asthma Control Test score less than 20 or an Asthma Control Questionnaire score of 1.5 or higher.[63] Inclusion criteria were frequently poorly described in individual articles. The criteria used to define severe asthma was supplemented by reviewers accessing trial descriptions on clinicaltrials.gov registration records. The inclusion criteria from the registration and/or articles are provided in Table 9.

Randomized Controlled Trials

The number of RCTs by biologic drug and asthma subgroup are presented in Table 3, and the number of participants in these trials by biologic drug and asthma subgroup are presented in Table 4, according to (refer to Appendix 8, Table 10, Table 11, and Table 12 for general information on these RCTs). Characterizing study populations by asthma severity and subtypes was challenging given the changing definitions, evolving understanding of asthma subtypes, and overlap of asthma subtypes. Using available data from included studies, characterization of subtypes was attempted when possible. Trials may have targeted recruitment of a specific subtype and may or may not have reported other information on subtype (e.g., study target population was type 2 eosinophilic asthma, but information on allergic status was or was not reported).

In half the trials, enrolment was open to both adults and children, whereas the other half allowed only adult participants (Table 3). Enrolment of children in the trials was notably limited (Table 4), with a relatively small

number of confirmed child participants (229 of a total 7,773 participants; additional children may have been enrolled but not reported).

The largest enrolled asthma subtype was type 2 eosinophilic asthma (Table 4). Trials that targeted patients with this specific subtype of severe asthma investigated the effect of benralizumab (ANDHI, SOLANA) and mepolizumab (MENSA and MUSCA) (Table 9 and Table 10); no data were available on the efficacy of mepolizumab for noneosinophilic patients (Table 13). Although the SIROCCO and CALIMA trial (benralizumab) recruited patients with severe asthma (with no subtype targeted), enrolment was stratified to ensure a large portion of participants had type 2 eosinophilic asthma. RCTs investigating omalizumab targeted enrolment of patients with severe type 2 allergic asthma (EXTRA, NCT01202903, NCT02049294). Although eosinophilic status was reported in some of these trials (Table 14). Trials investigating dupilumab (LIBERTY ASTHMA VENTURE) and tezepelumab (NAVIGATOR, PATHWAY, SOURCE) enrolled patients with severe asthma with no subtype targeted. None of the studies specifically enrolled participants with non–type 2 severe asthma.

Systematic Reviews

Characteristics of the study populations were not well described within the included systematic reviews. Reviews frequently combined trials with varying populations (Table 15) and were classified as type 2 eosinophilic or allergic subtypes. Some systematic reviews did use meta-analysis methods to adjust for differences in populations across the trials.

Table 3: Number of Randomized Controlled Trials by Biologic Drug and Asthma Subgroup

Biologic	N	Patient groups, n		Non–type 2, n	Type 2, n					
		Adult	Children		All type 2	EOS	Non-EOS	Allergic	Non-allergic	EOS and allergic
Benralizumab[11,21,23,31,33,39]	4	4	2	2	4	4	2	4	4	4
Dupilumab[22,29,41]	1	1	1	1	1	1	1	1	1	1
Mepolizumab[20,32,34,40,42]	2	2	1	0	2	2	0	2	2	2
Omalizumab[30,35,38]	3	3	1	0	3	3	3	3	0	3
Tezepelumab[9,24-28,36,37,43]	3	3	1	3	3	3	3	3	3	3

EOS = eosinophilic.

Note: Non–type 2 indicates individuals without markers of either EOS or allergic asthma. "EOS and allergic" indicates individuals with indicators of both EOS and allergic asthma.

Table 4: Number of Participants in Each Randomized Controlled Trial by Biologic Drug and Asthma Subgroup

Trial	N	Patient groups, n		Non–type 2, n	Type 2, n					
		Adult	Children		All type 2	EOS	Non-EOS	Allergic	Non-allergic	EOS and allergic
Benralizumab										
ANDHI[31]	656	656	0	0	656	656[a]	0	352	304	352
CALIMA[11,21,23,33]	1,306	1,251	55	157	934	728[b]	363	828	478	464
SIROCCO[11,21,23,33]	1,204	1,151	53	167	1,037	809[b]	395	705	499	477
SOLANA[39]	233	233	0	0	233	233[b]	0	NR	NR	NR
Dupilumab										
LIBERTY ASTHMA VENTURE[22,29,41]	210	NR	NR	NR	NR	89[b]	121	86	124	NR
Mepolizumab										
MENSA and MUSCA[20,32,34,40,42]	936	NR	NR	0	936	936[a]	0	253	683	253
Omalizumab										
EXTRA[30]	850	809	39	0	850	414[c]	383	850	0	414
NCT01202903[35]	608	608	0	0	608	252[b]	337	608	0	252
NCT02049294[38]	9	9	0	0	9	NR	NR	9	0	NR
Tezepelumab										
NAVIGATOR[9,24,36,37]	1,061	979	82	221	820	431[b]	610	680	361	291
PATHWAY[9,25-28]	550	550	0	134[d]	416 to 468[d]	310[e]	240	296	218	138[d]
SOURCE[9,21,37,43]	150	150	0	NR	NR	52[b]	98	59	83	NR

EOS = eosinophilic; NR = not reported.

Note: Non–type 2 indicates individuals without indication of either eosinophilic or allergic asthma. The method of determining allergic status varied and was based on immunoglobulin E levels, radioallergosorbent tests, skin prick tests, fluoroenzyme immunoassays, and/or other allergy measures. "EOS and allergic" indicates individuals with indicators of both eosinophilic and allergic asthma. Trial information on clinicaltrials.gov was checked to determine or verify these values. Trial-specific criteria for eosinophilic asthma was determined using blood eosinophil count levels (cells/μL).

[a]Blood eosinophil of 150 cells/μL or higher at baseline or a history of 300 cells/μL or higher.

[b]Blood eosinophil of 300 cells/μL or higher.

[c]Blood eosinophil of 260 cells/μL or higher.

[d]Values estimated based on 2 of the 4 arms of the PATHWAY study in the pooled analysis by Corren et al.[9]

[e]Blood eosinophil of 250 cells/μL or higher.

Interventions and Comparators

Randomized Controlled Trials

In the included trials, the active interventions were benralizumab (4 trials, among which SIROCCO and CALIMA were pooled), dupilumab (1 trial), mepolizumab (2 trials that were pooled), omalizumab (3 trials), and tezepelumab (3 trials) (Table 4, Table 9). In all identified studies, the comparator was a subcutaneous placebo injection that was physically similar to the study drug. In general, "standard-of-care" asthma

therapies were allowed in both arms. This is in line with the use of biologic drugs as add-on medications; they are not intended to replace standard asthma therapies (although it is hoped they will reduce the need for oral corticosteroids).

Systematic Reviews

The included systematic reviews compared biologics to placebos. Benralizumab was the most evaluated biologic compared to a placebo (included in 14 SRs), and omalizumab was the least evaluated (included in 4 SRs) (Table 15). Ten of the systematic reviews included a comparative efficacy component — either a network meta-analysis or indirect treatment comparison or matching-adjusted indirect comparison. Mepolizumab (10 systematic reviews), benralizumab (9 systematic reviews), and dupilumab (8 systematic reviews) were evaluated in most of these reviews. Tezepelumab and omalizumab were considered in 3 comparative efficacy reviews each.

Outcome Measures

Randomized Controlled Trials

Main study outcomes are reported in Table 13. AEX was the most common outcome reported (most often as an annualized rate; reported in 11 trials [includes 2 sets of pooled trials]). FEV_1 and/or HRQoL outcomes were reported in 12 trials (includes 2 sets of pooled trials). NCT01202903 did not report FEV_1, and EXTRA did not report HRQoL. Safety outcomes were less commonly reported (included in 5 studies). Safety outcomes may have been previously reported and were not included in articles identified for this Rapid Review. Hospitalization outcomes were reported in 2 trials, and mortality results were not reported separately in any trial.

Outcomes for subgroups are summarized in Appendix 8 in Tables 14, 16, 17, 18, 19, and 20. Although trials that enrolled individuals with a specific subtype of asthma may have also characterized other subtype characteristics (e.g., enrolled a type 2 eosinophilic population but also characterized allergic status of the population), outcomes were infrequently reported for many specific subgroups (Table 14). Outcomes reported by specific subgroups of asthma are shown in Table 14; outcomes for non–type 2 inflammation were rarely reported (i.e., only 2 of 11), and outcomes by characterization of both eosinophilic status and allergic status were infrequent (5 of 11).

Reporting of trial outcome measures by biologic drug (benralizumab, dupilumab, mepolizumab, and tezepelumab) and type 2 eosinophilic asthma subgroups are presented based on characterization by BEC level (Table 17) and fractional exhaled nitric oxide level (Table 18). Only trials that investigated tezepelumab reported type 2 eosinophilic asthma classified by fractional exhaled nitric oxide levels.

Type 2 allergic asthma subgroups were challenging to assess because a standardized method of characterizing allergic status was not consistently used. Therefore, outcomes for type 2 allergic asthma subtypes are presented in 2 different formats of characterization. Omalizumab eligibility criteria subgroups were reported in Table 19, and other allergic marker subgroups were reported in Table 20). AEX was almost always reported (41 of 47 reported subgroups), and FEV_1 and HRQoL were reported for approximately half of extracted 47 subgroup results. No other outcomes were reported for the asthma subgroupings.

Systematic Reviews

Details regarding reported outcomes from the systematic reviews can be found in Appendix 8. Definitions of AEX in the reviews are listed in Table 21. These reviews and meta-analyses reported outcomes on few of the patient subgroups (Table 22) while reporting 20 primary patient population and drug intervention combinations (Table 23). Outcomes were also reported for 23 subgroup and drug intervention combinations (Table 24). Subgroups were stratified primarily by BEC level or fractional exhaled nitric oxide level, by adult and pediatric populations for omalizumab, and by severe asthma type 2 allergic subgroup for tezepelumab. In the primary patient populations, AEX outcomes were consistently reported (95%; 19 of 20 reviews), whereas FEV_1 and HRQoL were reported in 13 reviews (65%). Safety outcomes were reported in 11 out of 20 reviews (55%). In the subgroups, AEX outcomes were consistently reported (100%; 23 of 23 subgroups reported), whereas FEV_1 (26%; 6 of 23 subgroups reported), HRQoL (13%; 3 of 23 subgroups reported), and safety (9%; 2 of 23 subgroups reported) were reported less frequently.

The identified comparative efficacy reviews (network meta-analyses, indirect treatment comparisons, matching-adjusted indirect comparisons) reported outcomes on 27 primary patient population and drug intervention combinations, as well as 50 subgroup and drug intervention combinations. Eosinophilic subgroups (determined by BEC levels in 34 instances, and fractional exhaled nitric oxide levels in 12 instances) were reported in 46 instances, and allergic subgroups (with unclear cut-offs) were reported in 4 instances (Table 25 and Table 26). In the primary patient population, AEX outcomes were consistently reported (88%; 24 of 27 reviews), whereas FEV_1 (44%; 12 instances), HRQoL (30%; 8 of 27 reviews), safety (26%; 7 of 27), and hospitalization (19%; 5 of 27 reviews) outcomes were reported less frequently. Similarly, in the subgroups, AEX outcomes were consistently reported (100%; 50 instances), whereas FEV_1 (36%; 18 of 50 subgroups reported) and HRQoL (16%; 8 of 50 subgroups reported) were reported less frequently. All 10 systematic reviews that included a comparative efficacy component reported AEX outcomes in the primary patient population; FEV_1 was reported in 5 reviews, HRQoL in 4 reviews, safety in 3 reviews, and hospitalizations in 1 review (Table 27). Half the systematic reviews that included a comparative efficacy component also reported outcomes in a combined 17 subgroups (Table 28). Subgroups were stratified primarily by BEC level (9 subgroups reported) or fractional exhaled nitric oxide level (6 subgroups reported); an allergic subgroup (with unclear cut-offs) and a subgroup based on oral corticosteroid use status were also assessed. All subgroups reported AEX outcomes. FEV_1 was reported in 10 subgroups, HRQoL in 8 subgroups, and safety in 1 subgroup; hospitalizations were not reported.

Critical Appraisal

Summary

Although clear study objectives, interventions, comparators, and outcomes were identified in the trials, there were inconsistencies in reporting the characterization of enrolled populations and subtypes of severe asthma.

The severity of asthma was not precisely defined or characterized in many of the trials and systematic reviews.

The recruitment methods, definitions, and criteria for subtypes of severe asthma, such as type 2 eosinophilic or allergic asthma, varied across studies.

Risk of bias assessments revealed little to no risk of bias in the RCTs.

Risk of bias assessments revealed a noteworthy concern for bias in systematic reviews, with most having at least 1 critical weakness and several with noncritical weaknesses.

Randomized Controlled Trials

All identified trials had clear study objectives, intervention(s), comparators, and outcomes. Trial registration information was provided, and no significant deviations from the planned studies were noted. However, specific details about the characteristics of enrolled populations were reported inconsistently, and several publications lacked sufficient information about how severe asthma was defined and characterized. In these cases, trial registration information was used to determine enrolment criteria. The variability of the enrolled populations was increased in the included trials because they were conducted during a period when there were shifting standards for the diagnosis of severe asthma.

A Cochrane risk of bias assessment (second version[17]) was conducted, and the results are shown in Table 5. Our assessment did not identify any high levels of concern for bias. Overall, 4 trials had a low level of concern for bias (ANDHI, NCT02049294, NAVIGATOR, and PATHWAY), and 9 had some level of concern for bias (CALIMA [domains 3 and 5], SIROCCO [domains 3 and 5], SOLANA [domain 1], LIBERTY ASHTMA VENTURE [domain 4], MENSA [domain 5], MUSCA [domain 5], EXTRA [domains 3 and 5], NCT01202903 [domain 3], and SOURCE [domains 4 and 5]). Most of the potential sources of bias were concentrated in a few domains, particularly domain 3 (bias due to missing outcome data), although it was unlikely that the extent of missing data could offset the reported differences in key outcomes, and domain 5 (bias in selection of overall result) that was related to the selection of results based on the number of planned analyses and what was presented in the final publications. The LIBERTY ASTHMA VENTURE and SOURCE trials had levels of some concern within domain 4 (bias in the measurement of outcomes), and the SOLANA trial had some level of concern within domain 1 (bias arising from the randomization process) due to an unclear description of the randomization process in the manuscript. These concerns were unlikely to significantly bias the results in a way that would negate the observed outcomes for the investigated biologics.

Thirteen of the included systematic reviews also conducted Cochrane risk of bias assessments on the included RCTs.[15,16,44-46,51,54-56,58,59,61,62] Their findings were similar to our assessment, with the exception of Agache et al. who rated some of the trials (CALIMA, SIROCCO, LIBERTY ASTHMA VENTURE, MENSA, and MUSCA) as having high levels of concern in the domains of attrition, reporting, and/or other bias.[15,16,44] However, the rationale for these ratings was unclear.

The various subtypes of severe asthma were not consistently reported. Various studies defined subtypes (such as type 2 eosinophilic or allergic) differently and used different criteria. For example, there were varying thresholds of eosinophil counts to define type 2 eosinophilic asthma (refer to Appendix 8, Table 17 and Table 18). More recent trials focused on patients with severe asthma without restrictions for asthma subtype, while older trials tended to focus on specific asthma subtypes with broader criteria for asthma severity. The internal validity of these trials appears to be acceptable based on our assessments. However, the variation in trial inclusion criteria and protocols limits generalization across trials and outside of the inclusion criteria.

Table 5: Risk of Bias Assessment for Included Randomized Controlled Trials

Biologic	Trial	Risk of bias[a]					
		Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Benralizumab	ANDHI[31]	Low	Low	Low	Low	Low	Low
Benralizumab	CALIMA[11,21,23,33]	Low	Low	Some	Low	Some	Some
Benralizumab	SIROCCO[11,21,23,33]	Low	Low	Some	Low	Some	Some
Benralizumab	SOLANA[39]	Some	Low	Low	Low	Low	Some
Dupilumab	LIBERTY ASTHMA VENTURE[22,29,41]	Low	Low	Low	Some	Some	Some
Mepolizumab	MENSA[20,32,34,40,42]	Low	Low	Low	Low	Some	Some
Mepolizumab	MUSCA[20,32,34,40,42]	Low	Low	Low	Low	Some	Some
Omalizumab	EXTRA[30]	Low	Low	Some	Low	Some	Some
Omalizumab	NCT01202903[35]	Low	Low	Some	Low	Low	Some
Omalizumab	NCT02049294[38]	Low	Low	Low	Low	Low	Low
Tezepelumab	NAVIGATOR[9,24,36,37]	Low	Low	Low	Low	Low	Low
Tezepelumab	PATHWAY[9,25-28]	Low	Low	Low	Low	Low	Low
Tezepelumab	SOURCE[9,21,37,43]	Low	Low	Low	Some	Some	Some

NR = not reported.

Note: Overall bias was assessed using "'low," "'some," and "high" concerns. Information within published articles was cross-referenced to protocols published on clinicaltrials.gov.

[a]Definitions of risk of bias domains: Domain 1 = Bias arising from the randomization process. Domain 2 = Bias due to deviations from intended intervention. Domain 3 = Bias due to missing outcome data. Domain 4 = Bias in measurement of outcome. Domain 5 = Bias in selection of overall result.

Systematic Reviews

Similar to individual RCTs, many systematic reviews did not provide a clear description of the included patient populations. In many cases, it was unclear whether the reviews included similar populations. Despite the inclusion and exclusion restrictions applied by the systematic reviews, issues with population variation

persisted. Some of the biologics were extensively tested among subgroups of asthma patients, but this occurred without complete characterization, such as type 2 eosinophilic asthma without characterization of allergic status. Despite this issue, biologic drugs were compared with one another in some reviews. Some studies recognized this issue and used sample adjustment methods, such as filtering, matching, and/or weighting, to minimize population differences.

All the included systematic reviews underwent an AMSTAR 2 assessment (refer to Table 29). The framework proposed by Shea et al.[18] was used to inform an overall level of confidence (high, moderate, low, critically low) in the results of the systematic reviews based on critical and noncritical domains of weakness. Based on the AMSTAR 2 assessment, the levels of confidence in results of the systematic reviews were considered to be high in 3 reviews,[15,16,44] moderate in 2 reviews,[52,53] and low or critically low in the remaining 16 reviews. A full description of the AMSTAR 2 assessment is detailed subsequently.

Of the critical domains (AMSTAR 2 items 1, 2, 4, 9, 11, 13, and 15), all the 21 included systematic reviews adequately described their PICO criteria (item 1). However, 13 reviews did not provide sufficient justification for their search strategy, such as language restriction justification (item 4).[45-49,51,54,57-62] Although the majority of reviews published their protocols before commencing the review (item 2), 9 reviews did not follow this practice,[46,48,49,51,54-56,60,62] which suggests a potential risk of bias due to ad hoc study decisions. In the majority of reviews, a satisfactory approach for assessing the risk of bias was used (item 9). However, 9 did not account for risk of bias when interpreting the results of the review (item 13).[47-51,54,59,60,62] The application of meta-analytic methods was appropriate (item 11) with the exception of 1 review[51] that employed unsuitable methods (converted rate outcomes into binary outcomes so that odds ratios could be reported). Nine reviews did not report sufficient exploration of potential publication bias (item 15).[47-50,55-57,59,62] However, this omission may have been due to the small number of included trials, which prevented this assessment.

