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College of Pharmacy

Drug Use Research & Management Program

Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079

Phone 503-947-5220 | Fax 503-947-2596



Drug Effectiveness Review Project Summary Report – Biologics in Asthma

Date of Review: August 2021

Date of Last Review: July 2018 & July 2019 (dupilumab)

Literature Search: 08/07/20-5/01/21

Current Status of PDL Class:

See **Appendix 1**.

Research Questions:

1. What is the efficacy for the monoclonal antibodies approved for the treatment of eosinophilic asthma which include: benralizumab, dupilumab, mepolizumab, and reslizumab?
2. What is the tolerability and frequency of adverse events (AEs) for benralizumab, dupilumab, mepolizumab, and reslizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of using omalizumab to treat patients with moderate-to-severe allergic asthma?
4. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which monoclonal antibodies used to treat asthma differ in efficacy, or frequency of adverse events?

Conclusions:

DERP Report

- The Drug Effectiveness Review Project (DERP) identified 44 randomized clinical trials (RCTs) in 52 publications that reported on the use of 5 monoclonal antibodies for asthma management.¹ Eighteen new trials were identified for the 2021 update. Most of the trials compared the monoclonal antibody to placebo while maintaining standard background therapy with an asthma controller, rescue therapy or oral corticosteroids.¹ Most of the RCTs evaluating the effectiveness of add-on therapy generally enrolled or primarily reported outcomes for the participants with the allergic asthma phenotype; thus, the applicability of findings to other asthma phenotypes is not certain.¹ Eight studies were rated as having a high risk of bias for various methodological issues; the rest were rated as having a moderate risk of bias, typically due to extensive manufacturer involvement in study design, execution, and reporting.¹ No head-to-head studies were identified for this report.¹ Data on safety and effectiveness beyond 56 weeks is not available.¹ In addition to standard measures of symptom control and quality of life, studies evaluating asthma commonly reported on the impact of treatment on asthma exacerbations and reduction in corticosteroid usage.¹ Although many statistically significant differences across studies and outcomes were observed, the average magnitude of some differences may not be clinically relevant, as the minimal clinically important difference (MCID) was not achieved.¹
- A range of very low to high quality evidence (depending on drug) suggests that for people with asthma, benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab are more effective than placebo for controlling symptoms as evaluated by achieving an MCID of 0.5 points on the Asthma

Author: Deanna Moretz, PharmD

Control Questionnaire (ACQ) over the duration of the trials (12 to 56 weeks).¹ Data from 3 add-on efficacy RCTs showed benralizumab was more effective compared to placebo as measured by the proportion of patients achieving an MCID of 0.5 points at 12 to 24 weeks on the ACQ (pooled risk ratio [RR], 1.17; 95% confidence interval [CI], 1.06 to 1.28; high quality of evidence [QoE]).¹ Data from 1 add-on efficacy RCT showed dupilumab was more effective than placebo as measured by the proportion of participants achieving an MCID of 0.5 points on the ACQ (RR, 1.22; 95% CI, 1.06 to 1.40; moderate QoE).¹ Two add-on efficacy RCTs and 1 steroid-sparing RCT demonstrated mepolizumab was more effective compared with placebo as measured by difference in mean change from baseline on ACQ (range of estimates, -0.43 to -0.52; moderate QoE).¹ Very low quality evidence from 2 add-on efficacy RCTs showed omalizumab was more effective than placebo as measured by the difference in mean change from baseline on the ACQ; findings were mixed regarding achieving an MCID of 0.5 points (range of estimates, 0 to -0.87).¹ High quality evidence from 4 add-on efficacy RCTs demonstrated reslizumab was more effective than placebo as measured by the proportion of participants achieving an MCID of 0.5 points on the ACQ (range of pooled RRs, 1.24 [95% CI 1.13 to 12.35] to 1.28 [95% CI 1.08 to 1.52] from 4 add-on efficacy trials at 15 to 52 weeks, respectively).¹