In the case of noncritical domains (AMSTAR 2 items 3, 5, 6, 7, 8, 10, 12, 14, and 16), numerous reviews did not meet several of these criteria. None of the authors of the systematic reviews explained their rationale for selecting only RCTs for inclusion (item 3). Although study selection was always performed in duplicate (item 5), data extraction was not described as being performed in duplicate in 10 of the reviews (item 6).[46,48,49,51,54-56,58,60,62] Only systematic reviews performed by Agache et al.[15,16,44] provided a list of excluded studies and the reasons for their exclusion (item 7). Only 1 study failed to describe the included studies in enough detail (item 8).[59] Furthermore, these were the only reviews that assessed the sources of funding for included studies and whether they might introduce bias (item 10). Eight reviews did not assess possible effects of risk of bias on results (item 12).[46-51,54,59,60] Heterogeneity observed in the results of the reviews was not sufficiently discussed in 6 reviews.[47-50,54,59] In 9 reviews, potential relevant conflicts of interests were not sufficiently detailed to determine whether safeguards against conflicts were taken (item 16).[15,16,44,47-51,57]

Findings

Summary

The included studies focused on a limited number of asthma subtypes and age groups, with limited evidence for non–type 2 asthma subtypes and children.

Biologics indicated for type 2 eosinophilic severe asthma characterized by eosinophilic markers (benralizumab, dupilumab, mepolizumab, and tezepelumab) were found to provide benefit for this subgroup of patients.

There were no head-to-head trials to determine the most effective biologic for type 2 eosinophilic asthma.

The same biologics also seemed to work for those with type 2 eosinophilic asthma who also had allergic asthma markers.

The findings for biologics used in type 2 allergic asthma, beyond omalizumab, were limited due to the differences in classifying this subtype.

The efficacy of tezepelumab in reducing asthma exacerbations in a non–type 2 allergic severe asthma subgroup was not supported by included studies, but the evidence was limited. HRQoL and safety outcomes were not reported.

Our analysis of the included 47 articles indicated that biologics appeared to be effective across important clinical (AEX, FEV_1) and patient-reported outcomes (HRQoL) for their current indications with similar outcomes for safety. However, there were gaps in the evidence for each of these drugs among the subgroups of severe asthma (type 2 inflammation further characterized by eosinophilic and allergic markers, and non–type 2 asthma). Assessment of the comparative efficacy of biologic drugs was challenging due to heterogenous definitions of asthma severity and inconsistent application of severity criteria in RCTs, and therefore remains uncertain. Evidence on comparative safety is limited. There was also a lack of evidence on the efficacy and safety of these biologics in severe asthma among children.

Included RCTs enrolled primarily a type 2 inflammatory phenotype patient population (Table 3). Further characterization of this study population by subtype was performed in some studies (e.g., reporting on allergic status in a study that targeted enrolment of a type 2 eosinophilic population), although outcome reporting by asthma subgroups was incomplete (Table 14). Table 30 summarizes the main findings and evidence gaps for the 5 biologics of interest, and Table 31 provides a summary of findings for asthma subgroups (severe asthma, type 2 eosinophilic and/or allergic, and non–type 2).

Mepolizumab and omalizumab had the largest evidence gaps due to trials including only 1 specific asthma subtype. Mepolizumab was only evaluated in type 2 eosinophilic severe asthma; evidence for patients with a type 2 eosinophilic and allergic asthma subtype was also reported (Table 16), but results in a type 2 allergic and noneosinophilic subgroup was not available. Omalizumab was exclusively studied in patients with type

2 allergic severe asthma. Efficacy by eosinophilic status (high or low BEC) was not commonly reported (Table 16).

Eosinophilic status in severe asthma was frequently characterized by BEC levels in both the RCTs and systematic reviews. Although the results generally favoured the intervention across BEC levels, the low BEC subgroups were less likely to be statistically significant. Subgroups for type 2 allergic asthma were regularly reported from trial data in eosinophilic and severe asthma populations, however, the classification of this subtype was less consistent. Few systematic reviews examined this subtype.

In the few trials that enrolled individuals with severe asthma who had a non–type 2 inflammatory phenotype, benralizumab, dupilumab, and tezepelumab were investigated. The trials evaluating benralizumab and tezepelumab reported outcomes in this subtype. These biologics consistently demonstrated a statistically significant improvement in AEX compared to placebo (Table 16). A cut-off of less than 300 BEC was used for benralizumab; however, a cut-off of less than 150 BEC would more clearly identify non–type 2 patients. The direction of this effect was maintained for tezepelumab in a recent re-analysis of the PATHWAY and NAVIGATOR trials[9] within a narrow subgroup (N = 96) that more rigorously classified non–type 2 asthma by also including only those with fractional exhaled nitric oxide less than 25 parts per billion (in addition to < 150 BEC and perennial allergies). The reported between-group difference in AEX in this small sample size was not statistically significant.

Among the included RCTs that evaluated the use of biologics in patients with severe asthma, some studies recruited participants younger than 18 years but only a small portion were confirmed as children (n = 229, 3% of the included trial participants). Reporting of outcomes for participants younger than 18 years was infrequent, with only 1 review[15] reporting outcomes within this population (pediatric patients with type 2 allergic asthma with omalizumab investigated). A number of studies that evaluated efficacy and safety of biologics in moderate to severe asthma among pediatric populations are listed in Appendix 6 for reference.

Included systematic reviews were consistent with our assessment of the current evidence, with main clinical outcomes and HRQoL generally favouring biologics over placebos (Table 23). Reviews also generally did not identify any risk of serious adverse events, with only 1 review finding a statistically significant risk of adverse events for mepolizumab.[16] Assessment of subgroups was more limited in reviews than in published articles on RCTs.

Among the included systematic reviews, 10 reported on comparative efficacy (Table 25). These reviews examined populations that were broadly classified as severe asthma or were based on eosinophilic criteria, without specific characterization of allergic status and limited by a lack of direct comparisons (indirect comparison with attendant limitations). Most comparisons did not reveal significant differences between the included drugs in the targeted patient populations of interest. Although these reviews selected pertinent trials and effectively summarized main study outcomes, they lacked systematic subgroup assessments and often did not fully account for population variations across the trials. In light of these limitations, statistical adjustments were made in some reviews to better compare dissimilar populations (although inconsistencies remained), and some statistically significant differences were found in some of those studies. Benralizumab, mepolizumab, and omalizumab were inferior to tezepelumab and dupilumab in some

reviews listed as including trials of type 2 eosinophilic or severe asthma not otherwise. Mepolizumab was superior to benralizumab in HRQoL outcomes and superior to dupilumab in safety outcomes in some reviews of type 2 eosinophilic asthma trials. However, given the underlying heterogeneity across trials, comparative effectiveness between biologics is still uncertain. Subgroup analyses were mostly consistent with overall group results.

Limitations

This was a focused rapid systematic review that searched articles in English that were recently published (from 2018 onward); a more fulsome review may have identified additional studies. Severity of asthma was inconsistently defined. Many trials that studied patients with moderate to severe asthma that were not clearly "severe" asthma were excluded. Handsearching was limited due to the nature of this study; however, PROSPERO and clinical trial registries were checked (including any linked studies listed on the registries). Results of RCTs are reported as simplified positive or negative outcomes with significance noted as a means of simplifying the large volume of complex data, and because of potential variation in effect sizes due to differences in baseline populations. This analysis did not adjust for any potential concerns related to multiple testing or reporting bias due to the substantial number of outcomes that are frequently recorded and published from the included RCTs.

This review was intended to identify and quickly map the available evidence from recent RCTs and systematic reviews. Therefore, an in-depth extraction of specific effect sizes or a meta-analysis or comparative efficacy testing were not performed.

Conclusions and Implications for Decision- or Policy-Making

Main Takeaway

It is difficult to compare the safety and efficacy of different asthma treatments because the studies lack standardized eligibility criteria and outcome reporting for all asthma subtypes and patient populations, especially pediatric patients. As a result, it is highly uncertain that evidence synthesis using data from available trials would lead to meaningful and policy-relevant conclusions. Based on this, CADTH will not proceed with conducting a more fulsome HTA (part 2).

Conclusions

- Recent RCTs and systematic reviews (published in 2018 onward) predominately focused on a limited range of severe asthma subtypes. Children were infrequently included. Outcome reporting for biologic drugs by the subtypes of severe asthma and by age was limited.

- In this review, most participants included in RCTs were those with primarily type 2 eosinophilic severe asthma. Biologics indicated for this subtype demonstrated benefit for this patient population (benralizumab, dupilumab, mepolizumab, and tezepelumab) and this benefit may extend to those who also have markers of allergic asthma (type 2 eosinophilic and allergic).
- Included systematic reviews that assessed comparative efficacy primarily included trials on the type 2 eosinophilic asthma population. Although conclusions were heterogenous, most found no significant differences among the biologics assessed. Conclusions were limited by population characterization, power, and method (indirect treatment comparison).
- Biologics studied in type 2 allergic asthma, other than omalizumab (indicated for this patient population), were limited by variable definition of this subtype. Although there was limited evidence, tezepelumab was shown to be effective in a type 2 allergic severe asthma population defined by the same criteria indicated for omalizumab. Dupilumab was shown to be statistically significantly better for some outcomes compared to omalizumab in an indirect treatment comparison conducted in included systematic reviews in which the dupilumab data were adjusted to match the population from omalizumab trials. However, clinical relevance and validity of this result is uncertain.
- There was limited research on the non–type 2 severe asthma population. No trial specifically enrolled individuals with this phenotype. Among a small number of participants with non–type 2 severe asthma, benralizumab and tezepelumab reported positive outcomes (consistently showed a statistically significant reduction in AEXs compared with placebo). However, the benralizumab analysis used a higher than normal BEC level as their cut-off point, which limits clinical interpretation.
- There is evidence from subgroup analyses in the PATHWAY and NAVIGATOR studies on tezepelumab that patients with non–type 2 asthma, defined rigorously as those with BEC less than 150 cells/μL, fractional exhaled nitric oxide less than 25 parts per billion, and negative perennial allergy skin tests, may benefit from treatment with tezepelumab. However, data showing efficacy for the other biologic therapies in this subgroup are lacking.
- There was insufficient evidence to inform efficacy and safety of biologics in pediatric populations with severe asthma. Full assessment of efficacy and safety would require using subject-specific characteristics (to identify age if not reported) but is likely to be challenging given access to data and the small numbers of children enrolled. Studies on the efficacy and safety of biologics in pediatric populations with moderate to severe asthma have been conducted and could contribute to further evidence synthesis.
- Conduct of de novo evidence synthesis would be constrained by incomplete inclusion, characterization, and outcome reporting of study populations by both type 2 allergic and eosinophilic subtypes for each biologic, and small numbers of identified children enrolled in trials. This is unlikely to result in evidence to inform alignment of criteria of biologics in severe asthma.
- Overall, biologic drugs are better than placebo across all outcomes for their respective indications. However, comparative efficacy of biologics for these indications is uncertain, and evidence on comparative safety is limited.

Implications for Decision- or Policy-Making

- In this part 1 Rapid Review, potential comparative efficacy and safety analysis to answer the proposed research and policy questions is limited by lack of similar eligibility criteria and outcome reporting for all asthma subtypes and patient populations, especially pediatric populations.
- Part 2 was to be an HTA to provide guidance concerning the alignment of the drug funding criteria by the public drug plans. Based on the findings of part 1, it is highly unlikely that further evidence synthesis using data from available trials would generate policy-relevant conclusions. As such, CADTH will not proceed with part 2 (the HTA).

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Authors and Contributors

Jason R. Randall was involved with conception and design and drafted the original project protocol; screening studies, data extraction, and data analysis; and drafting and revising of the report.

Richard Leigh provided content input to analysis and interpretation of data, key messages, and conclusions and provided revisions on the initial draft and on subsequent revisions for important intellectual content.

Ellen T. Crumley conducted all searches, was the second screener of all results, provided details about how to write up searches, and read the final report and suggested edits.

Sylvia Aponte-Hao contributed to the systematic review, data extraction, and data analysis of the study and reviewed the report.

Ngoc Khanh Vu participated in the development of the study protocol and data collection tools, data collection by extracting information from papers, contributed to the contents of the report, and provided comments for report draft and revisions.

Karen Martins provided substantial contributions to interpretation of study results, including the key messages and conclusion, and contributed to revising the report critically for important intellectual content.

Scott Klarenbach was the senior author and investigator and was involved in the conception, study design, oversight of data acquisition and analysis, critical revision of report including policy implications, and oversight of the project.

Contributors

Content Expert

This individual kindly provided comments on this report:

Karen E. Binkley, HBSc MD FRCPC

Associate Professor

Divisions of Clinical Immunology and Allergy and Clinical Pharmacology, University of Toronto

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Christine Perras and David Stock reviewed the drafts and final report.

Emily Farrell provided knowledge mobilization support.

Brandy Appleby provided project management support.

Sarah C. McGill conducted a quality check of the references.

Conflicts of Interest

Jason R. Randall disclosed the following:

Current employment

- Real World Evidence Unit, University of Alberta, 2022 to 2024, various drugs and technologies

Ellen T. Crumley disclosed the following:

Payment as advisor or consultant

- Liv Agency – Upadacitinib, 2022: Wrote report from recording of live consultancy meeting.
- Fusion MD Network – Avelumab, 2022: Attended and wrote report from live consultancy meeting.

Scott Klarenbach disclosed the following:

Research funding or grants

- Real World Evidence Consortium (via Bayer) – Outcomes in diabetic kidney disease
- Alberta Drug and Technology Evidence Consortium with funding from CADTH – CoLab PMDE Core Network Partner
- Real World Evidence Unit and Real World Evidence Consortium (RWEU and RWEC) through the University Hospital Foundation (UHF) (funding to UHF from Roche) – Pathways of care for multiple sclerosis; DMT use in patients with multiple sclerosis
- RWEU and RWEC with funding from Allergan – Health care resource use in subjects with migraine; pathways of care post stroke; economic impact of discontinuing or reducing injection frequency of botulinum toxin for the treatment chronic migraine.
- RWEU and RWEC with funding from Purdue – Analgesia use in trauma
- RWEU and RWEC with funding from GSK and in Partnership with Respiratory Strategic Clinical Network (AB) – Treatment patterns in patients with COPD
- RWEU and RWEC with funding from CSL – Immunoglobulin use in AB; treatment patterns in dermatomyositis; incremental cost of SCIg versus IVIg
- RWEU and RWEC with funding from Lundbeck – Health care resource use and treatment in depression
- RWEU and RWEC with funding from University Hospital Foundation (funding to UHF from NovoNordisk) – Health care resources use in patients with obesity
- RWEU and RWEC with funding from UHF (funding from UHF from Jansen) – Health care resource use in patients starting long-acting antipsychotics in schizophrenia
- RWEU and RWEC with funding through the University Hospital Foundation (UHF – funding originated from Novartis) – Economic burden of Multiple Sclerosis in Alberta

- RWEC funding through Ferring – Budesonide MMX treatment in ulcerative colitis
- RWEC funding through IQVIA – Completed a feasibility questionnaire related to data availability for evaluating the cost of cadaver islet cell transplant
- RWEC funding through RTI – Completed a feasibility questionnaire related to data availability for evaluating the risk/benefit of a particular drug among those with CKD and cardiovascular morbidity and mortality
- RWEU and RWEC funding through Janssen – Evaluating the feasibility of health system data to generate decision-grade real world evidence in Canada – under review
- RWEU and RWEC funding through Intuitive – Comparative outcomes between different surgical approaches

Karen Martins disclosed the following:

Member of the Alberta Real World Evidence consortium that conducts investigator-initiated research projects and receives funding from industry.

Richard Leigh disclosed the following:

Speaking engagements

- AstraZeneca – Alarmins: 2022–2023
- GlaxoSmithKline – Asthma, Precision Medicine: 2022–2023
- Sanofi – Asthma, Dupilumab: 2022–2023
- Vale – Asthma, inhalers: 2022–2023

Other

- Attendee – Advisory board meetings for AstraZeneca, GlaxoSmithKline, and Sanofi

Payment as advisor or consultant

- AstraZeneca – Asthma, Alarmins: 2018 to 2023
- GlaxoSmithKline – Asthma, precision medicine; biologics: 2018 to 2023
- Sanofi – Asthma, Dupilumab: 2019 to 2023

Research funding or grants

- AstraZeneca – Asthma, Alarmins: 2018 to 2023
- Sanofi – Asthma, Dupilumab: 2019 to 2023

Payment for academic appointments (endowed chairs)

- GlaxoSmithKline - Asthma, Precision Medicine; biologics: 2018 to 2023
- Received honorariums as advisor from AZ, GSK, and Sanofi. University of Calgary has received funding from AZ, GSK, and Sanofi for clinical trials where Richard Leigh is the Site Principal Investigator. The University of Calgary received an endowment from GSK for a Professorship in

Inflammatory Lung Disease – Richard Leigh is the current holder of that Professorship but does not benefit from any personal payments from the Professorship (all funds channelled into Operations).

Karen Binkley disclosed the following:

Speaking engagement and educational lecture

- Takeda – Firazyr, Takzhyra

Other – Advisory board member

- Takeda – Firazyr, Takzhyra
- Biocryst – Orladeo

Payment as advisor or consultant

- Medexus – Rupall. Speaker – education lectures on angioedema and urticaria

No other conflicts of interest were declared.

Appendix 1: Approved Indications for Biologics

Note that this appendix has not been copy-edited.

Table 6: Product Information

Biologics	Dose	Health Canada indication	CDEC recommendation

Benralizumab	30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by SC injection into the thigh, or abdomen.	As an add-on maintenance treatment of adult patients with severe eosinophilic asthma.	As an add-on maintenance treatment for adult patients with severe eosinophilic asthma if the following criteria are met:
			• Patient is inadequately controlled with high-dose inhaled corticosteroids and 1 or more additional asthma controller(s) (e.g., long-acting beta agonists), if 1 of the following 2 clinical criteria is met:
			  ◦ Blood eosinophil count of ≥ 300 cells/μL AND has experienced 2 or more clinically significant asthma exacerbations in the past 12 months; OR
			  ◦ Blood eosinophil count of ≥ 150 cells/μL AND is treated chronically with oral corticosteroids.
			• Benralizumab should not be prescribed to patients who smoke.
			• Benralizumab should not be used in combination with other biologics used to treat asthma.

Dupilumab	Initial dose of 600 mg SC (two 300 mg injections), followed by 300 mg every other week.	As an add-on maintenance treatment in patients aged 6 years and older with severe asthma with a type 2/ eosinophilic phenotype or oral corticosteroid–dependent asthma.	For the treatment of severe asthma and with a type 2 or eosinophilic phenotype or oral corticosteroid–dependent asthma if certain conditions are met.
Mepolizumab	100 mg administered SC once every 4 weeks.	As add-on maintenance treatment for adults, adolescents, and children (aged 6 years and older) with severe eosinophilic asthma who: • are inadequately controlled with high-dose inhaled corticosteroids (patients ≥ 18 years of age) or medium- to high-dose inhaled corticosteroids (patients 6 to 17 years of age) and an additional asthma controller(s) (e.g.,	As an add-on maintenance treatment for adult patients with severe eosinophilic asthma, if the following criteria are met: Initiation Criteria: 1. Patient must have a documented diagnosis of asthma. 2. Patient is inadequately controlled with high-dose inhaled corticosteroids, defined as greater or equal to 500 mcg of fluticasone propionate or equivalent daily, and 1 or more additional asthma controller(s) (e.g., long-acting beta agonists). 3. Patient has 1 of the following:

Biologics	Dose	Health Canada indication	CDEC recommendation
		LABA); and ◦ have a blood eosinophil count of ≥ 150 cells/μL (0.15 GI/L) at initiation of treatment OR ◦ ≥ 300 cells/μL (0.3 GI/L) in the past 12 months.	3.1. blood eosinophil count of ≥ 300 cells/μL AND has experienced 2 or more clinically significant asthma exacerbations in the past 12 months, or 3.2. blood eosinophil count of ≥ 150 cells/μL AND is receiving maintenance treatment with oral corticosteroids.
Omalizumab	75 to 375 mg is administered SC every 2 or 4 weeks. Doses of more than 150 mg are divided among more than 1 injection site to limit injections to not more than 150 mg per site	For adult and pediatric patients (6 years of age and above) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids.	For adults and adolescents (12 years of age and older) with moderate to severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen, if the following clinical criterion is met: Inability to use, intolerance to, or inadequate response to an inhaled corticosteroid long-acting beta-agonist combination, and at least 1 other reimbursed alternative asthma treatment.
Tezepelumab	210 mg SC once every 4 weeks	As an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma	Add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma, only if: Asthma uncontrolled with high-dose ICS and 1 or more additional asthma controllers. AND Experienced 2 or more clinically significant asthma exacerbations in the past 12 months AND A baseline assessment of asthma symptom control using a validated Asthma Control Questionnaire must be completed before initiation of tezepelumab treatment.

ICS = inhaled corticosteroids; LABA = long-acting beta agonist; SC = subcutaneous.

Appendix 2: Literature Search Strategy

Note that this appendix has not been copy-edited.

Search Strategies – Final

Updated May 12, 2023

Clinical Trials Registries

Biomed Central. ISRCTN Registry

https://www.isrctn.com/

Searched March 20, 2023, Tezepelumab searched April 13, 2023

Narrowed results to: Condition Category: Respiratory

1. Xolair
2. Omalizumab
3. Nucala
4. Mepolizumab
5. Fasenra
6. Benralizumab
7. Dupilumab
8. Dupixent

Searched April 13, 2023

1. Tezepelumab
2. Tezspire
3. Severe asthma

US National Institutes of Health. ClinicalTrials.gov

https://classic.clinicaltrials.gov/ct2/search/advanced

Searched March 20, 2023

1. (Xolair or omalizumab) and Interventional Studies and severe asthma
2. (Nucala or mepolizumab) and Interventional Studies and severe asthma
3. (Fasenra or benralizumab) and Interventional Studies and severe asthma
4. (Dupilumab or Dupixent) and Interventional Studies and severe asthma
5. (Tezepelumab or Tezspire) and Interventional Studies and severe asthma

Searched April 13, 2023

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched 20 March 2023, Tezepelumab searched 13 April 2023

1. (xolair OR omalizumab OR Nucala OR mepolizumab OR Fasenra OR benralizumab OR Dupilumab OR Dupixent) AND severe asthma
2. (Tezepelumab or Tezspire) AND severe asthma

Searched April 13, 2023

WHO. International Clinical Trials Registry Platform Search Portal (ICTRP)

https://trialsearch.who.int/Default.aspx

Searched April 13, 2023

Narrowed to 2018+

1. (xolair OR omalizumab) AND severe asthma
2. (Nucala OR mepolizumab) AND severe asthma
3. (Fasenra OR benralizumab) AND severe asthma
4. (Dupilumab OR Dupixent) AND severe asthma
5. (Tezepelumab or Tezspire) AND severe asthma

PROSPERO: International prospective register of systematic reviews https://www.crd.york.ac.uk/prospero/

Searched 20 March 2023, Tezepelumab searched 13 April 2023

1. (omalizumab OR xolair OR Nucala OR mepolizumab OR Fasenra OR benralizumab OR Dupilumab OR Dupixent) AND severe asthma AND (Systematic Review OR Meta-Analysis OR Network meta-analysis):RT NOT Animal:DB
2. (Tezepelumab or Tezspire) AND severe asthma AND (Systematic Review OR Meta-Analysis OR Network meta-analysis):RT NOT Animal:DB

Searched April 13, 2023

MEDLINE

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations and Daily 1946 to May 4, 2023

Searched May 8, 2023

1. (nucala* or mepolizumab* or bosatria* or SB240563 or SB-240563 or 90Z2UFOE52).ti,ab,ot,rn,hw,nm,kf. 1323
2. 196078-29-2.rn,nm. 0
3. (Xolair* or omalizumab* or rhuMab-E25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901).ti,ab,ot,sh,hw,rn,nm. 3464
4. exp Omalizumab/ 2308
5. ("242138 07 4" or "242138074" or 24213807 4 or "242318 074" or 2421380 74).rn,nm. 0
6. (dupilumab* or dupixent* or regn668 or regn 668 or sar231893 or sar 231893 or 420K487FSG).ti,ab,kf,ot,hw,rn,nm. 2290
7. (Fasenra* or benralizumab* or BIW 8405 or BIW8405 or medi563 or medi 563 or 71492GE1FX).ti,ab,kf,ot,hw,rn,nm. 719
8. (tezepelumab* or Tezspire* or amg-157 or amg157 or medi-9929 or medi9929 or medi-19929 or medi19929 or GTPL-8933 or GTPL8933 or RJ1IW3B4QX).ti,ab,kf,ot,hw,nm,rn. 147
9. or/1-8 6743
10. exp asthma/ 141601
11. asthma*.ti,ab,kf. 180248
12. 10 or 11 200291
13. (severe or eosinophil* or allerg* or type 2 or T2).ti,ab,kf. 1761191
14. exp Eosinophilia/ 27256
15. 13 or 14 1765364
16. 12 and 15 78179
17. 9 and 16 2752
18. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt. 689435
19. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt. 609848
20. Multicenter Study.pt. 333420
21. Clinical Studies as Topic/ 782
22. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/ 1271981
23. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/ 352706
24. Randomization/ 106927
25. Random Allocation/ 106927
26. Double-Blind Method/ 175065
27. Double Blind Procedure/ 0

28. Double-Blind Studies/ 175065
29. Single-Blind Method/ 32682
30. Single Blind Procedure/ 0
31. Single-Blind Studies/ 32682
32. Placebos/ 35926
33. Placebo/ 0
34. Control Groups/ 1936
35. Control Group/ 1936
36. Cross-Over Studies/ or Crossover Procedure/ 55047
37. (random* or sham or placebo*).ti,ab,hw,kf. 1798183
38. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 266193
39. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 1582
40. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf. 1911610
41. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.1422796
42. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. 54080
43. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf. 176614
44. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf. 76401
45. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf. 405419
46. allocated.ti,ab,hw. 82977
47. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. 44243
48. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. 11909
49. (pragmatic study or pragmatic studies).ti,ab,hw,kf. 596
50. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. 7616
51. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. 11997
52. trial.ti,kf. 304877
53. or/18-52 3769161
54. exp animals/ 26345052
55. exp animal experimentation/ 10316
56. exp models animal/ 639361
57. exp animal experiment/ 10316
58. nonhuman/ 0
59. exp vertebrate/ 25603896
60. or/53-59 26851439

61. exp humans/ 21226470
62. exp human experiment/ 0
63. or/61-62 21226470
64. 60 not 63 5624969
65. 53 not 64 2867628
66. (systematic review or meta-analysis).pt. 309498
67. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/ 347491
68. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. 313818
69. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf. 15390
70. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf. 38315
71. (data synthes* or data extraction* or data abstraction*).ti,ab,kf. 39741
72. (handsearch* or hand search*).ti,ab,kf. 11067
73. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf. 35193
74. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 12007
75. (meta regression* or metaregression*).ti,ab,kf. 14284
76. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 459513
77. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. 335574
78. (cochrane or (health adj2 technology assessment) or evidence report).jw. 21358
79. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf. 17358
80. (outcomes research or relative effectiveness).ti,ab,kf. 11151
81. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 4290
82. (multi* adj3 treatment adj3 comparison*).ti,ab,kf. 291
83. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. 178
84. umbrella review*.ti,ab,kf. 1420
85. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 13
86. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf. 18
87. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 11

88. or/66-87 672747
89. 65 or 88 3298948
90. 17 and 89 1078
91. limit 90 to (english language and yr="2018 -Current") 528
92. 91 not conference abstract.pt. 528

Embase

OVID Embase 1974 to May 12, 2023

Searched May 12, 2023

1. (nucala* or mepolizumab* or bosatria* or SB240563 or SB-240563 or 90Z2UFOE52).ti,ab,kw,dq. 2533
2. *mepolizumab/ 1422
3. *dupilumab/ 3135
4. (dupilumab* or dupixent* or regn668 or regn 668 or sar231893 or sar 231893).ti,ab,kw,dq. 4338
5. *benralizumab/ 863
6. (Fasenra* or benralizumab* or BIW 8405 or BIW8405 or medi563 or medi 563).ti,ab,kw,dq. 1412
7. *omalizumab/ 4294
8. (Xolair* or omalizumab* or rhuMab-E25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901).ti,ab. 6698
9. *tezepelumab/ or (tezepelumab* or Tezspire* or amg-157 or amg157 or medi-9929 or medi9929 or medi-19929 or medi19929 or GTPL-8933 or GTPL8933).ti,ab,kf,dq. 294
10. or/1-9 13479
11. exp asthma/ 301745
12. asthma*.ti,ab,kw,dq. 267302
13. 11 or 12 341205
14. (severe or eosinophil* or allerg* or type 2 or T2).ti,ab,kw,dq. 2583236
15. exp Eosinophilia/ 66689
16. exp Eosinophil count/ 21990
17. or/14-16 2604229
18. 13 and 17 146121
19. 10 and 18 6866
20. randomized controlled trial/ 783392
21. randomization/ 99019
22. controlled clinical study/ 469226
23. (meta-anal$ or metaanal$).mp. 449740

24. ((systematic$ adj3 review$) or (systematic adj3 overview$)).mp. 566702
25. or/20-24 1767760
26. 19 and 25 1137
27. limit 26 to english language 1124
28. limit 27 to yr="2018 -Current" 723
29. 28 not conference abstract.pt. 336

Europe PMC

https://europepmc.org

Searched May 1, 2023

((TITLE:"nucala*" OR TITLE:"mepolizumab*" OR TITLE:"bosatria*" OR TITLE:"Xolair*" OR TITLE:"omalizumab*" OR TITLE:"dupilumab*" OR TITLE:"dupixent*" OR TITLE:"Fasenra*" OR TITLE:"benralizumab*" OR TITLE:"Tezepelumab" OR TITLE:"Tezspire") AND (TITLE:asthma* AND (TITLE:"severe" OR TITLE:"eosinophil*" OR TITLE:"allerg*" OR TITLE:"type 2" OR TITLE:"T2"))) AND (((SRC:MED) NOT (PUB_TYPE:"Review"))) AND (FIRST_PDATE:[2018 TO 2023])

Cochrane Library

Searched March 24, 2023, Tezepelumab searched April 13, 2023

Cochrane Reviews

(nucala* or mepolizumab* or bosatria* or Xolair* or omalizumab* or dupilumab* or dupixent* or Fasenra* or benralizumab*) AND (asthma* AND (severe or eosinophil* or allerg* or type 2 or T2))

Year: 2018 to 2023

Language: English

(Tezepelumab or Tezspire) AND (asthma* AND (severe or eosinophil* or allerg* or type 2 or T2)

Year: 2018 to 2023

Language: English

Cochrane Central Register of Controlled Trials

Issue 2 of 12, February 2023

Year: 2018 to 2023

Language: English

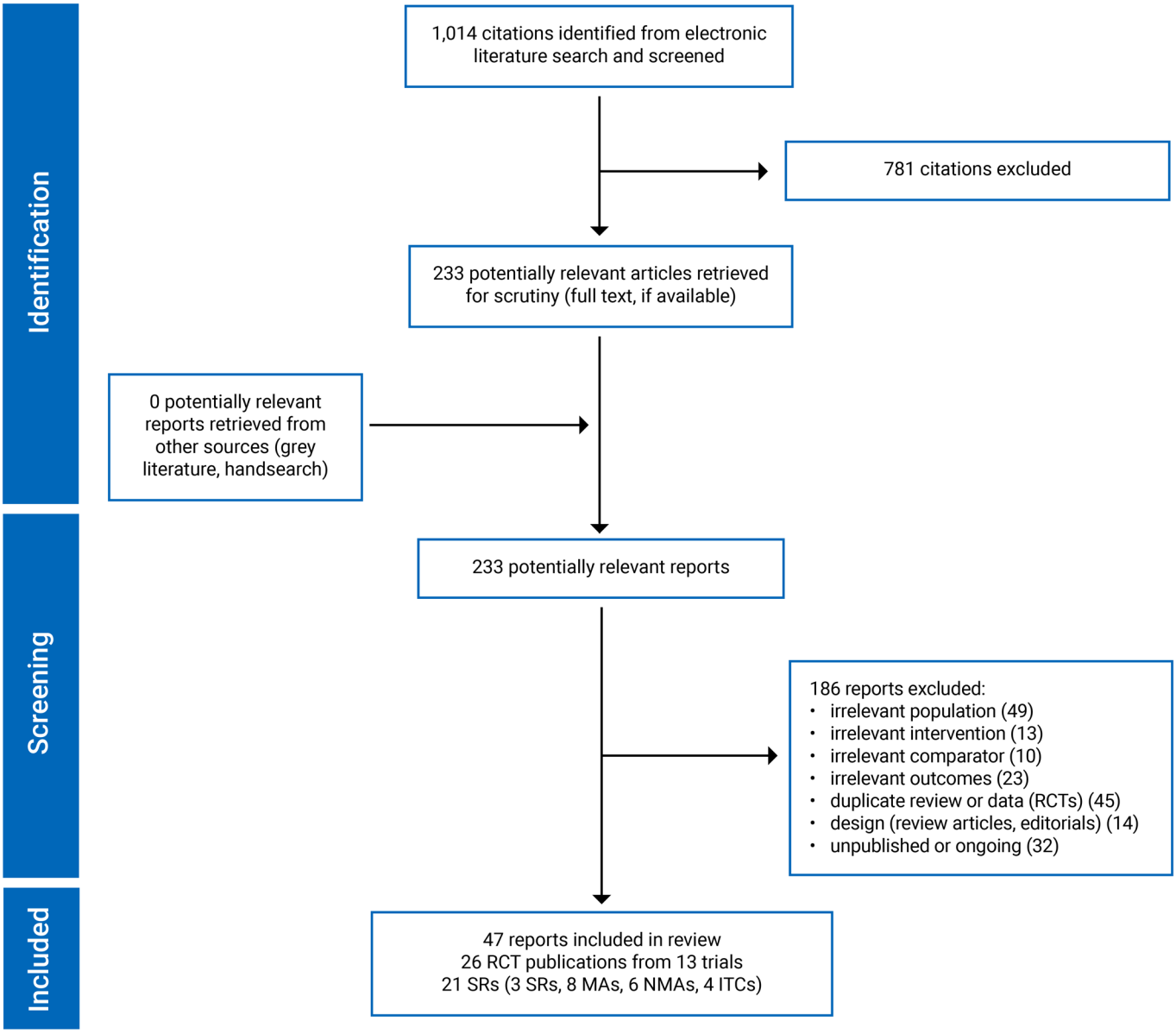
(nucala* or mepolizumab* or bosatria* or Xolair* or omalizumab* or dupilumab* or dupixent* or Fasenra* or benralizumab*) in Title Abstract Keyword AND asthma* in Title Abstract Keyword AND (severe or eosinophil* or allerg* or type 2 or T2) in Title Abstract Keyword NOT post-hoc or posthoc or post hoc in Title Abstract Keyword - (Word variations have been searched)

(Tezepelumab or Tezspire) in Title Abstract Keyword AND asthma* AND (severe or eosinophil* or allerg* or type 2 or T2) in Title Abstract Keyword NOT post-hoc or posthoc or post hoc in Title Abstract Keyword - with Publication Year from 2018 to 2023, with Cochrane Library publication date Between Jan 2018 and Jan 2023, in Trials (Word variations have been searched)

Appendix 3: Selection of Included Studies

Note that this appendix has not been copy-edited.

Figure 2: PRISMA Diagram



ITC = indirect treatment comparison; MA = meta-analysis; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review.

Appendix 4: Included Reports

Note that this appendix has not been copy-edited.

Included RCTs

Albers FC, Licskai C, Chanez P, et al. Baseline blood eosinophil count as a predictor of treatment response to the licensed dose of mepolizumab in severe eosinophilic asthma. *Respir Med.* 2019;159:105806. PubMed

Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. *European Respiratory Journal.* 2018;52(4):10. PubMed

Brusselle G, Quirce S, Papi A, et al. Dupilumab efficacy in patients with uncontrolled or oral corticosteroid-dependent allergic and nonallergic asthma. *J Allergy Clin Immunol Pract.* 2023;11(3):873-884 e811. PubMed

Chipps BE, Newbold P, Hirsch I, Trudo F, Goldman M. Benralizumab efficacy by atopy status and serum immunoglobulin E for patients with severe, uncontrolled asthma. *Ann Allergy Asthma Immunol.* 2018;120(5):504-511.e504. PubMed

Corren J, Ambrose CS, Griffiths JM, et al. Efficacy of tezepelumab in patients with evidence of severe allergic asthma: Results from the phase 3 NAVIGATOR study. *Clin Exp Allergy.* 2023;53(4):417-428. PubMed

Corren J, Ambrose CS, Salapa K, et al. Efficacy of tezepelumab in patients with severe, uncontrolled asthma and perennial allergy. *J Allergy Clin Immunol Pract.* 2021;9(12):4334-4342.e4336. PubMed

Corren J, Chen S, Callan L, Garcia Gil E. The impact of tezepelumab on hospitalization and emergency department visits in patients with severe uncontrolled asthma: results from the pathway phase 2b trial. *Am J Resp Crit Care Med.* 2019;199(9).