- Moderate to high QoE (depending on drug) suggests benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab were more effective than placebo for reducing asthma exacerbations.¹ Data from 3 add-on efficacy RCTs showed benralizumab was more effective compared to placebo as measured by incidence of exacerbations (pooled RR, 0.75; 95% CI, 0.65 to 0.89; moderate QoE).¹ Moderate quality evidence from 2 add-on efficacy RCTs and 1 steroid-sparing RCT showed dupilumab was more effective than placebo as measured by annualized rate of severe exacerbations (incident rate ratio [IRR], 0.30; 95% CI, not reported [NR]).¹ Data from 2 add-on efficacy RCTs and 1 steroid-sparing RCT showed mepolizumab was more effective as measured by annualized rate of exacerbations (IRR range, 0.42 [95% CI 0.31 to 0.56] to 0.68 [95% CI 0.47 to 0.99]; moderate QoE).¹ Twelve add-on efficacy RCTs and 4 steroid-sparing RCTs demonstrated omalizumab was more effective compared to placebo as measured by the incidence of exacerbations (pooled RR, 0.71; 95% CI, 0.61 to 0.82 for add-on efficacy trials; range of pooled RRs, 0.57; [95% CI 0.46 to 0.67 for steroid reduction phase] to 0.64; [95% CI 0.51 to 0.77 for steroid stable phase]) in steroid-sparing RCTs; high QoE).¹ Three add-on efficacy RCTs showed reslizumab was more effective compared to placebo as measured by annualized rate of exacerbations (pooled IRR, 0.53; 95% CI, 0.36 to 0.71; high QoE).¹
- Low to high QoE (depending on drug) suggests benralizumab, dupilumab, mepolizumab, and omalizumab reduce corticosteroid use in people with asthma compared to placebo.¹ In 1 steroid-sparing RCT, benralizumab every 4 weeks was more effective compared to placebo as measured by the proportion of participants reducing oral maintenance oral steroid dose by 50% or more (RR, 1.79; 95% CI, 1.28 to 2.50; moderate QoE).¹ One steroid-sparing RCT showed dupilumab was more effective compared to placebo at reducing the use of maintenance corticosteroids as measured by 50% or greater reduction in corticosteroid dose (calculated RR 1.49; 9% CI 1.22 to 1.83; moderate QoE).¹ Low quality evidence from 1 steroid-sparing RCT demonstrated mepolizumab was more effective compared to placebo as measured by the proportion of participants able to reduce oral steroid doses by 50% or more (RR, 1.61; 95% CI, 1.07 to 2.41).¹ High quality evidence from 3 steroid-sparing RCTs revealed omalizumab was more effective than placebo as measured by the proportion of participants who reduced their maintenance inhaled steroid dose by 50% or more (pooled RRs range, 1.39 to 1.40 across various steroid trial phases: steroid-stable, steroid-reduction, and extension).¹ However, no difference in corticosteroid use was observed for reslizumab compared to placebo (difference in mean percentage steroid dose change, -17.8; 95% CI, -39.0 to 3.5; low QoE).¹
- The evidence suggests either fewer adverse effects (AEs) with the monoclonal antibodies, or no difference in events, compared to placebo (moderate to high QoE, depending on drug) in patients with asthma.¹ Fewer adverse events occurred among participants allocated to benralizumab compared to placebo (7 RCTs; pooled RR, 0.94; 95% CI, 0.90 to 0.98; moderate QoE).¹ No significant difference between dupilumab and placebo in the incidence of adverse events was detected (4 RCTs; pooled RR, 0.99; 95% CI, 0.95 to 1.03; high QoE).¹ Fewer events occurred among participants allocated to mepolizumab versus placebo (pooled RR, 0.93; 95% CI, 0.88 to 0.99; high QoE).¹ No difference in events was observed between omalizumab and placebo (17 RCTs; pooled RR, 1.00; 95% CI, 0.97 to 1.03; high QoE).¹ No difference in events was detected between reslizumab and placebo (7 RCTs; pooled RR, 0.92; 95% CI, 0.84 to 1.00; high QoE).¹ Specific AEs associated with monoclonal antibody administration were not discussed in the DERP report, nor were absolute rates of AEs.