Corren J, Garcia Gil E, Griffiths JM, et al. Tezepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma in PATHWAY. *Ann Allergy Asthma Immunol.* 2021;126(2):187-193. PubMed

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Included Systematic Reviews

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Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy of omalizumab in children, adolescents, and adults with severe allergic asthma: a systematic review, meta-analysis, and call for new trials using current guidelines for assessment of severe asthma. *Allergy Asthma Clin Immunol.* 2020;16:49. PubMed

Lee J, Song J-U, Kim YH. The clinical efficacy of type 2 inflammation-specific agents targeting interleukins in reducing exacerbations in severe asthma: a meta-analysis. *Yonsei Med Jl.* 2022;63(6):511-519. PubMed

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Praetorius K, Henriksen DP, Schmid JM, et al. Indirect comparison of efficacy of dupilumab versus mepolizumab and omalizumab for severe type 2 asthma. *ERJ Open Res.* 2021;7(3). PubMed

Ramonell RP, Iftikhar IH. Effect of anti-IL5, anti-IL5R, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. *Lung.* 2020;198(1):95-103. PubMed

Shaban Abdelgalil M, Ahmed Elrashedy A, Awad AK, et al. Safety and efficacy of tezepelumab vs. placebo in adult patients with severe uncontrolled asthma: a systematic review and meta-analysis. *Sci Rep.* 2022;12(1):20905. PubMed

Zoumot Z, Al Busaidi N, Tashkandi W, et al. Tezepelumab for patients with severe uncontrolled asthma: a systematic review and meta-analysis. *J Asthma Allergy.* 2022;15:1665-1679. PubMed

Appendix 5: Co-Occurrence of Included RCTs

Table 7: Co-Occurrence of Included RCTs in This Review Within the Included Systematic Reviews

Author Year	Included RCTs										
	ANDHI	EXTRA	LIBERY ASTHMA VENTURE	MENSA/ MUSCA	NAVI-GATOR	NCT 01202903	NCT 02049294	PATHWAY	SIROCCO/ CALIMA	SOLANA	SOURCE
Abdelgalil 2022[61]	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	NO
AGACHE 2020a[16]	NO	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO
AGACHE 2020b[15]	NO	YES	NO	NO	NO	YES	NO	NO	YES	NO	NO
AGACHE 2020c[44]	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO
Akenroye 2022[45]	YES	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO
Ando 2022[46]	YES	NO	NO	YES	YES	NO	NO	NO	YES	YES	NO
Bateman 2022[47]	NO	YES	NO	YES	NO	NO	NO	NO	YES	NO	NO
Bourdin 2020[48]	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO	NO
Busse 2019[49]	NO	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO
Chagas 2023[50]	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	YES
Chen 2019[51]	NO	NO	NO	YES	NO	NO	NO	NO	YES	NO	NO
Henriksen 2018[52]	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO	NO

Author Year	Included RCTs										
	ANDHI	EXTRA	LIBERY ASTHMA VENTURE	MENSA/ MUSCA	NAVI-GATOR	NCT 01202903	NCT 02049294	PATHWAY	SIROCCO/ CALIMA	SOLANA	SOURCE
Henriksen 2020[53]	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Lee 2022[54]	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES	NO
Mahdavian 2019[55]	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO
Mahdavian 2020[56]	NO	NO	NO	NO	NO	NO	NO	NO	YES	NO	NO
Menzies-gow 2022[57]	YES	NO	NO	YES	YES	NO	NO	YES	YES	NO	NO
Nopsopon 2023[58]	YES	NO	NO	YES	YES	NO	NO	YES	YES	NO	NO
Praetorius 2021[59]	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO
Ramonell 2020[60]	NO	NO	YES	YES	NO	NO	NO	NO	YES	NO	NO
Zoumot 2022[62]	NO	NO	NO	NO	YES	NO	NO	YES	NO	NO	YES

Notes: This table has not been copy-edited.

Yes indicates RCT is included in listed review. No indicates RCT is not included in that review.

Appendix 6: Studies Conducted in Moderate to Severe Asthma

Note that this appendix has not been copy-edited.

Systematic Reviews

Ando K, Tanaka A, Sagara H. Comparative efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma: a systematic review. *Int J of Mol Sci.* 2020;21(3):30. PubMed

Edris A, Lahousse L. Monoclonal antibodies in type 2 asthma: an updated network meta-analysis. *Minerva Medica.* 2021;112(5):573-581. PubMed

Farne HA, Wilson A, Milan S, Banchoff E, Yang F, Powell CV. Anti-IL-5 therapies for asthma. *Cochrane Database Syst Rev.* 2022;7:CD010834. PubMed

Fenu G, La Tessa A, Calogero C, Lombardi E. Severe pediatric asthma therapy: omalizumab-a systematic review and meta-analysis of efficacy and safety profile. *Front Ped.* 2022;10:1033511. PubMed

Fu Z, Xu Y, Cai C. Efficacy and safety of omalizumab in children with moderate-to-severe asthma: a meta-analysis. *J Asthma.* 2021;58(10):1350-1358. PubMed

Iftikhar IH, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung.* 2018;196(5):517-530. PubMed

Li J, Yang J, Kong L, et al. Efficacy and safety of omalizumab in patients with moderate-to-severe asthma: An analytic comparison of data from randomized controlled trials between Chinese and Caucasians. *Asian Pac J Allergy Immunol.* 2022;40(3):223-231. PubMed

Liu L, Zhou P, Wang Z, Zhai S, Zhou W. Efficacy and safety of omalizumab for the treatment of severe or poorly controlled allergic diseases in children: a systematic review and meta-analysis. *Front Pediatr.* 2022;10:851177. PubMed

Liu W, Ma X, Zhou W. Adverse events of benralizumab in moderate to severe eosinophilic asthma: A meta-analysis. *Medicine.* 2019;98(22):e15868. PubMed

Meng X, Gan J, Liu G, Qin E, Ning H. Efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: A meta-analysis. *Int J Clin Exp Med.* 2018;11(3):1483-1489.

Pitre T, Jassal T, Angjeli A, et al. A comparison of the effectiveness of biologic therapies for asthma: a systematic review and network meta-analysis. *Ann Allergy Asthma Immunol.* 2022. PubMed

Tian BP, Zhang GS, Lou J, Zhou HB, Cui W. Efficacy and safety of benralizumab for eosinophilic asthma: a systematic review and meta-analysis of randomized controlled trials. *J Asthma.* 2018;55(9):956-965. PubMed

Xiong XF, Zhu M, Wu HX, Fan LL, Cheng DY. Efficacy and safety of dupilumab for the treatment of uncontrolled asthma: a meta-analysis of randomized clinical trials. *Respiratory Research.* 2019;20(1):108. PubMed

Yan K, Balijepalli C, Sharma R, et al. Reslizumab and mepolizumab for moderate-to-severe poorly controlled asthma: an indirect comparison meta-analysis. *Immunotherapy.* 2019;11(17):1491-1505. PubMed

Zaazouee MS, Alwarraqi AG, Mohammed YA, et al. Dupilumab efficacy and safety in patients with moderate to severe asthma: A systematic review and meta-analysis. *Front Pharmacol.* 2022;13:992731. PubMed

Randomized Controlled Trials

Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. *New Engl J Med.* 2021;385(24):2230-2240. PubMed

Bansal A, Simpson E, L. Paller ASS, E. C. Blauvelt, A., et al. Conjunctivitis in dupilumab clinical trials for adolescents with atopic dermatitis or asthma. *Am J Clin Dermatol.* 2021;22(1):101-115. PubMed

Bourdin A, Papi AA, Corren J, et al. Dupilumab is effective in type 2-high asthma patients receiving high-dose inhaled corticosteroids at baseline. *Allergy: Eur J Allergy Clin Immunol.* 2021;76(1):269-280. PubMed

Busse WW, Humbert M, Haselkorn T, et al. Effect of omalizumab on lung function and eosinophil levels in adolescents with moderate-to-severe allergic asthma. *Ann Allergy Asthma Immunol.* 2020;124(2):190-196. PubMed

Canonica GW, Bourdin A, Peters AT, et al. Dupilumab demonstrates rapid onset of response across three type 2 inflammatory diseases. *J Allergy Clin Immunol Pract.* 2022;10(6):1515-1526. PubMed

Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med.* 2018;378(26):2486-2496. PubMed

Castro M, Rabe KF, Corren J, et al. Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. *Erj Open Research.* 2020;6(1). PubMed

Cheng L, Yang T, Ma X, Han Y, Wang Y. Effectiveness and safety studies of omalizumab in children and adolescents with moderate-to-severe asthma. *J Pharm Pract.* 2021:8971900211038251. PubMed

Corren J, Castro M, Chanez P, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Ann Allergy Asthma Immunol.* 2019;122(1):41-49.e42. PubMed

Corren J, Castro M, O'Riordan TH, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):516-526. PubMed

Corren J, Katelaris CH, Castro M, et al. Effect of exacerbation history on clinical response to dupilumab in moderate-to-severe uncontrolled asthma. *Eur Resp J.* 2021;58(4):10. PubMed

Diver S, Khalfaoui L, Emson C, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Resp Med.* 2021;9(11):1299-1312. PubMed

Hanania NA, Castro M, Bateman E, et al. Efficacy of dupilumab in patients with moderate-to-severe asthma and persistent airflow obstruction. *Ann Allergy Asthma Immunol.* 2023;130(2):206-214.e202. PubMed

Jackson DJ, Bacharier LB, Gergen PJ, et al. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet.* 2022;400(10351):502-511. PubMed

Rogers L, Holweg CT, Pazwash H et al. Age of asthma onset does not impact the response to omalizumab. *Chron Respir Dis.* 2023:20(5):14799731231159673. PubMed

Maspero JF, Cardona G, Schonffeldt P, et al. Dupilumab efficacy and safety in Latin American patients with uncontrolled, moderate-to-severe asthma: phase 3 LIBERTY ASTHMA QUEST study. *J Asthma.* 2022:1-10. PubMed

Maspero JF, Katelaris CH, Busse WW, et al. Dupilumab Efficacy in Uncontrolled, Moderate-to-Severe Asthma with Self-Reported Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract.* 2020;8(2):527-539.e529. PubMed

Papi A, Corren J, Castro M, et al. Dupilumab reduced impact of severe exacerbations on lung function in patients with moderate-to-severe type 2 asthma. *Allergy: Eur J Allergy Clin Immunol.* 2023;78(1):233-243. PubMed

Rabe KF, FitzGerald JM, Bateman ED, et al. Dupilumab is effective in patients with moderate-to-severe uncontrolled GINA-defined type 2 asthma irrespective of an allergic asthma phenotype. *J Allergy Clin Immunol Pract.* 2022;10(11):2916-2924. PubMed

Rhee CK, Park JW, Park HW, Cho YS. Effect of dupilumab in Korean patients with uncontrolled moderate-to-severe asthma: a LIBERTY ASTHMA QUEST Sub-analysis. *Allergy Asthma Immunol Res.* 2022;14(2):182-195. PubMed

Szefler SJ, Casale TB, Haselkorn T, et al. Treatment benefit with omalizumab in children by indicators of asthma severity. *J Allergy Clin Immunol Pract.* 2020;8(8):2673-2680.e2673. PubMed

Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. *New Engl J Med.* 2021;385(18):1656-1668. PubMed

Appendix 7: List of Major Trials for Biologics and Trials

Note that this appendix has not been copy-edited.

Table 8: List of Major Trials for Biologics and Trials Included in the Systematic Reviews, Including Out-of-Scope Trials, and Their Broad Inclusion Criteria

Biologic	Trial name	Age	Asthma typology		Extension study
			Severity	Type[a]	
Benralizumab	ANDHI[b, c]	Adults	Severe	Eosinophilic	No
Benralizumab	BORA	Adults and children	Severe	Eosinophilic	Yes
Benralizumab	CALIMA[b, c]	Adults and children	Severe	None	No
Benralizumab	SIROCCO[b, c]	Adults and children	Severe	None	No
Benralizumab	SOLANA[b]	Adults	Severe	Eosinophilic	No
Benralizumab	ZONDA[c]	Adults	Severe	Eosinophilic	No
Dupilumab	DRI12544[c]	Adults	Moderate to severe	None	No
Dupilumab	LIBERTY ASTHMA QUEST[c]	Adults and children	Uncontrolled persistent	None	No
Dupilumab	LIBERTY ASTHMA VENTURE[b, c]	Adults and children	Severe	OCS dependent	No
Dupilumab	Phase IIb[c]	Adults	Uncontrolled persistent	None	No
Dupilumab	TRAVERSE	Adults and children	Moderate to severe	None	Yes
Dupilumab	VOYAGE	Children	Moderate to severe	None	No
Mepolizumab	DREAM[c]	Adults and children	Severe	Eosinophilic	No
Mepolizumab	Haldar 2009[c]	Adults	Refractory	Eosinophilic	No
Mepolizumab	MENSA[b, c]	Adults	Severe	Eosinophilic	No
Mepolizumab	MUSCA[b, c]	Adults and children	Severe	Eosinophilic	No
Mepolizumab	NCT01691508[c]	Adults and Children	Severe	Eosinophilic	No
Mepolizumab	NCT02281318[c]	Adults and Children	Severe	Eosinophilic	No
Mepolizumab	SIRIUS[c]	Adults	Severe	Eosinophilic	No
Omalizumab	008, 009 and 011[c]	Adults and children	Moderate to severe	Allergic	No

Biologic	Trial name	Age	Asthma typology		Extension study
			Severity	Type[a]	
Omalizumab	AERO[c]	Adults	Moderate	Allergic	No
Omalizumab	ALTO	Adults and children	Moderate to severe	Allergic	No
Omalizumab	Ayres 2009 [c]	Adults and children	Moderate to severe	Allergic	No
Omalizumab	Bardelas 2012[c]	Adults and children	Inadequately controlled asthma	Allergic	No
Omalizumab	Bousquet 2011[c]	Adults and children	Severe	Allergic	No
Omalizumab	Buhl 2001[c]	Adults and children	Moderate to severe	Allergic	No
Omalizumab	Busse 2001[c]	Adults and children	Severe	Allergic	No
Omalizumab	EXTRA[b, c]	Adults	Severe	Allergic	No
Omalizumab	Hoshino 2012[c]	Adults	Severe	Allergic	No
Omalizumab	ICATA[c]	Children	Persistent	Allergic	No
Omalizumab	INNOVATE[c]	Adults and children	Moderate to severe	Allergic	No
Omalizumab	Holgate 2004[c]	Adults and children	Severe	Allergic	No
Omalizumab	Lanier 2009[c]	Children	Moderate to severe	Allergic	No
Omalizumab	Massanair 2009[c]	Adults and children	Moderate to severe	Allergic	No
Omalizumab	NCT00079937[c]	Children	Moderate to severe	Allergic	No
Omalizumab	NCT00264849[c]	Adults and children	Severe	Allergic	No
Omalizumab	NCT00454051[c]	Adult	Severe	Allergic	No
Omalizumab	NCT01202903[b, c]	Adult	Moderate to severe/ severe	Allergic	No
Omalizumab	NCT02049294[b]	Adult	Severe	Allergic	No
Omalizumab	PROSE[c]	Children	Moderate to severe	Allergic	No
Omalizumab	QUALITX[c]	Adults and children	Severe	Allergic	No
Omalizumab	Soler 2001[c]	Adults and children	Moderate to severe	Allergic	No
Omalizumab	Vignola 2004[c]	Adults and children	Moderate to severe	Allergic	No
Tezepelumab	CASCADE	Adults	Moderate to severe	None	No

Biologic	Trial name	Age	Asthma typology		Extension study
			Severity	Type[a]	
Tezepelumab	DESTINATION	Adults and children	Severe	None	Yes
Tezepelumab	NAVIGATOR[b, c]	Adults and children	Severe	None	No
Tezepelumab	PATHWAY[b, c]	Adults	Severe	None	No
Tezepelumab	SOURCE[b, c]	Adults	Severe	OCS dependent	No

OCS = oral corticosteroids.

[a]Asthma type is the target study population of the trial. "None" indicates that a specific subtype of asthma was not specifically recruited.

[b]Trial included in randomized controlled trial portion of this report.

[c]Trial included in 1 or more systematic reviews included in this report.

Appendix 8: Supplementary Tables and Figures

Note that this appendix has not been copy-edited.

Table 9: Inclusion Criteria of the Included RCTs

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
Benralizumab	ANDHI[31] NCT03170271	Eosinophilic	A history of physician-diagnosed asthma requiring treatment with medium-to-high dose Inhaled Corticosteroids (ICS) plus asthma controller, for at least 12 months before visit 1. Documented current treatment with high daily doses of ICS plus at least 1 other asthma controller for at least 3 months before visit 1. History of at least 2 asthma exacerbations while on ICS plus another asthma controller that required treatment with systemic corticosteroids (IM, IV, or oral) in the 12 months before visit 1. ACQ6 score ≥ 1.5 at visit 1. Screening pre-bronchodilator (pre-BD) FEV_1 of < 80% predicted at visit 2. Excessive variability in lung function by satisfying ≥ 1 of the following criteria: Airway reversibility (FEV_1 ≥ 12%) using a short-acting bronchodilator demonstrated at visit 2 or visit 3. Airway reversibility to short-acting bronchodilator (FEV_1 ≥ 12%) documented during the 12 months before enrolment visit 1. Daily diurnal peak flow variability of > 10% when averaged more than 7 continuous days during the study run-in period An increase in FEV_1 of ≥ 12% and 200 mL after a therapeutic trial of systemic corticosteroid (e.g., OCS), given outside of an asthma exacerbation, documented in the 12 months prior enrolment visit 1. Airway hyperresponsiveness (methacholine: PC20 of < 8 mg/mL, histamine: PD20 of < 7.8 µmol, mannitol: decrease in FEV_1 as per the labelled product instructions) documented in the 24 months before randomization visit 4. Peripheral blood eosinophil count either: 300 cells/µL assessed by central laboratory at either visit 1 or visit 2 OR ≥ 150 to < 300 cells/µL assessed by central laboratory at either visit 1 or visit 2, IF ≥ 1 of the following 5 clinical criteria is met: Using maintenance OCS (daily or every other day OCS requirement to maintain asthma control; maximum total daily dose 20 mg prednisone or equivalent) at screening History of nasal polyposis Age of asthma onset ≥ 18 years Three or more documented exacerbations requiring systemic

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			corticosteroid treatment during the 12 months before screening Pre-bronchodilator forced vital capacity < 65% of predicted, as assessed at visit 2 (note that screening pre-BD FEV Inclusion Criterion #6 must still be satisfied)
Benralizumab	SIROCCO/CALIMA [11,21,23,33] NCT01928771/ NCT01914757	Severe asthma NOS	Provision of informed consent before any study specific procedures Female and male aged 12 to 75 years, inclusively, at the time of visit 1 History of physician-diagnosed asthma requiring treatment with medium-to-high dose ICS (> 250mcg fluticasone dry powder formulation equivalents total daily dose) and a LABA, for at least 12 months before visit 1. Documented treatment with ICS and LABA for at least 3 months Patients with baseline blood eosinophil counts < 300 cells/ µL and ≥ 300 cells/ µL were recruited at a ratio of approximately 2:1, respectively.
Benralizumab	SOLANA[39] NCT02869438	Eosinophilic	Documented current treatment with ICS and LABA for at least 30 days before visit 1. The ICS and LABA can be parts of a combination product or given by separate inhalers. The ICS dose must be greater than or equal to 500 mcg/day fluticasone propionate dry powder formulation or equivalent daily. Additional asthma controller medications, e.g., oral corticosteroids, long-acting antimuscarinics (LAMAs), LTRAs, theophylline. are allowed if they have been used for at least 30 days before visit 1. History of at least 2 asthma exacerbations that required treatment with systemic corticosteroids (intramuscular, IV, or oral) in the 12 months before visit 1. For patients receiving corticosteroids as a maintenance therapy, the corticosteroid treatment for the exacerbation is defined as a temporary increase of their maintenance dose. Pre-bronchodilator (pre-BD) FEV_1 of < 80% predicted at visit 2 or visit 3 ACQ-6 score ≥ 1.5 at visit 1 Evidence of asthma as documented by airway reversibility (FEV_1 ≥ 12% and 200 mL) demonstrated at visit 1, visit 2, or visit 3. For patients entering the body plethysmography substudy, reversibility must be demonstrated at visit 1 or at visit 2 only. Peripheral blood eosinophil count of ≥ 300 cells/µL assessed by central lab at visit 1. Weight of ≥ 40 kg
Dupilumab	LIBERTY ASTHMA VENTURE[22,29,41] NCT02528213	Severe Asthma NOS	Participants with severe asthma and a well-documented, regular prescribed treatment of maintenance corticosteroids in the 6 months before visit 1 and using a stable OCS dose (i.e., no change of OCS dose) for 4 weeks before visit 1. Participants must be taking 5 to 35 mg/day of prednisone/prednisolone, or the equivalent, at visit 1 and at the randomization visit. In

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			addition, the participants must agree to switch to study-required prednisone/prednisolone as their OCS and use it per protocol for the duration of the study. Existing treatment with high-dose inhaled corticosteroid (ICS; > 500 mcg total daily dose of fluticasone propionate or equivalent) in combination with a second controller (i.e., long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA]) for at least 3 months with a stable dose of ICS for > = 1 month before visit 1. In addition, participants requiring a third controller for their asthma are considered eligible for this study, and it should also be used for at least 3 months with a stable dose > = 1 month before visit 1. A forced expiratory volume in 1 second (FEV_1) < 80% of predicted normal for adults and < = 90% of predicted normal for adolescents at visit 1. Evidence of asthma as documented by either: reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 mcg (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization or documented in the 12 months before visit 1 OR airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC20] of < 8 mg/mL) documented in the 12 months before visit 1. Weight > = 30.0 kg
Mepolizumab	MENSA/MUSCA [20,32,34,40,42] NCT02281318/ NCT01691521	Eosinophilic	At least 12 years of age at visit 1 and a minimum weight of 45 kg (kg) A well-documented requirement for regular treatment with high-dose inhaled corticosteroid (ICS) in the 12 months before visit 1 with or without maintenance oral corticosteroids Current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months Prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma At visit 1, a pre-bronchodilator FEV_1 < 80% (for participants > = 18 years of age), a pre-bronchodilator FEV_1 < 90% or FEV_1: FVC ratio < 0.8 (for participants 12 to 17 years of age). Previously confirmed history of 2 or more exacerbations requiring treatment with systemic CS
Omalizumab	EXTRA[30] NCT00314574	Allergic	Have had a history of moderate to severe asthma for at least one year before screening. Have had treatment with a stable regimen of salmeterol 50 mcg twice a day (BID) or formoterol 12 mcg BID for at least 8 weeks before screening Have had treatment with a stable regimen of high-dose inhaled

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			corticosteroids (ICS) for at least 8 weeks before screening Have inadequately controlled asthma Have had at least one asthma exacerbation requiring systemic corticosteroid rescue in the 12 months before the screening visit while receiving treatment with high-dose ICS Have a positive skin test for or a positive, in vitro response to one relevant perennial aeroallergen documented within the 12 months before screening If a patient has not had a positive skin test or in vitro reactivity in the 12 months before screening, the patient must demonstrate a positive response to at least one relevant perennial aeroallergen in a skin or in vitro test before randomization
Omalizumab	NCT01202903[35]	Allergic	Patients who met the following criteria at the time of screening (visit 1) and visit 2 were eligible for inclusion in this study: • Written informed consent was obtained before any assessment was performed, including any adjustments to medication during the screening period. • Age 18 to 75 years inclusive • Serum baseline total immunoglobulin E level ≥ 30 to ≤ 700 IU/mL and body weight > 20 kg and ≤ 150 kg. Patients with a total immunoglobulin E level of ≤ 76 IU/mL required an unequivocal positive RAST or ImmunoCAP test to be eligible. • Confirmed diagnosis of asthma for a duration of ≥ 1 year at screening, and a history of asthma that was not adequately controlled with GINA (2009) Step-4 therapy. • Receiving medium- to high-dose inhaled corticosteroid > 500 mcg beclomethasone, or equivalent, plus regularly inhaled long-acting Beta agonist, either separately or in combination, for at least 8 weeks before screening • Meet 1 of the following asthma exacerbations eligibility criteria before the screening period. All exacerbations required the use of additional systemic steroids and/or IV theophylline (aminophylline) to qualify: ◦ Had at least 2 reported exacerbations in the previous 12 months OR ◦ Three reported exacerbations in the previous 24 months; 1 of these exacerbations had to have occurred in the previous 12 months OR ◦ Had been admitted to hospital as an inpatient (including intensive care unit) or received urgent care as an outpatient (including emergency room or observational room treatment) in the past 12 months for an asthma exacerbation. • During any 1 week of the 4-week stable dose run-in period (immediately before randomization), patients exhibited inadequate symptom control as demonstrated by one or more of the following (in keeping with GINA [2009]

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			guidelines): ◦ Daytime symptoms more than twice per week (i.e., ≥ 3 times in a 7-day period) ◦ Any limitation on activity ◦ Any nocturnal symptoms or awakenings ◦ Need for reliever/rescue treatment more than twice per week (i.e., ≥ 3 times in a 7-day period) ◦ High variance in daily PEF (mean of the daily variance over a 1-week period was ≥ 20%) • Positive reaction to at least 1 perennial aeroallergen (e.g., dog, cat, cockroach [whole body], dust mite [Dermatophagoides farinae, D. pteronyssinus]) as documented by a historical skin prick test within 12 months before screening, or at visit 1. Alternatively, if no positive skin prick test was available, or there was no historical record of reaction to cockroach, then a positive RAST or ImmunoCAP test to at least one relevant perennial aeroallergen was required at screening. • Demonstrated ≥ 12% (and 200 mL) increase in FEV1 within 30 minutes after taking salbutamol/albuterol. If during the visit 1 reversibility assessment, change in FEV1 was ≥ 8% and < 12%, then the patient was considered as 'suitable for re-assessment and could repeat the assessment at visit 2 • FEV1 ≥ 40% and < 80% of the predicted normal value for the patient (using local standards), after withholding bronchodilators) at visit 2 • Compliance with completion of PEF/eDiary during the run-in period – compliance was defined as ≥ 85% of the PEF assessments and ≥ 85% of the morning or evening eDiary sessions completed correctly in the 28 days before randomization. At the investigators' discretion, the run-in period could be extended to ensure that at least 85% of the PEF/eDiary data were collected over a 28-day period
Omalizumab	NCT02049294[38]	Allergic	Patients with confirmed asthma (12% bronchodilator reversibility or PC20 methacholine less than 8 mg/mL), atopy (skin prick test positive to common aeroallergens and elevated serum immunoglobulin E levels), who were symptomatic (ACQ-5 ≥ 1.5) with evidence of sputum eosinophils (> 3%) despite high-dose maintenance corticosteroid therapy.
Tezepelumab	NAVIGATOR[9,24,36,37] NCT03347279	Severe asthma NOS	Age 12 to 80 Documented physician-diagnosed asthma for at least 12 months Participants who have received a physician-prescribed asthma controller medication with medium- or high-dose ICS for at least 12 months. Documented treatment with a total daily dose of either medium or high dose ICS (≥ 500 mcg fluticasone propionate dry powder

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			formulation equivalent total daily dose) for at least 3 months. At least one additional maintenance asthma controller medication is required according to standard practice of care and must be documented for at least 3 months. Morning pre-BD FEV_1 < 80% predicted normal (< 90% for participants 12 to 17 yrs.) Evidence of asthma as documented by either: Documented historical reversibility of FEV_1 ≥ 12% and ≥ 200 mL in the previous 12 months OR Post-BD (albuterol/salbutamol) reversibility of FEV_1 ≥ 12% and ≥ 200 mL during screening. Documented history of at least 2 asthma exacerbation events within 12 months. ACQ-6 score ≥ 1.5 at screening and on day of randomization
Tezepelumab	PATHWAY[9,25-28] NCT02054130	Severe Asthma NOS	Body mass index between 18 and 40 kg/m^2 and weight greater than or equal 40 kg Documented physician-diagnosed asthma – Participants must have received a physician-prescribed asthma controller regimen with medium- or high-dose inhaled corticosteroids (ICS) plus long-acting Beta2 agonist (LABA). If on asthma controller medications in addition to ICS plus LABA, the dose of the other asthma controller medications (leukotriene receptor inhibitors, theophylline, secondary ICS, long-acting antimuscarinics (LAMA), cromones, or maintenance oral prednisone or equivalent up to a maximum of 10 mg daily or 20 mg every other day for the maintenance treatment of asthma) must be stable. Participants must have a documented history of at least 2 asthma exacerbation events OR at least 1 severe asthma exacerbation resulting in hospitalization within the 12 months before first study visit.
Tezepelumab	SOURCE[37,43] NCT03406078	Severe Asthma NOS	Participants were aged 18 to 80 years with physician-diagnosed asthma, who had been receiving medium-dose inhaled corticosteroids (daily dose of 250 to 500 mcg fluticasone propionate or equivalent) or high-dose inhaled corticosteroids (daily dose of > 500 mcg fluticasone propionate or equivalent) for at least 12 months before screening. Participants who were receiving medium-dose inhaled corticosteroids must have had their dose increased to a high dose for at least 3 months before screening. Participants must have been receiving a long-acting beta 2 agonist with or without additional controller medications for at least 3 months before screening. Participants must have been receiving oral corticosteroids for the treatment of asthma for at least 6 months before screening and must have been taking a stable dose of prednisone or prednisolone 7·5 to 30 mg daily or daily equivalent for at least 1 month before screening. Participants must also have had at least 1 asthma exacerbation (defined as a worsening of asthma symptoms that led to either hospitalization, an emergency department visit that resulted

Intervention	Trial	Asthma enrolment criteria/subtype[a]	Inclusion criteria
			in the use of systemic corticosteroids for ≥ 3 consecutive days, or requirement for systemic corticosteroids for ≥ 3 consecutive days) in the 12 months before screening. Morning pre-bronchodilator FEV_1 must have been less than 80% of the predicted normal value at visit 1 (week – 10) or visit 2 (week – 8). Post-bronchodilator FEV_1 reversibility of at least 12% and at least 200 mL must have been documented during the 12 months before screening or visit 1 or visit 2.

ACQ = Asthma Control Questionnaire; BD = bronchodilator; BID = medication taken twice a day; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; IU = international unit; LABA = long-acting beta agonist; LAMA = long-acting antimuscarinics; LTRA = Leukotriene receptor agonist; OCS = oral corticosteroid; PEF = peak expiratory flow.

[a]Population determined by whether trial required participants to have biomarkers for allergic asthma (allergic), eosinophilic asthma (eosinophilic), or were admitted solely based on having severe asthma (severe asthma).

Table 10: RCT Intervention Characteristics by Biologic, RCT, Enrolled Asthma Subtype, and Patient Subgroup

Intervention	RCT	Asthma subtype enrolled	Patient subgroup	Dosage	Treatment duration
Benralizumab	ANDHI[31] NCT03170271	Eosinophilic[a]	Adults	30 mg Q4W	24 weeks
Benralizumab	SIROCCO/ CALIMA[11,21,23,33] NCT01928771/ NCT01914757	Severe Asthma NOS[b]	Adults and Children	30 mg Q4W or Q8W	48 to 56 weeks
Benralizumab	SOLANA[39] NCT02869438	Eosinophilic[a]	Adults	30 mg Q4W	12 weeks
Dupilumab	LIBERTY ASTHMA VENTURE[22,29,41] NCT02528213	Severe Asthma NOS[b]	Adults and Children	300 mg SC Q2W	24 weeks
Mepolizumab	MENSA/MUSCA[20,32, 34,40,42] NCT02281318/ NCT01691521	Eosinophilic[a]	Adults and Children	100 mg SC Q4W	24 to 32 weeks
Omalizumab	EXTRA[30] NCT00314574	Allergic[c]	Adults and Children	0.008 mg/kg/IgE Q2W or 0.016 mg/kg/IgE Q4W	48 weeks
Omalizumab	NCT01202903[35]	Allergic[c]	Adults	0.008 mg/kg/IgE Q2W or 0.016 mg/kg/IgE Q4W	24 weeks
Omalizumab	NCT02049294[38]	Allergic[c]	Adults	0.008 mg/kg/IgE Q2W or 0.016 mg/kg/IgE Q4W	32 weeks
Tezepelumab	NAVIGATOR[9,24,36,37] NCT03347279	Severe Asthma NOS[b]	Adults and Children	210 mg SC Q4W	52 weeks

Intervention	RCT	Asthma subtype enrolled	Patient subgroup	Dosage	Treatment duration
Tezepelumab	PATHWAY[9,25-28] NCT02054130	Severe Asthma NOS[b]	Adults	70/210 mg SC Q4W or 280 mg SC Q2W	50 weeks
Tezepelumab	SOURCE[37,43] NCT03406078	Severe Asthma NOS[b]	Adults	210 mg SC Q4W	48 weeks

IgE = immunoglobulin E; NOS = not otherwise specified; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

[a]Eosinophilic asthma studies recruited patients based on a minimum eosinophil biomarker level, but may also include patients with concurrent allergic asthma.

[b]Severe asthma NOS patients recruited based on the severity of asthma without additional requirements for biomarkers of allergic or eosinophilic asthma.

[c]Allergic asthma studies included patients with a minimum classification of allergic asthma determined by allergic biomarkers, but may also include other subtypes that are not mutually exclusive.

Table 11: Concomitant Medications in RCTs Described in Clinical Trials Registry and/or Publications

Intervention	RCT	Concomitant medications
Benralizumab	ANDHI[31] NCT03170271	ICS plus 1 other controller medication
Benralizumab	SIROCCO/CALIMA[11,21,23,33] NCT01928771/NCT01914757	ICS, LABA, with or without OCS and additional controllers
Benralizumab	SOLANA[39] NCT02869438	ICS and LABA Other asthma controller medications are allowed if they have been used for at least 30 days at time of trial start
Dupilumab	LIBERTY ASTHMA VENTURE[22,29,41] NCT02528213	OCS, ICS, plus second controller
Mepolizumab	MENSA/MUSCA[20,32,34,40,42] NCT02281318, NCT01691521	ICS plus an additional controller, OCS allowed
Omalizumab	EXTRA[30] NCT00314574	ICS, LABA, permitted to use albuterol as rescue medicine
Omalizumab	NCT01202903[35]	no co-medications were discussed
Omalizumab	NCT02049294[38]	ICS/OCS
Tezepelumab	NAVIGATOR[9,24,36,37] NCT03347279	Participants continued to receive their prescribed controller medications throughout the study. Step-down of oral corticosteroid or inhaled corticosteroids could be done at the discretion of the study physician using the GINA protocol guidance for changes to background asthma medication
Tezepelumab	PATHWAY[9,25-28] NCT02054130	ICS, LABA, other controller medications allowed if dosage is stable
Tezepelumab	SOURCE[37,43] NCT03406078	oral corticosteroid Medium- to high-dose ICS LABA, LAMA with or without additional control medications

GINA = Global Initiative for Asthma; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LAMA = long-acting antimuscarinics; OCS = oral corticosteroid.

Table 12: RCT-Specific Asthma Exacerbation Definitions From Clinical Trial Registry and/or Publication

Intervention	RCT	Asthma exacerbation definition
Benralizumab	ANDHI[31]	An asthma exacerbation was defined as a worsening of asthma that led to any of the following: • Use of systemic corticosteroids (or temporary increase in stable oral corticosteroids background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids. • An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above). • An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a health care facility for ≥ 24 hours) due to asthma.
Benralizumab	SIROCCO/CALIMA[11,21,23,33]	An exacerbation was defined as a worsening of asthma that led to 1 of the following: use of systemic corticosteroids (or temporary increase in a stable oral corticosteroid background dosage) for at least 3 days or a single depot-injectable dose of corticosteroid; an asthma-related emergency department or urgent care visit (duration < 24 hour) that required use of systemic corticosteroids; or an asthma-related inpatient hospital admission (duration ≥ 24 hours).
Benralizumab	SOLANA[39]	Requiring systemic corticosteroid therapy or a temporary increase in maintenance oral corticosteroid dosage within 12 months before enrolment.
Dupilumab	LIBERTY ASTHMA VENTURE[22,29,41]	A severe asthma exacerbation event was defined as a deterioration of asthma during the 24-week treatment period requiring: use of systemic corticosteroids for ≥ 3 days (at least double the dose currently used); and/or hospitalization related to asthma symptoms or emergency room visit because of asthma requiring intervention with a systemic corticosteroid treatment. Annualized event rate was the total number of exacerbations that occurred during the treatment period divided by the total number of participant-years treated.
Mepolizumab	MENSA/MUSCA[20,32,34,40,42]	Clinically significant exacerbations of asthma are defined as worsening of asthma which required use of systemic corticosteroids (IV or oral steroid like prednisone, for at least 3 days or a single intramuscular corticosteroid dose is required. For maintenance of systemic corticosteroids, at least double the existing maintenance dose for at least 3 days was required) and/or hospitalization and/or emergency department visits.
Omalizumab	EXTRA[30]	A protocol-defined asthma exacerbation was defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids for 3 or more days; for patients receiving long-term oral corticosteroids, an exacerbation was a 20 mg or more increase in average daily dose of oral prednisone (or a similar dose of another systemic corticosteroid). The rate of protocol-defined asthma exacerbations, normalized by subject-time at risk and computed over the 48-week treatment period in each treatment group.
Omalizumab	NCT01202903[35]	Not specified
Omalizumab	NCT02049294[38]	Not specified

Intervention	RCT	Asthma exacerbation definition
Tezepelumab	NAVIGATOR[9,24,36,37]	Defined for trial eligibility and end point measures as a worsening of asthma symptoms that led to hospitalization, an emergency department visit that resulted in the use of systemic glucocorticoids for ≥ 3 consecutive days, or the use of systemic glucocorticoids for ≥ 3 consecutive days
Tezepelumab	PATHWAY[9,25-28]	Asthma exacerbation is defined as worsening of asthma that leads to any of the following: use of systemic corticosteroids for at least 3 days, an emergency department visit due to asthma that required systemic corticosteroids, and an inpatient hospitalization due to asthma. The annual annualized exacerbation rate was presented as the total number of exacerbations for the treatment group divided by the total duration of person follow-up.
Tezepelumab	SOURCE[37,43]	Worsening of asthma symptoms that led to either hospitalization, an emergency department visit that resulted in the use of systemic corticosteroids for ≥ 3 consecutive days, or requirement for systemic corticosteroids for ≥ 3 consecutive days

Table 13: Main Study Outcomes

RCT	Asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospitalization	Mortality
Intervention								
Benralizumab								
ANDHI[31]	Eosino-philic	Adult	++	++	ACQ ++	+	NR	NR
SIROCCO/ CALIMA[11,21,23,33]	Severe Asthma NOS	Adult and Children	++	++	ACQ ++, AQLQ ++	NR	NR	NR
SOLANA[39]	Eosino-philic	Adult	NR	+	ACQ ++	+	NR	NR
Dupilumab								
LIBERTY ASTHMA VENTURE[22,29,41]	Severe Asthma NOS	Adult and Children	++	++	ACQ ++	-	NR	NR
Mepolizumab								
MENSA/ MUSCA [20,32,34,40,42]	Eosino-philic	Adult and Children	++	++	ACQ ++	NR	NR	NR
Omalizumab								
EXTRA[30]	Allergic	Adult and Children	++	++	NR	NR	NR	NR
NCT01202903[35]	Allergic	Adult	NR	++	ACQ +, AQLQ ++	NR	NR	NR
NCT02049294[38]	Allergic	Adult	+	+	ACQ +	NR	NR	NR

RCT	Asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospitalization	Mortality
Tezepelumab								
NAVIGATOR [9,24,36,37]	Severe Asthma NOS	Adult and Children	++	++	ACQ ++, AQLQ ++	+	++	NR
PATHWAY [9,25-28]	Severe Asthma NOS	Adult	++	++	ACQ ++, AQLQ ++	NR	++	NR
SOURCE [3 7,43]	Severe Asthma NOS	Adult	+	++	ACQ-6 ++, AQLQ ++	+	NR	NR

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related quality of life; NOS = not otherwise specified; NR = not reported.