- The evidence suggests benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab are more effective than placebo for treatment of asthma among children, adolescents and adults.¹ No additional subgroups were identified for this report.¹
- Thirteen RCTs of monoclonal therapies for asthma are ongoing, including 1 head-to-head study comparing omalizumab to mepolizumab.¹

New Indications

- Mepolizumab received FDA-approval in September 2020 for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause.²
- In November 2020 omalizumab received FDA-approval for treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add on maintenance treatment.³

New Formulations

- Mepolizumab, omalizumab, and dupilumab are FDA-approved as pre-filled syringes for self-subcutaneous administration.^{2,3}

Recommendations:

- Recent evidence summarized in the Drug Effectiveness Review Project (DERP) report for the asthma biologic medications does not support specific changes to the current Preferred Drug List (PDL).
- Create a PDL class entitled “Biologics for Severe Asthma” and include benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in this PDL class.
- Modify “Monoclonal Antibodies for Severe Asthma” Prior Authorization (PA) criteria to include expanded indications for mepolizumab in treatment of HES and chronic sinusitis with nasal polyps and omalizumab for treatment of nasal polyps.
- Retire current dupilumab PA criteria. Add dupilumab to “Monoclonal Antibodies for Severe Asthma” PA criteria.
- Extend PA criteria to physician administered drugs for all monoclonal antibodies used to treat asthma.

Summary of Prior Reviews and Current Policy

A drug class update focused on asthma and COPD maintenance medications was presented to the Pharmacy & Therapeutics (P & T) Committee at the October 2020 meeting. A class update focused solely on monoclonal antibodies (i.e., biologics) used to treat asthma was presented at the July 2018 P & T meeting. Recommendations for the July 2018 presentation were informed by the April 2018 report researched by the DERP.⁴ The Oregon Health Plan (OHP) provides coverage through PA criteria for 4 biologic agents approved to manage eosinophilic asthma refractory to other asthma therapies: benralizumab, dupilumab, mepolizumab, and reslizumab. Mepolizumab is also Food and Drug Administration (FDA)-approved for treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). Dupilumab has additional FDA-approved indications including treatment of atopic dermatitis in adolescents and adults and as maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).⁵ An additional biologic agent (omalizumab), is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizumab is also indicated for management of chronic urticaria; however, according to the Health Evidence Review Commission (HERC) prioritized list, this diagnosis is not funded. Current criteria require that auto-injectable epinephrine be co-prescribed with all asthma biologics due to the risk of delayed anaphylaxis. There are no preferred monoclonal antibodies for asthma. During the first quarter of 2021 the only asthma biologic agents billed through point of sale pharmacy claims in the fee-for-service (FFS) population were omalizumab with 1 claim and mepolizumab with 4 claims. On average, fewer than 24 claims per quarter were billed as provider administered drugs in 2020.

Methods:

The February 2021 drug class report on Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria by the DERP was used to inform recommendations for this class update.¹

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. DERP does not recommend or endorse any guideline or recommendation developed by users of these reports.

Background:

Asthma is a heterogeneous disease, characterized by chronic airway inflammation which results in bronchial hyper-responsiveness.⁶ It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.⁶ The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side-effects of treatment.⁶ According to the 2020 Global Initiative for Asthma (GINA) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.⁶ Intermittent, mild asthma (Step 1) is well controlled with low dose inhaled corticosteroid (ICS) therapy in combination with long-acting beta-agonists (LABAs).⁶ The preferred Step 2 treatment includes daily low-dose ICS with as-needed short-acting beta-agonists (SABAs) in children or in fixed-dose combination with LABAs for adults and adolescents.⁶ Daily leukotriene receptor antagonists (LTRAs) are alternative options for Step 2 in those patients who are unable or unwilling to use ICS.⁶ Preferred Step 3 controller options for adults and adolescents with moderate asthma include low- or medium-dose ICS-LABA with or without as-needed SABAs or the addition of a LTRA.⁶ For children, the preferred Step 3 controller options include a medium-dose ICS or low-dose ICS-LABAs combination.⁶ The preferred Step 4 treatment for severe asthma varies depending on what has been tried for Step 3, but often includes low- or medium-dose ICS-LABAs with additional controllers, including LTRAs or tiotropium, with SABAs as needed.⁶ The 2020 GINA guidelines recommend a monoclonal antibody for patients with severe asthma unresponsive to controller-drug treatments (Step 5).⁶ Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.⁷ Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.⁸

Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called asthma phenotypes.⁶ In patients with more severe asthma, some phenotype-guided treatments are available.⁶ Phenotyping severe asthma based on demographic or clinical characteristics may help to effectively target treatment. More recently, individual treatment has been geared toward treating the specific asthma phenotype, which includes allergic, nonallergic, exercise-induced, fixed-obstruction, and occupational asthma.⁹ Allergic asthma is the most common phenotype, describing between 40% and 50% of cases, and can be identified through allergy testing for environmental allergens, eosinophilia, blood immunoglobulin E (IgE) levels, and exhaled nitric oxide testing.¹ Patients with eosinophilic asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines define the threshold as blood eosinophils of ≥ 150 cells/ μ L.⁶ Studies of biologic therapies have evaluated use in patients with eosinophil levels of greater than 150 cells per μ L to more than 400 cells per μ L.

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Interleukin-5 is critical for eosinophil maturation and activation. Activated eosinophils can increase

airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Dupilumab, an IL-4 receptor antagonist, is also indicated as add on maintenance therapy for moderate to severe asthma.

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab; therefore, the drug carries an FDA boxed warning recommending observation after infusion.¹⁰ Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.^{2,11} There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. **Table 1** summarizes significant prescribing information for the 5 biologic agents with FDA approval to treat moderate to severe asthma.

Table 1. Monoclonal Antibodies FDA-Approved to Manage Moderate to Severe Asthma^{2,3,5,10,11}

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age for Asthma	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Dupilumab	DUPIXENT	2018	IL-4 Receptor	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Adults and Adolescents: 200 to 300 mg SC every 2 weeks	≥ 12 yo	No	Subjects enrolled in clinical trials without requiring a minimum baseline blood eosinophil count
Benralizumab	FASENRA	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/μL
Reslizumab	CINQAIR	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/μL
Mepolizumab	NUCALA	2015	IL-5	Severe asthma with an eosinophilic phenotype	Ages ≥ 6 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks	≥ 6 yo	No	≥ 150 cells/μL at screening or ≥ 300 cells/μL in the previous year
Omalizumab	XOLAIR	2003	IgE	Moderate to severe persistent asthma	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels	≥ 6 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: FDA = Food and Drug Administration; IgE = immunoglobulin E; IL = interleukin; IV = intravenous; SC = subcutaneous; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; or 4) improved symptom management. Several instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ) is a 5-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.¹² Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the MCID.¹³ An ACQ score consistently greater than 1.5 indicates poor symptom control.¹³ The Asthma Quality of Life Questionnaire (AQLQ) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli with a 2-week recall.¹ The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.¹ The MCID for this tool is 0.5 points for each item.¹ The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.¹⁴ The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.¹ The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/ limitations).¹ Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.¹ The MCID for the SGRQ is 4 points.¹ The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.¹ Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.¹ The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.¹ Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.¹ The MCID for the ACT is 3 points.¹ A summary of the outcomes discussed in the DERP report is presented in **Table 2**.

Table 2. Summary of Outcome Measures for Asthma¹

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ)	0 (totally controlled) to 6 (severely uncontrolled)	0.5
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3
Asthma Quality of Life Questionnaire (AQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4

Change from baseline in forced expiratory volume is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. A decline in lung function is observed when forced expiratory volume in 1 second [FEV₁] is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.¹

Summary DERP Report Findings:

The 2021 DERP report focuses on adults and children with moderate to severe asthma or chronic spontaneous urticaria (CSU).¹ Because CSU is not funded by HERC, this class update will focus on evidence identified for asthma management. Randomized trials that evaluated the effectiveness and safety of benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab in treating patients with asthma were included in the DERP report.¹ Eligible comparators included active treatment with another FDA-approved biologic, placebo, or usual care. Eligible outcomes for asthma included measures of symptom control, quality of life, oral steroid use, severe exacerbations requiring emergency department (ED) or hospital admission, all-cause ED or hospital admission, and mortality.¹