Note: Asthma enrolment criteria indicates whether a specific type of asthma patients was sampled. + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, and an additional + or - indicates whether this effect was statistically significant. All RCTs compared biologics as an add-on to standard of care against standard of care plus a placebo.

Table 14: Outcomes Reported for Each Asthma Subgroup

Intervention	RCT	Patient subgroup	Non–Type 2	Type 2				
				EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	Eosinophilic NOS	Allergic NOS
Benralizumab	ANDHI [31]	Adults	No	No	No	No	Yes	No
Benralizumab	SIROCCO/ CALIMA [11,21,23,33]	Adults and Children	Yes	Yes	Yes	Yes	Yes	Yes
Benralizumab	SOLANA [39]	Adults	No	Yes	No	Yes	Yes	No
Dupilumab	LIBERTY ASTHMA VENTURE [22,29,41]	Adults and Children	No	No	No	No	Yes	Yes
Mepolizumab	MENSA/ MUSCA [20,32,34,40,42]	Adults and Children	No	Yes	No	Yes	Yes	No
Omalizumab	EXTRA [30]	Adults and Children	No	No	No	No	No	Yes
Omalizumab	NCT01202903 [35]	Adults	No	No	Yes	Yes	No	Yes
Omalizumab	NCT02049294 [38]	Adults	No	No	No	No	No	Yes
Tezepelumab	NAVIGATOR [9,24,36,37]	Adults and Children	Yes	Yes	Yes	Yes	Yes	Yes
Tezepelumab	PATHWAY [9,25-28]	Adults	No	No	No	No	Yes	Yes
Tezepelumab	SOURCE [37,43]	Adults	No	No	No	No	Yes	No

ALL = allergic; EOS = eosinophilic; NOS = not otherwise specified.

Note: YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup.

Table 15: Included Systematic Review Summary Table

Author year	Design	PICO population[a]	Population	Intervention	# of results	# primary trials	# Patients
Abdelgalil 2022[61]	MA	Severe asthma[b]	Adults	Tezepelumab	1	4	1,600
Agache, 2020a[16]	SR	Severe asthma[b]	Adults and Children	Benralizumab	1	3	2,731
Agache, 2020a[16]	SR	Severe asthma[b]	Adults and Children	Dupilumab	1	3	2,888
Agache, 2020a[16]	SR	Severe asthma[b]	Adults and Children	Mepolizumab	1	3	1,262
Agache, 2020a[16]	SR	Severe asthma[b]	Adults and Children	Omalizumab	1	5	2,127
Agache, 2020b[15]	SR	Allergic	Adults and Children	Benralizumab	1	3	3,208
Agache, 2020b[15]	SR	Allergic	Adults and Children	Dupilumab	1	1	1,083
Agache, 2020b[15]	SR	Allergic	Adults and Children	Omalizumab	1	NR	NR
Agache, 2020b[15]	SR	Allergic	Children	Omalizumab	1	NR	NR
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	Dupilumab	6	3	2,888
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	B, D, M	3	8	7,592
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	Benralizumab	3	3	3,166
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	Dupilumab	3	2	2,678
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	Mepolizumab	3	3	1,748
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	B, D, M, T	5	8	4,671
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	Benralizumab	5	4	2,574
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	D, T	4	2	1,161
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	Dupilumab	9	1	633
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	Mepolizumab	5	2	936
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	Tezepelumab	9	1	528

Author year	Design	PICO population[a]	Population	Intervention	# of results	# primary trials	# Patients
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	B, D, M, O	1	12	7,550
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	Benralizumab	1	3	2,173
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	Dupilumab	1	2	2,367
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	Mepolizumab	1	3	1,435
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	Omalizumab	1	4	1,575
Bourdin 2020[48]	MAIC	Severe asthma[b]	Adults and Children	B, D, M	1	3	565
Bourdin 2020[48]	MAIC	Severe asthma[b]	Adults and Children	Benralizumab	1	1	220
Bourdin 2020[48]	MAIC	Severe asthma[b]	Adults and Children	Dupilumab	1	1	210
Bourdin 2020[48]	MAIC	Severe asthma[b]	Adults and Children	Mepolizumab	1	1	135
Busse 2019[49]	ITC	Eosinophilic	Adults and Children	B, M	4	4	2473
Busse 2019[49]	ITC	Eosinophilic	Adults and Children	Benralizumab	3	2	1,537
Busse 2019[49]	ITC	Eosinophilic	Adults and Children	Mepolizumab	3	2	936
Chagas 2023[50]	MA	Severe asthma[b]	Adults and Children	Tezepelumab	1	3	1,484
Chen 2019[51]	NMA	Severe asthma[b]	Adults and Children	B, M	1	8	4,049
Chen 2019[51]	NMA	Severe asthma[b]	Adults and Children	Benralizumab	1	3	2,515
Chen 2019[51]	NMA	Severe asthma[b]	Adults and Children	Mepolizumab	1	5	1,534
Henriksen 2018[52]	MA	Eosinophilic	Adults	Mepolizumab	1	8	1,244
Henriksen 2020[53]	MA	Allergic	Adults and Children	Omalizumab	2	16	3,729
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	Benralizumab	3	3	1,687
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	Dupilumab	3	3	2,735
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	Mepolizumab	1	5	1,822

Author year	Design	PICO population[a]	Population	Intervention	# of results	# primary trials	# Patients
Mahdavian 2019[55]	MA	Eosinophilic	Adults and Children	Benralizumab	1	4	3,081
Mahdavian 2020[56]	MA	Severe asthma[b]	Adults and Children	Benralizumab	3	3	2,730
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	B, D, M, O, T	1	16	NR
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	B, D, O	1	27	NR
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	Benralizumab	4	6	6,405
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	D, T	2	6	NR
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	Dupilumab	6	3	2,888
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	Mepolizumab	3	3	1,262
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	Omalizumab	2	18	5,080
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	Tezepelumab	6	3	1,759
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	B, D, M, T	1	10	9,201
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	Benralizumab	1	3	3,166
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	Dupilumab	1	2	2,678
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	Mepolizumab	1	3	1,748
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	Tezepelumab	1	2	1,609
Praetorius 2021[59]	ITC	Eosinophilic	Adults and Children	D, M	1	7	NR
Praetorius 2021[59]	ITC	Eosinophilic	Adults and Children	D, M, O	1	23	NR
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	B, D, M	1	8	2,701
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	Benralizumab	1	2	1,021
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	Dupilumab	1	4	744

Author year	Design	PICO population[a]	Population	Intervention	# of results	# primary trials	# Patients
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	Mepolizumab	1	2	936
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	Tezepelumab	12	6	2,667

B = benralizumab; D = dupilumab; ITC = Indirect treatment comparison; M = mepolizumab; MA = meta-analysis; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; NR = not reported O = omalizumab; PICO = population, intervention, comparison, outcomes; SR = systematic review; t = tezepelumab

Note: Initials indicate that a comparative effectiveness analysis was performed for those biologics.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 16: RCT Outcomes by Asthma Subtype

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention														
Benralizumab														
eosinophilic[39]	Adults	NR	+	NR	NR	NR	NR	8	No	Yes	No	Yes	Yes	No
Eosinophilic[31]	Adults	+	+	ACQ +	NR	NR	NR	1	No	No	No	No	Yes	No
Eosinophilic[39]	Adults	NR	+	ACQ ++	+	NR	NR	1	No	No	No	No	Yes	No
Eosinophilic[31]	Adults	++	++	ACQ ++	NR	NR	NR	3	No	No	No	No	Yes	No
Eosinophilic[31]	Adults	++	++	ACQ ++	+	NR	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	NR	NR	NR	NR	NR	6	No	Yes	No	Yes	No	Yes
Severe asthma NOS[11,21,23,33]	Adults and Children	+	-	NR	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	+	-	ACQ +, AQLQ +	NR	NR	NR	1	No	No	Yes	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	-	NR	NR	NR	NR	2	No	No	Yes	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	+	+	ACQ +	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	+	NR	NR	NR	NR	3	Yes	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	+	ACQ +, AQLQ ++	NR	NR	NR	1	Yes	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	++	NR	NR	NR	NR	9	No	Yes	No	Yes	Yes	Yes

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[11,21,23,33]	Adults and Children	++	++	ACQ ++	NR	NR	NR	2	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	++	++	ACQ ++, AQLQ ++	NR	NR	NR	6	No	Yes	No	Yes	Yes	No
Dupilumab														
Severe asthma NOS[22,29,41]	Adults and Children	++	+	NR	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[22,29,41]	Adults and Children	++	+	ACQ ++, AQLQ++	NR	NR	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[22,29,41]	Adults and Children	++	++	NR	NR	NR	NR	5	No	No	No	No	Yes	No
Severe asthma NOS[22,29,41]	Adults and Children	++	++	ACQ ++, AQLQ +	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[22,29,41]	Adults and Children	++	++	ACQ ++	-	NR	NR	1	No	No	No	No	No	No
Mepolizumab														
Eosinophilic [20,32,34,40,42]	Adults and Children	-	NR	ACQ-5 +	NR	NR	NR	1	No	Yes	No	No	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	+	NR	NR	NR	NR	NR	1	No	Yes	No	No	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	+	NR	ACQ-5 -	NR	NR	NR	2	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	+	NR	ACQ-5 +	NR	NR	NR	3	No	Yes	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	NR	NR	NR	NR	NR	14	No	Yes	No	Yes	Yes	No

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Eosinophilic [20,32,34,40,42]	Adults and Children	++	NR	ACQ-5 +	NR	NR	NR	3	No	Yes	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	NR	ACQ-5 ++	NR	NR	NR	5	No	Yes	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	NR	NR	ACQ-5 +	NR	NR	NR	2	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	NR	NR	NR	NR	NR	NR	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	+	+	ACQ ++	NR	NR	NR	1	No	No	No	No	Yes	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	+	ACQ +	NR	NR	NR	4	No	Yes	No	Yes	Yes	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	+	ACQ ++	NR	NR	NR	2	No	No	No	No	Yes	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	++	ACQ +	NR	NR	NR	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	++	++	ACQ ++	NR	NR	NR	8	No	Yes	No	No	Yes	No
Omalizumab														
Allergic [35]	Adults	NR	NR	ACQ ++, AQLQ ++	NR	NR	NR	1	No	No	No	No	No	Yes
Allergic [35]	Adults	NR	NR	ACQ +, AQLQ +	NR	NR	NR	2	No	No	No	No	No	Yes
Allergic [35]	Adults	NR	++	ACQ +, AQLQ ++	NR	NR	NR	1	No	No	No	No	No	Yes

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Allergic[35]	Adults	NR	NR	ACQ = , AQLQ -	NR	NR	NR	1	No	No	No	No	No	Yes
Allergic[35]	Adults	NR	+	ACQ -, AQLQ +	NR	NR	NR	1	No	No	No	Yes	No	No
Allergic[35]	Adults	NR	+	ACQ +, AQLQ +	NR	NR	NR	1	No	No	Yes	No	No	No
Allergic[35]	Adults	NR	+	ACQ +, AQLQ ++	NR	NR	NR	1	No	No	Yes	No	No	No
Allergic[38]	Adults	+	+	ACQ +	NR	NR	NR	1	No	No	No	No	No	Yes
Allergic[35]	Adults	NR	++	AQLQ +	NR	NR	NR	1	No	No	No	Yes	No	No
Allergic[30]	Adults and Children	+	+	NR	NR	NR	NR	2	No	No	No	No	No	Yes
Allergic[30]	Adults and Children	++	+	NR	NR	NR	NR	1	No	No	No	No	No	Yes
Allergic[30]	Adults and Children	++	++	NR	NR	NR	NR	2	No	No	No	No	No	Yes
Tezepelumab														
Severe asthma NOS[9,25-28]	Adults	++	NR	NR	NR	NR	NR	14	No	No	No	No	Yes	Yes
Severe asthma NOS[37,43]	Adults	-	+	ACQ-6 +	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[37,43]	Adults	+	++	ACQ-6 -	NR	NR	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[9,25-28]	Adults	++	++	NR	NR	NR	NR	2	No	No	No	No	No	Yes

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[37,43]	Adults	++	++	ACQ-6 +	NR	NR	NR	2	No	No	No	No	Yes	No
Severe asthma NOS[9,25-28]	Adults	++	++	ACQ ++, AQLQ ++	NR	++	NR	1	No	No	No	No	No	No
Severe asthma NOS[37,43]	Adults	+	++	ACQ-6 ++, AQLQ ++	+	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[37,43]	Adults	++	++	ACQ ++	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	+	NR	NR	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	NR	NR	NR	NR	NR	5	No	No	No	No	No	Yes
Severe asthma NOS[9,24,36,37]	Adults and Children	NR	-	NR	NR	NR	NR	2	No	No	Yes	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	+	-	NR	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	-	NR	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	+	NR	NR	NR	NR	1	Yes	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	+	ACQ ++, AQLQ ++	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	+	ACQ +, AQLQ +	NR	NR	NR	2	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	NR	++	NR	NR	NR	NR	2	No	Yes	No	No	No	No

Intervention and asthma subtype enrolled	Patient subgroup	AEX	FEV_1	HRQoL	Safety	Hospital-ization	Mortality	# of Results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[9,24,36,37]	Adults and Children	+	++	ACQ ++, AQLQ ++	NR	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	++	NR	NR	NR	NR	9	Yes	No	No	Yes	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	++	++	ACQ ++, AQLQ ++	NR	NR	NR	12	No	No	No	No	Yes	Yes
Severe asthma NOS[9,24,36,37]	Adults and Children	++	++	ACQ ++, AQLQ ++	+	++	NR	1	No	No	No	No	No	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; ALL = Allergic asthma; BEC = blood eosinophil count; EOS = Eosinophilic asthma; FEV_1 = Forced Expiratory Volume in 1 second; HRQoL = Health-related Quality of Life; NOS = not otherwise specified; NR = not reported.

Note: YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup. + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, AND an additional + or - indicates whether this effect was statistically significant.

Table 17: RCT Outcomes by BEC Level Characterization

Intervention and asthma subtype enrolled	Patient subgroup	Classification of eosinophilic asthma	AEX	FEV_1	HRQoL	# of Results	Non–type 2	Type 2				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention												
Benralizumab												
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC < 150	+	-	NR	1	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC < 300	+	+	ACQ +	1	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC > = 150	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Eosinophilic[31]	Adults	BEC > = 150 to < 300	+	+	ACQ +	1	No	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC > = 150 to < 300	++	++	NR	1	No	No	No	No	Yes	No
Eosinophilic[31]	Adults	BEC > = 300	++	++	ACQ ++	1	No	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC > = 300	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Eosinophilic[39]	Adults	BEC > = 300 to 449	NR	+	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC > = 300 to 449	++	+	NR	1	No	No	No	No	Yes	No
Eosinophilic[39]	Adults	BEC > = 450	NR	+	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[11,21,23,33]	Adults and Children	BEC > = 450	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No

Intervention and asthma subtype enrolled	Patient subgroup	Classification of eosinophilic asthma	AEX	FEV_1	HRQoL	# of Results	Non–type 2	Type 2				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Dupilumab												
Severe asthma NOS[22,29,41]	Adults and Children	BEC < 150	++	++	NR	1	No	No	No	No	No	No
Severe asthma NOS[22,29,41]	Adults and Children	BEC < 300	++	+	NR	1	No	No	No	No	No	No
Severe asthma NOS[22,29,41]	Adults and Children	BEC > = 150	++	++	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[22,29,41]	Adults and Children	BEC ≥ 300	++	++	NR	1	No	No	No	No	Yes	No
Mepolizumab												
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC < 150	++	+	ACQ +	1	No	No	No	No	Yes	No
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC > = 150	++	++	ACQ ++	1	No	No	No	No	Yes	No
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC > = 150 to < 300	+	+	ACQ ++	1	No	No	No	No	Yes	No
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC > = 300	++	++	ACQ ++	1	No	No	No	No	Yes	No
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC > = 300 to 499	++	+	ACQ ++	1	No	No	No	No	Yes	No
Eosinophilic[20,32,34,40,42]	Adults and Children	BEC > = 500	++	++	ACQ ++	1	No	No	No	No	Yes	No
Tezepelumab												
Severe asthma NOS[37,43]	Adults	BEC < 150	-	+	ACQ-6 +	1	No	No	No	No	No	No
Severe asthma NOS[9,25-28]	Adults	BEC < 150	++	NR	NR	1	No	No	No	No	No	No

Intervention and asthma subtype enrolled	Patient subgroup	Classification of eosinophilic asthma	AEX	FEV_1	HRQoL	# of Results	Non–type 2	Type 2				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC < 150	++	+	ACQ +, AQLQ +	1	No	No	No	No	No	No
Severe asthma NOS[9,25-28]	Adults	BEC < 300	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC < 300	++	+	ACQ ++, AQLQ ++	1	No	No	No	No	No	No
Severe asthma NOS[9,25-28]	Adults	BEC > = 150	++	NR	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[37,43]	Adults	BEC > = 150	++	++	ACQ-6 +	1	No	No	No	No	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC > = 150	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe asthma NOS[37,43]	Adults	BEC > = 150 to < 300	+	++	ACQ-6 -	1	No	No	No	No	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC > = 150 to < 300	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe asthma NOS[9,25-28]	Adults	BEC > = 300	++	NR	NR	1	No	No	No	No	Yes	No
Severe asthma NOS[37,43]	Adults	BEC > = 300	++	++	ACQ-6 +	1	No	No	No	No	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC > = 300	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC > = 300 to 449	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe asthma NOS[9,24,36,37]	Adults and Children	BEC > = 450	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; ALL = Allergic asthma; BEC = blood eosinophil count; EOS = Eosinophilic asthma; FEV_1 = Forced Expiratory Volume in 1 second; HRQoL = Health-related Quality of Life; NOS = not otherwise specified; NR = not reported.

Note: YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup. + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, and an additional + or - indicates whether this effect was statistically significant. No results for hospitalization or mortality outcomes were reported.

Table 18: RCT Outcomes by Fractional Exhaled Nitric Oxide Characterization

Intervention and asthma subtype enrolled	Population	FeNO sub-groups	AEX	FEV_1	HRQoL	# of results	Non-type 2	Type 2				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ALL	EOS NOS	All NOS
Intervention												
Tezepelumab												
Severe Asthma NOS[9,25-28]	Adults	FeNO < 25 ppb	++	NR	NR	1	No	No	No	No	No	No
Severe Asthma NOS[9,24,36,37]	Adults and Children	FeNO < 25 ppb	++	+	ACQ +, AQLQ +	1	No	No	No	No	No	No
Severe Asthma NOS[9,25-28]	Adults	FeNO < 50 ppb	++	NR	NR	1	No	No	No	No	No	No
Severe Asthma NOS[9,25-28]	Adults	FeNO > = 25 ppb	++	NR	NR	1	No	No	No	No	Yes	No
Severe Asthma NOS[9,25-28]	Adults and Children	FeNO 25 to < 50 ppb	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe Asthma NOS[9,24,36,37]	Adults	FeNO > = 50 ppb	++	NR	NR	1	No	No	No	No	Yes	No
Severe Asthma NOS[9,24,36,37]	Adults and Children	FeNO > = 50 ppb	++	++	ACQ ++, AQLQ ++	1	No	No	No	No	Yes	No
Severe Asthma NOS[9,24,36,37]	Adults and Children	Extension: FeNO < 25	++	NR	NR	1	No	No	No	No	No	No
Severe Asthma NOS[9,24,36,37]	Adults and Children	Extension: FeNO > = 25	++	NR	NR	1	No	No	No	No	Yes	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; ALL = Allergic asthma; EOS = Eosinophilic asthma; FeNO = fractional exhaled nitric oxide; FEV_1 = Forced Expiratory Volume in 1 second; HRQoL = Health-related Quality of Life; NOS = not otherwise specified; NR = not reported; ppb = parts per billion.

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, AND an additional + or - indicates whether this effect was statistically significant. No results for hospitalization, mortality, or safety outcomes were reported. YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup. FeNO > 25 is used to determine presence of eosinophilic asthma in this table.

Table 19: RCT Outcomes by Omalizumab (Eligibility) Criteria

Asthma subtype enrolled	Population	Omalizumab criteria[a]	AEX	FEV_1	HRQoL	# of Results	Non–type 2	EOS/non-ALL	Non-EOS/ ALL	Type 2 High		
										EOS/ ALL	EOS NOS	ALL NOS
Intervention												
Mepolizumab												
Eosinophilic [20,32,34,40,42]	Adults and Children	EU OMA eligible	++	+	ACQ +	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	EU OMA ineligible	++	++	ACQ ++	1	No	Yes	No	No	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	US OMA eligible	++	++	ACQ +	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	US OMA ineligible	++	++	ACQ ++	1	No	Yes	No	No	No	No
Tezepelumab												
severe asthma NOS[9,25-28]	Adults	EU OMA eligible	++	NR	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[9,24,36,37]	Adults and Children	EU OMA eligible	++	NR	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[9,25-28]	Adults	EU OMA ineligible	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	EU OMA ineligible	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,25-28]	Adults	US OMA eligible	++	NR	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[9,24,36,37]	Adults and Children	US OMA eligible	++	NR	NR	1	No	No	No	No	No	Yes

Asthma subtype enrolled	Population	Omalizumab criteria[a]	AEX	FEV_1	HRQoL	# of Results	Non–type 2	EOS/non-ALL	Non-EOS/ ALL	Type 2 High		
										EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[9,25-28]	Adults	US OMA ineligible	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	US OMA ineligible	++	NR	NR	1	No	No	No	No	No	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; ALL = Allergic asthma; EOS = Eosinophilic asthma; FEV_1 = Forced Expiratory Volume in 1 second; HRQoL = Health-related Quality of Life; NOS = not otherwise specified; NR = not reported; OMA = omalizumab.

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, and an additional + or - indicates whether this effect was statistically significant. YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup.

[a]OMA eligible means that the group meets the criteria for prescription of omalizumab in the US or EU based on age and a positive skin test or in vitro reactivity to a perennial allergen in inadequately controlled asthma.

Table 20: RCT Outcomes by Recombined Allergy Status

Intervention and asthma subtype enrolled	Population	Allergic/ atopic[a]	AEX	FEV_1	HRQoL	# of results	Non–type 2	Type 2 High				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention												
Benralizumab												
Severe asthma NOS[11,21,23,33]	Adults and Children	NO	++	NR	NR	1	No	No	No	No	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	NO	++	++	NR	1	No	Yes	No	No	No	No
Eosinophilic[39]	Adults	YES	NR	+	NR	1	No	No	No	Yes	No	No
Severe asthma NOS[11,21,23,33]	Adults and Children	YES	++	NR	NR	1	No	No	No	No	No	Yes

Intervention and asthma subtype enrolled	Population	Allergic/ atopic[a]	AEX	FEV_1	HRQoL	# of results	Non–type 2	Type 2 High				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Severe asthma NOS[11,21,23,33]	Adults and Children	YES	++	++	NR	2	No	No	No	No	No	Yes
Dupilumab												
Severe asthma NOS[22,29,41]	Adults and Children	NO	++	++	ACQ ++, AQLQ +	1	No	No	No	No	No	No
Severe asthma NOS[22,29,41]	Adults and Children	YES	++	+	ACQ ++, AQLQ++	1	No	No	No	No	No	Yes
Mepolizumab												
Eosinophilic [20,32,34,40,42]	Adults and Children	NO	++	NR	NR	2	No	Yes	No	No	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	NO	++	+	ACQ +	1	No	Yes	No	No	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	+	NR	ACQ-5 +	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	++	NR	NR	5	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	++	NR	ACQ-5 +	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	++	NR	ACQ-5 ++	4	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	++	+	ACQ +	1	No	No	No	Yes	No	No
Eosinophilic [20,32,34,40,42]	Adults and Children	YES	NR	NR	ACQ-5 +	1	No	No	No	Yes	No	No

Intervention and asthma subtype enrolled	Population	Allergic/ atopic[a]	AEX	FEV_1	HRQoL	# of results	Non–type 2	Type 2 High				
								EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Omalizumab												
Allergic[35]	Adults	YES	NR	NR	ACQ ++, AQLQ ++	1	No	No	No	No	No	Yes
Allergic[35]	Adults	YES	NR	NR	ACQ +, AQLQ +	2	No	No	No	No	No	Yes
Allergic[35]	Adults	YES	NR	NR	ACQ =, AQLQ -	1	No	No	No	No	No	Yes
Tezepelumab												
Severe asthma NOS[9,25-28]	Adults	NO	++	++	NR	1	No	No	No	No	No	No
Severe asthma NOS[9,24,36,37]	Adults and Children	NO	++	++	ACQ ++, AQLQ ++	2	No	No	No	No	No	No
Severe asthma NOS[9,25-28]	Adults	YES	++	NR	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[9,25-28]	Adults	YES	++	++	NR	1	No	No	No	No	No	Yes
Severe asthma NOS[9,24,36,37]	Adults and Children	YES	++	++	ACQ ++, AQLQ ++	2	No	No	No	No	No	Yes

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; ALL = Allergic asthma; EOS = Eosinophilic asthma; FEV_1 = Forced Expiratory Volume in 1 second; HRQoL = Health-related Quality of Life; NOS = not otherwise specified; NR = not reported

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, and an additional + or - indicates whether this effect was statistically significant. YES indicates at least 1 outcome reported for that subgroup. NO indicates that no outcomes were reported for that subgroup.

[a]Allergic/atopic status was determined by a positive on any test for allergic asthma. Different trials tested for allergic sensitivity using different methods.

Table 21: Asthma Exacerbation Definitions From Systematic Reviews

Author year	Asthma exacerbation definition
Abdelgalil 2020[61]	Not specified
Agache, 2020a[16]	Clinically significant asthma exacerbations: episodes of asthma worsening with systemic corticosteroids for 3 or more days, a 2-times increase in the dose of either inhaled corticosteroids or the need for asthma-related emergency treatment. Exacerbation
Agache, 2020b[15]	Clinically significant asthma exacerbation: episodes of asthma worsening requiring treatment with systemic corticosteroids
Agache, 2020c[44]	Severe exacerbation defined as a deterioration of asthma requiring: (a) the use of systemic corticosteroids for ≥ 3 days or (b) hospitalization/emergency room visit because of asthma, requiring systemic corticosteroids
Akenroye 2022[45]	Not specified
Ando 2022[46]	Not specified
Bateman 2022[47]	Definitions listed by study in a table
Bourdin 2020[48]	Not specified
Busse 2019[49]	Clinically significant exacerbations, defined as an exacerbation requiring treatment with oral/systemic corticosteroids (for patients on maintenance oral corticosteroids, a ≥ 2-fold increase in dose was required) or requiring an emergency department visit or hospital
Chagas 2023[50]	Defined as hospitalization, worsening of asthma symptoms that led to either an emergency department visit that resulted in the use of systemic corticosteroids for ≥ 3 consecutive days or use of systemic corticosteroids for ≥ 3 consecutive days
Chen 2019[51]	Not specified
Henriksen 2018[52]	Not specified
Henriksen 2020[53]	Not specified
Lee 2022[54]	Asthma exacerbation was defined as treatment with a course of systemic corticosteroids for at least 3 days irrespective of hospitalization
Mahdavian 2019[55]	Not specified
Mahdavian 2020[56]	Worsening of asthma leading to increase in systemic glucocorticoid dose for ≥ 3 days, emergency department visit due to asthma treated with systemic glucocorticoids additional to the patient's regular maintenance medications, or hospital admission
Menzies-Gow 2022[57]	Overall annualized asthma exacerbation rate, including events that did not require hospital/emergency treatment
Nopsopon 2023[58]	Clinically significant exacerbations
Praetorius 2021[59]	Not specified
Ramonell 2020[60]	Clinical asthma exacerbations were defined as a worsening of asthma that resulted in corticosteroid treatment, emergency department or urgent care, or hospitalization
Zoumot 2022[62]	Not specified

Table 22: Systematic Review Patient Subgroups With Reported Outcomes

Intervention	Population	Non–type 2	Type 2				
			EOS/non-ALL	Non-EOS/ALL	EOS/ALL	EOS NOS	All NOS
Benralizumab[15,16,45-49,51,54-58,60]	Adults and children	No	No	No	No	Yes	Yes
Dupilumab[15,16,45-48,54,57,58,60]	Adults and children	No	No	No	No	Yes	Yes
Mepolizumab[52]	Adults	No	No	No	No	Yes	No
Mepolizumab[16,45-49,51,54,57,58,60]	Adults and children	No	No	No	No	Yes	Yes
Omalizumab[15,16,47,53,57]	Adults and children	No	No	No	No	Yes	Yes
Omalizumab[15]	Children	No	No	No	No	No	Yes
Tezepelumab[61]	Adults	No	No	No	No	No	No
Tezepelumab[46,50,57,58,62]	Adults and children	No	No	No	No	Yes	Yes

ALL = allergic asthma; EOS = eosinophilic asthma; NOS = not otherwise specified.

Note: Cells with YES or NO indicate whether any results were reported for that subgroup by biologic drug and population.

Table 23: Systematic Review and Meta-Analysis Main Outcomes

Author, Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	# of results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention														
Benralizumab														
Agache 2020a[16]	SR	Severe asthma[b]	Adults and Children	++	++	AQLQ ++	-	1	No	No	No	No	No	No
Agache 2020b[15]	SR	Allergic	Adults and Children	++	+	ACQ-6 ++, AQLQ -	-	1	No	No	No	No	No	Yes
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	1	No	No	No	No	No	No
Mahdavian 2019[55]	MA	Eosinophilic	Adults and Children	NR	++	ACQ-6 ++, AQLQ ++	NR	1	No	No	No	No	Yes	No
Mahdavian 2020[56]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	=	1	No	No	No	No	No	No
Dupilumab														
Agache 2020a[16]	SR	Severe asthma[b]	Adults and Children	++	++	ACQ ++, AQLQ ++	-	1	No	No	No	No	No	No
Agache 2020b[15]	SR	Allergic	Adults and Children	++	++	ACQ-5 ++	NR	1	No	No	No	No	No	Yes

Author, Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	# of results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Agache 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	++	ACQ-5: ++, AQLQ: ++	-	1	No	No	No	No	No	No
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	1	No	No	No	No	No	No
Mepolizumab														
Agache 2020a[16]	SR	Severe asthma[b]	Adults and Children	++	++	ACQ ++	- -	1	No	No	No	No	No	No
Henriksen 2018[52]	MA	Eosinophilic	Adults	++	++	ACQ ++, AQLQ ++	++	1	No	No	No	No	Yes	No
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	1	No	No	No	No	No	No
Omalizumab														
Agache 2020a[16]	SR	Severe asthma[b]	Adults and Children	++	++	AQLQ ++	NR	1	No	No	No	No	No	No
Agache 2020b[15]	SR	Allergic	Adults and Children	++	++	ACQ-6 ++, AQLQ ++	-	1	No	No	No	No	No	Yes
Tezepelumab														
Abdelgalil 2022[61]	MA	Severe asthma[b]	Adults	++	++	ACQ-6 ++, AQLQ12 ++	++	1	No	No	No	No	No	No

Author, Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	# of results	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Chagas 2023[50]	MA	Severe asthma[b]	Adults and Children	++	++	ACQ ++, AQLQ ++	++	1	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	+	NR	NR	NR	1	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	2	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	++	++	+	1	No	No	No	No	No	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related Quality of Life; MA = Meta-analysis; NOS = not otherwise specified; NR = Not reported; PICO = population, intervention, comparison, outcomes; S = safety outcomes; SR = Systematic review.

Note: All analyses compared biologic to a placebo. + indicates effect favouring treatment; - indicates effect favouring control; = indicates exact equality of outcome; an additional + or - indicates whether this effect was statistically significant.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 24: Systematic Review and Meta-Analysis Subgroup Outcomes

Author Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	Subgroups	# of results	Non-type 2	Type 2				
											EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention															
Benralizumab															
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC < 300	1	No	No	No	No	No	No
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 300	1	No	No	No	No	Yes	No
Mahdavian 2020[56]	MA	Severe asthma[b]	Adults and Children	-	NR	NR	NR	low BEC	1	No	No	No	No	No	No
Mahdavian 2020[56]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 300 or 150	1	No	No	No	No	Yes	No
Dupilumab															
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	+	NR	NR	FeNO < 25ppb	1	No	No	No	No	No	No
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	++	NR	NR	BEC < 300	1	No	No	No	No	No	No
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	++	NR	NR	BEC > = 300	1	No	No	No	No	Yes	No

Author Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	Subgroups	# of results	Non-type 2	Type 2				
											EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	++	NR	NR	FeNO > = 50 ppb	1	No	No	No	No	No	No
Agache, 2020c[44]	SR	Severe asthma[b]	Adults and Children	++	++	NR	NR	FeNO 25 to < 50 ppb	1	No	No	No	No	No	No
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC < 300	1	No	No	No	No	No	No
Lee 2022[54]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 300	1	No	No	No	No	Yes	No
Omalizumab															
Agache, 2020b[15]	SR	Allergic	Children	++	NR	AQLQ++	NR	6 to 12 years old	1	No	No	No	No	No	Yes
Henriksen 2020[53]	MA	Allergic	Adults and Children	+	NR	ACT*	++	Children	1	No	No	No	No	No	Yes
Henriksen 2020[53]	MA	Allergic	Adults and Children	++	++	ACQ ++, AQLQ ++	+	Adults	1	No	No	No	No	No	Yes
Tezepelumab															
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	Allergic/ Atopic = YES	2	No	No	No	No	No	Yes

Author Year	Design	PICO population[a]	Popu-lation	AEX	FEV_1	HRQoL	S	Subgroups	# of results	Non-type 2	Type 2				
											EOS/ non-ALL	Non-EOS/ ALL	EOS/ ALL	EOS NOS	ALL NOS
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	Allergic/ Atopic = NO	1	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC < 150	1	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 150 to < 300	1	No	No	No	No	Yes	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 300 to 449	1	No	No	No	No	Yes	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	BEC > = 450	1	No	No	No	No	Yes	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	FeNO < 25ppb	1	No	No	No	No	No	No
Zoumot 2022[62]	MA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	FeNO > = 25 ppb	1	No	No	No	No	No	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; ALL = Allergic asthma; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; EOS = Eosinophilic asthma; FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related Quality of Life; ITC = Indirect treatment comparison; MA = Meta-analysis; NMA = network meta-analysis; NOS = not otherwise specified; NR = not reported; ppb = parts per billion; PICO = population, intervention, comparison, outcomes; S = safety outcomes; SR = Systematic review;

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, and an additional + or - indicates whether this effect was statistically significant. All analyses compared biologic to a placebo.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 25: Comparative Efficacy Reviews Main Outcomes

Author Year	Design	PICO population[a]	Population	AEX	FEV_1	HRQoL	S	H	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention														
Benralizumab														
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	NR	NR	NR	++	NR	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	++	++	ACT ++, AQLQ ++	+	NR	No	No	No	No	No	No
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	++	++	NR	NR	NR	No	No	No	No	No	No
Busse 2019[49]	ITC	Eosinophilic	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	Yes	No
Chen 2019[51]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	+	No	No	No	No	No	No
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	++	+	ACQ +	NR	NR	No	No	No	No	Yes	No
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	Yes	No
Dupilumab														
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	NR	NR	NR	=	NR	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	++	++	ACT ++, AQLQ ++	+	NR	No	No	No	No	No	No

Author Year	Design	PICO population[a]	Population	AEX	FEV_1	HRQoL	S	H	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	++	++	NR	NR	NR	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	+	No	No	No	No	No	No
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	++	++	ACQ +	NR	NR	No	No	No	No	Yes	No
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	Yes	No
Mepolizumab														
Akenroye 2022[45]	NMA	Eosinophilic	Adults and Children	NR	NR	NR	++	NR	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	++	++	ACT ++	+	NR	No	No	No	No	No	No
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	++	++	NR	NR	NR	No	No	No	No	No	No
Busse 2019[49]	ITC	Eosinophilic	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	Yes	No
Chen 2019[51]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	+	No	No	No	No	No	No
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	++	+	ACQ +	NR	NR	No	No	No	No	Yes	No
Ramonell 2020[60]	NMA	Eosinophilic	Adults and Children	++	NR	NR	NR	NR	No	No	No	No	Yes	No

Author Year	Design	PICO population[a]	Population	AEX	FEV_1	HRQoL	S	H	Non–type 2	Type 2				
										EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Omalizumab														
Bateman 2022[47]	ITC	Severe asthma[b]	Adults and Children	++	++	NR	NR	NR	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	+	No	No	No	No	No	No
Tezepelumab														
Ando 2022[46]	NMA	Severe asthma[b]	Adults and Children	++	++	ACT ++, AQLQ ++	+	NR	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	Adults and Children	++	NR	NR	NR	++	No	No	No	No	No	No
Nopsopon 2023[58]	NMA	Eosinophilic	Adults and Children	++	++	ACQ ++	NR	NR	NO	No	No	No	Yes	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; ALL = Allergic asthma; AQLQ = Asthma Quality of Life Questionnaire; EOS = Eosinophilic asthma; FEV_1 = forced expiratory volume in 1 second; H = hospitalizations; HRQoL = Health-related Quality of Life; ITC = Indirect treatment comparison; NMA = network meta-analysis; NOS = not otherwise specified; NR = not reported; PICO = population, intervention, comparison, outcomes; S = safety outcomes.

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, an additional + or - indicates whether this effect was statistically significant. All studies made indirect comparisons through the included placebo control groups.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 26: NMA and ITC Subgroup Outcomes

Author Year	Design	Population	PICO population[a]	AEX	FEV_1	HRQoL	Subgroups	Non–type 2	Type 2				
									EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Intervention													
Benralizumab													
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	Allergic: unclear cut-offs	No	No	No	No	No	Yes
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	+	+	NR	BEC < 150	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	+	NR	BEC < 300	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	BEC < 300	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	AQLQ ++	BEC ≥ 150	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Adults and Children	Eosinophilic	++	NR	NR	BEC ≥ 150	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	++	++	NR	BEC ≥ 150 to < 300	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	++	++	ACQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	ACT ++, AQLQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Adults and Children	Eosinophilic	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No

Author Year	Design	Population	PICO population[a]	AEX	FEV_1	HRQoL	Subgroups	Non–type 2	Type 2				
									EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Dupilumab													
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	Allergic: unclear cut-offs	No	No	No	No	No	Yes
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	+	+	NR	BEC < 150	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	+	+	NR	BEC < 300	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	BEC < 300	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	NR	BEC ≥ 150	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	++	+	NR	BEC ≥ 150 to < 300	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	++	++	ACQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	AQLQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	FeNO < 25 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO < 50 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	No	No

Author Year	Design	Population	PICO population[a]	AEX	FEV_1	HRQoL	Subgroups	Non–type 2	Type 2				
									EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	No	No
Mepolizumab													
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	Allergic: unclear cut-offs	No	No	No	No	No	Yes
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	BEC < 150	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC < 300	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 150	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Adults and Children	Eosinophilic	++	NR	NR	BEC ≥ 150	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	+	+	NR	BEC ≥ 150 to < 300	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Adults and Children	Eosinophilic	++	++	ACQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Adults and Children	Eosinophilic	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No

Author Year	Design	Population	PICO population[a]	AEX	FEV_1	HRQoL	Subgroups	Non–type 2	Type 2				
									EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Omalizumab													
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Tezepelumab													
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	Allergic: unclear cut-offs	No	No	No	No	No	Yes
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	+	NR	BEC < 150	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	NR	BEC < 300	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	+	NR	NR	BEC < 300	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	AQLQ ++	BEC ≥ 150	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	++	ACT ++, AQLQ ++	BEC ≥ 300	No	No	No	No	Yes	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO < 25 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO < 50 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	No	No

Author Year	Design	Population	PICO population[a]	AEX	FEV_1	HRQoL	Subgroups	Non–type 2	Type 2				
									EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Adults and Children	Severe asthma[b]	++	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	No	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; ALL = Allergic asthma; AQLQ = Asthma Quality of Life Questionnaire; BEC = blood eosinophil count; EOS = Eosinophilic asthma; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related Quality of Life; ITC = Indirect treatment comparison; NMA = network meta-analysis; NOS = Not otherwise specified; NR = Not reported; PICO = population, intervention, comparison, outcomes; ppb = parts per billion.

Note: The symbol + indicates effect favouring treatment, - indicates effect favouring control, = indicates exact equality of outcome, an additional + or - indicates whether this effect was statistically significant. All studies made indirect comparisons through the included placebo control groups.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 27: NMA, ITC, and MAIC Comparative Effectiveness Main Outcomes

Author Year	Design	PICO population[a]	Intervention	AEX	FEV_1	HRQoL	Safety	Hospitalization
Akenroye 2022[45]	NMA	Eosinophilic	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	NR	BENRA, DUPI, MEPO MEPO > DUPI	NR
Ando 2022[46]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE TEZE > BENRA	BENRA, DUPI, MEPO, TEZE	ACT: BENRA, DUPI, MEPO, TEZE AQLQ: BENRA, DUPI, TEZE	BENRA, DUPI, MEPO, TEZE	NR
Bateman 2022[47]	ITC	Severe asthma[b]	BENRA, DUPI, MEPO, OMA	BENRA, DUPI, MEPO, OMA DUPI > BENRA, MEPO	BENRA, DUPI, MEPO, OMA; DUPI > BENRA	NR	NR	NR

Author Year	Design	PICO population[a]	Intervention	AEX	FEV_1	HRQoL	Safety	Hospitalization
Bourdin 2020[48]	MAIC	Severe asthma[b]	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	NR	NR	NR	NR
Busse 2019[49]	ITC	Eosinophilic	BENRA, MEPO	BENRA, MEPO MEPO > BENRA	NR	ACQ: BENRA, MEPO MEPO > BENRA	NR	NR
Chen 2019[51]	NMA	Severe asthma[b]	BENRA, MEPO	BENRA, MEPO	NR	NR	NR	NR
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, OMA, TEZE	BENRA, DUPI, MEPO, OMA, TEZE	NR	NR	NR	BENRA, DUPI, MEPO, OMA, TEZE
Nopsopon 2023[58]	NMA	Eosinophilic	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE TEZE > BENRA	BENRA, DUPI, MEPO, TEZE	ACQ: BENRA, DUPI, MEPO, TEZE	NR	NR
Praetorius 2021[59]	ITC	Eosinophilic	DUPI, MEPO, OMA	DUPI, MEPO, OMA	DUPI, MEPO, OMA; DUPI > MEPO, OMA	ACQ: DUPI, MEPO, OMA AQLQ: DUPI, MEPO, OMA	DUPI, MEPO, OMA	NR
Ramonell 2020[60]	NMA	Eosinophilic	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	NR	NR	NR	NR

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; AQLQ = Asthma Quality of Life Questionnaire; BENRA = benralizumab; DUPI = dupilumab; FEV_1 = forced expiratory volume in 1 second; H = hospitalization; HRQoL = Health-related Quality of Life; ITC = Indirect treatment comparison; M = mepolizumab; MAIC = Matching-adjusted indirect comparison; NMA = network meta-analysis; NR = Not reported; OMA = omalizumab; PICO = population, intervention, comparison, outcomes; S = safety outcomes; TEZE = tezepelumab.

Note: Biologics tested are indicated by their first initial. If a biologic significantly outperformed 1 or more of the other tested biologics, then the best performing biologic and the statistically inferior biologics are identified using a ">" to mark the superior and inferior biologics (e.g., t > B,O). All studies made indirect comparisons through the included placebo control groups.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the papers.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 28: NMA and ITC Comparative Effectiveness Subgroup Outcomes

Author Year	Design	PICO population[a]	Intervention	AEX	FEV_1	HRQoL	S	H	Subgroups	Non–type 2	Type 2				
											EOS/non-ALL	Non-EOS/ALL	EOS/ALL	EOS NOS	ALL NOS
Akenroye 2022[45]	NMA	Eosinophilic	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	NR	NR	NR	BEC ≥ 150 to < 300	No	No	No	No	Yes	No
Akenroye 2022[45]	NMA	Eosinophilic	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	BENRA, DUPI, MEPO	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, TEZE	NR	NR	NR	BEC < 150	No	No	No	No	No	No
Ando 2022[46]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE; MEPO >BENRA	BENRA, DUPI, TEZE	ACT: BENRA, TEZE AQLQ: BENRA, TEZE	NR	NR	BEC ≥ 150	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO < 25 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO < 50 ppb	No	No	No	No	No	No
Ando 2022[46]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	Yes	No
Ando 2022[46]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	Yes	No

Author Year	Design	PICO population[a]	Intervention	AEX	FEV_1	HRQoL	S	H	Subgroups	Non–type 2	Type 2				
											EOS/non-ALL	Non-EOS/ALL	EOS/ALL	EOS NOS	ALL NOS
Ando 2022[46]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, TEZE	ACT: BENRA, TEZE	NR	NR	BEC < 300	NO	NO	NO	NO	NO	NO
Ando 2022[46]	NMA	Severe asthma[b]	BENRA, DUPI, MEPO, TEZE	BENRA, DUPI, MEPO, TEZE; TEZE > BENRA	BENRA, DUPI, TEZE	ACT: BENRA, TEZE AQLQ: BENRA, DUPI, TEZE	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Eosinophilic	BENRA, MEPO	BENRA, MEPO; MEPO > BENRA	BENRA, MEPO	ACQ: BENRA, MEPO; MEPO > BENRA	NR	NR	BEC ≥ 400	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Eosinophilic	BENRA, MEPO	BENRA, MEPO; MEPO > BENRA	BENRA, MEPO	ACQ: BENRA, MEPO; MEPO >BENRA	NR	NR	BEC ≥ 150	No	No	No	No	Yes	No
Busse 2019[49]	ITC	Eosinophilic	BENRA, MEPO	BENRA, MEPO; MEPO >BENRA	BENRA, MEPO	ACQ: BENRA, MEPO; MEPO >BENRA	NR	NR	BEC ≥ 300	No	No	No	No	Yes	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	BENRA, DUPI, OMA	BENRA, DUPI, OMA	NR	NR	NR	NR	ALL: unclear cut-offs	No	No	No	No	No	Yes

Author Year	Design	PICO population[a]	Intervention	AEX	FEV_1	HRQoL	S	H	Subgroups	Non–type 2	Type 2				
											EOS/ non-ALL	Non-EOS/ALL	EOS/ ALL	EOS NOS	ALL NOS
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO ≥ 25 ppb	No	No	No	No	No	No
Menzies-Gow 2022[57]	NMA	Severe asthma[b]	DUPI, TEZE	DUPI, TEZE	NR	NR	NR	NR	FeNO ≥ 50 ppb	No	No	No	No	Yes	No
Praetorius 2021[59]	ITC	Eosinophilic	DUPI, MEPO	NR	DUPI, MEPO	ACQ: DUPI, MEPO AQLQ: DUPI, MEPO	MEPO >DUPI	NR	OCS: Yes	No	No	No	No	Yes	No

ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; AEX = Asthma exacerbation; ALL = allergic; AQLQ = Asthma Quality of Life Questionnaire; BENRA = benralizumab; BEC = blood eosinophil count; DUPI = dupilumab; EOS = eosinophilic; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related Quality of Life; ITC = Indirect treatment comparison; M = mepolizumab; MAIC = Matching-adjusted indirect comparison; NMA = network meta-analysis; NOS = not otherwise specified; NR = Not reported; OMA = omalizumab; OCS = oral corticosteroids; PICO = population, intervention, comparison, outcomes; ppb = parts per billion; TEZE = tezepelumab.

Note: Biologics tested are indicated by their first initial. If a biologic significantly outperformed 1 or more of the other tested biologics, then the best performing biologic and the statistically inferior biologics are identified using a ">" to mark the superior and inferior biologics (e.g., TEZE > BENRA). All studies made indirect comparisons through the included placebo control groups.

[a]PICO Population is the population of asthma patient targeted for inclusion as described by the publications.

[b]Severe asthma PICO population indicates no specific characterization or inclusion by asthma subtypes.

Table 29: A Measurement Tool to Assess Systematic Reviews Version 2 (AMSTAR 2): Evaluation of the Included Reviews

Author year	AMSTAR 2 question[a]															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Abdelgalil 2022[61]	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
AGACHE 2020a[16]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
AGACHE 2020b[15]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
AGACHE 2020c[44]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Akenroye 2022[45]	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Ando 2022[46]	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Bateman 2022[47]	Yes	Yes	No	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No	No	No
Bourdin 2020[48]	Yes	No	No	No	No	No	No	Yes	No	No	N/A	N/A	No	No	No	No
Busse 2019[49]	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	No	No	No	No
Chagas 2023[50]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	No	No	No
Chen 2019[51]	Yes	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	Yes	Yes	No
Henriksen 2018[52]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Henriksen 2020[53]	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Lee 2022[54]	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Mahdavian 2019[55]	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Mahdavian 2020[56]	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes
Menzies-Gow 2022[57]	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Nopsopon 2023[58]	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Praetorius 2021[59]	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	No	No	No	No	Yes
Ramonell 2020[60]	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes
Zoumot 2022[62]	Yes	No	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes

[a]AMSTAR 2 questions:

Question 1: Did the research questions and inclusion criteria for the review include the component of PICO (population, intervention, comparison, outcomes)?

Question 2: Did the report of the review contain and explicitly state that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?

Question 3: Did the review authors explain their selection of the study designs for inclusion in the review?

Question 4: Did the review authors use a comprehensive literature search strategy?

Question 5: Did the review authors perform study selection in duplicate?

Question 6: Did the review authors perform data extraction in duplicate?

Question 7: Did the reviews authors provide a list of excluded studies and justify the exclusions?

Question 8: Did the review authors describe the included studies in adequate detail?

Question 9: Did the reviews authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?

Question 10: Did the review authors report on the sources of funding for the studies included in the review?

Question 10: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

Question 12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

Question 13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

Question 14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

Question 15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

Question 16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table 30: Summary of Findings and Gaps in Evidence

Biologic	Findings and gaps in evidence
Benralizumab	**Findings**: Asthma exacerbations were reduced with benralizumab compared to placebo for a broad asthma population and for eosinophilic and allergic asthma subgroups. FEV_1 generally favoured benralizumab but statistical significance was limited to eosinophilic asthma patients. HRQoL outcomes favoured benralizumab but were not consistently significant in noneosinophilic patients. Evidence suggests that benralizumab is safe.
	Gaps in evidence: No outcomes were reported specifically in children. Limited evidence in non–type 2 patients.
Dupilumab	**Findings**: Dupilumab was shown to be superior to placebo for asthma exacerbations, FEV_1, and HRQoL outcomes in both eosinophilic and allergic populations. Safety outcomes were similar to placebo.
	Gaps in evidence: No outcomes were reported for specific subgroups: non–type 2, eosinophilic and allergic patients, and patients who were only eosinophilic or allergic, but not both. No outcomes were reported specifically in children.
Mepolizumab	**Findings**: Asthma exacerbations, FEV_1, HRQoL, and safety outcomes were significantly better when compared to the placebo group among eosinophilic patients regardless of concurrent allergic asthma status.
	Gaps in evidence: Reporting was limited to patients with eosinophilic markers with or without allergic markers. No evidence was reported for non–type 2 asthma, or allergic-only asthma. No outcomes were reported specifically in children.
Omalizumab	**Findings**: Asthma exacerbations, FEV_1, and HRQoL outcomes were superior to placebo for allergic asthma patients. No evidence for increased risk of adverse events reported. Asthma exacerbation and HRQoL outcomes were significantly improved in children.
	Gaps in evidence: No outcomes reported for eosinophilic patients without concurrent allergic markers, or for non–type 2 patients. Outcomes within a pediatric population were obtained from reviews including older studies which may not perfectly align with modern definition of severe asthma.
Tezepelumab	**Findings**: Asthma exacerbations, FEV_1, HRQoL were reduced with tezepelumab compared to placebo for a broad asthma population and for both eosinophilic and allergic subgroups. Asthma exacerbations and FEV_1 were improved for non–type 2 asthma patients. No evidence for risk of adverse events. Asthma exacerbations and FEV_1 were significantly improved in non–type 2, but evidence was limited.

Biologic	Findings and gaps in evidence
	Gaps in evidence: No outcomes were reported specifically in children. Limited evidence was reported for non–type 2 asthma patients.

FEV_1 = forced expiratory volume in 1 second; HRQoL = Health-related quality of life

Table 31: Summary of Findings by Key Asthma Subgroups

Asthma type	Definition and summary of findings
Severe asthma	**Definition**: Asthma categorized on severity alone, without specifying underlying type(s). Severe asthma is defined as: 1) controlled asthma worsens on tapering of medium- to high-dose inhaled corticosteroid(s) or systemic corticosteroids (or additional biologics), or 2) symptoms remain uncontrolled with the use of high-dose inhaled corticosteroid(s) plus a second controller (and/or systemic corticosteroids).
	Findings: • AEX, FEV_1, HRQoL, and hospitalizations outcomes favoured benralizumab, dupilumab, tezepelumab over placebo. • Not reported for mepolizumab or omalizumab. • Not clear if effect is consistent across all subgroups of severe asthma or is driven by a strong response within eosinophilic patients alone.
Non–type 2 asthma	**Definition**: Asthma without Type 2 inflammation or markers of eosinophilic or allergic asthma subtypes
	Findings: • AEX, and FEV_1 favoured biologics for benralizumab, and tezepelumab. • No results reported for this group for mepolizumab and omalizumab, and subgroup was not enrolled in included trials. • No non–type 2 results reported for dupilumab, but participants from this subgroup are included in included trials. • Non–type 2 results not reported in any recent systematic review.
Type 2 eosinophilic asthma	**Definition**: Subtype of Type 2 asthma normally identified using blood eosinophil count as marker. Allergic asthma status unspecified.
	Findings: • Consistent groups based on BEC in recent trials and systematic reviews. Summarized based on noneosinophilic (< 150/300 BEC), or eosinophilic (> 150/300). • HRQoL outcomes for benralizumab, dupilumab, mepolizumab and tezepelumab were generally statistically significant in favour of treatment at higher eosinophil levels compared with placebo. • Benralizumab reported nonstatistically significant effects for AEX, FEV_1, HRQoL in noneosinophilic groups compared with placebo. • Dupilumab and tezepelumab reported statistically significant positive effects in non-eosinophilic groups for AEX and non-significant effects for FEV_1 and HRQoL compared with placebo. • Omalizumab outcomes for the eosinophilic subtype were not reported in these studies.
Type 2 allergic asthma	**Definition**: Subtype of Type 2 asthma identified using immunoglobulin E, and allergen sensitivity as markers. Eosinophilic asthma status unspecified.
	Findings: • Inconsistently defined criteria for allergic status, limiting assessment. • Benralizumab, dupilumab, omalizumab, and tezepelumab reported significant positive effects in asthma exacerbation, FEV_1 and HRQoL outcomes in allergic patients. • Mepolizumab reported positive effects for eosinophilic/allergic asthma patients, but not in a predominantly allergic subtype specifically.

Asthma type	Definition and summary of findings
Type 2 eosinophilic and allergic asthma	**Definition**: Subgroup with markers for both eosinophilic and allergic asthma
	Findings: • AEX and FEV_1 outcomes had significant positive results for benralizumab, mepolizumab, and tezepelumab. • FEV_1 outcomes had some positive results for omalizumab. • HRQoL reported for benralizumab, mepolizumab, and omalizumab and favour biologics, but are not consistently significant. • No eosinophilic/allergic asthma subtype results reported for dupilumab, but participants in this subgroup are included in recent trials. • Eosinophilic/allergic asthma subgroup results not reported in any recent systematic review.

AEX = asthma exacerbation; BEC = blood eosinophil count; FEV_1 = forced expiratory volume in 1 second; HRQoL = health-related quality of life.

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