The literature search for the recently issued DERP report was conducted from August 2017 through December 2020.¹ A previous DERP systematic review on biologics for asthma included existing systematic reviews and only included primary studies if they were not covered within an existing systematic review.⁴ The 2021 DERP update relies entirely on primary RCTs and only used the previous DERP review to identify potentially eligible studies conducted before the most recent literature search. A total of 44 RCTs with 18 new studies reported on the use of biologics for asthma.¹ All but 3 RCTs used placebo controls. Two RCTs used a “best standard of care” control, and 1 RCT used a no-treatment control group.¹ No studies evaluating head-to-head comparisons were identified. Seven RCTs evaluated benralizumab, 4 RCTs evaluated dupilumab, 3 RCTs evaluated mepolizumab, 7 RCTs evaluated reslizumab, and 23 RCTs evaluated omalizumab.¹ All but 1 RCT reported effectiveness outcomes, and all but 3 RCTs reported safety outcomes.¹ Specific AEs and serious adverse events (SAEs) associated with monoclonal antibody administration were not discussed in the DERP report.

Eight studies were rated as having a high risk of bias for various methodological issues; the rest were rated as having a moderate risk of bias, typically due to extensive manufacturer involvement in study design, execution, and reporting.¹ Most trials evaluated the add-on efficacy of the biologic drug compared to placebo or control while maintaining standard background asthma controller and rescue therapy in both groups.¹ A fewer number of studies evaluated the add-on efficacy of the biologic drug compared to placebo while tapering inhaled or oral maintenance corticosteroids (or other controller treatment) in both groups.¹ Outcomes were reported between 12 and 56 weeks of duration.¹

The risk of bias for the included RCTs was evaluated using specific parameters. Low-risk-of-bias RCTs included a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses.¹ Low-risk-of-bias randomized controlled trials also had low potential for bias from conflicts of interest and funding source(s).¹ Moderate-risk-of-bias RCTs had incomplete information about methods that might mask important limitations or a meaningful conflict of interest.¹ High-risk-of-bias RCTs had clear flaws that could introduce significant bias.¹

Key Findings for Benralizumab Compared to Placebo

Seven industry-sponsored RCTs evaluated 1 or more dosing regimens of benralizumab compared to placebo (SIROCCO,¹⁵ BISE,¹⁶ CALIMA,¹⁷ ANDHI,¹⁸ Park et al.,¹⁹ SOLANA,²⁰ and ZONDA²¹). All 7 RCTs were multicenter, international studies; 6 studies were phase 3 trials, whereas Park et al. was a phase 2 trial.¹ The CALIMA and SIROCCO trials enrolled participants aged 12 and older; all other studies only enrolled adults.¹ Six studies required participants to be taking moderate- to high-dose ICS; only the BISE trial enrolled persons taking low- to moderate-dose ICS.¹ Four trials (ANDHI, SOLANA, ZONDA, and Park et al.) enrolled only

participants with allergic asthma while SIROCCO did not limit enrollment to persons with allergic asthma but reported all results by subgroup based on baseline eosinophil level (less than 300 cells per μL versus 300 cells per μL and greater).¹ CALIMA did not limit enrollment to persons with allergic asthma, but only reported findings among the 56% of enrolled persons with eosinophils of 300 cells per μL and greater, which was reported as the primary group of interest.¹ The BISE trial enrolled persons with and without allergic asthma but did not report the findings separately.¹ The study populations, interventions, and outcomes are summarized in **Table 3**.

Symptom Control

- Pooled estimates from 3 add-on efficacy RCTs (N = 1,100)^{16,18,20} showed benralizumab was more effective compared to placebo for improving symptom control as measured by the proportion of subjects achieving a MCID of 0.5 points on the ACQ at 12 to 24 weeks (pooled RR] 1.17; 95% CI, 1.06 to 1.28); high QoE.¹

Quality of Life

- Data from 1 add-on efficacy RCT (N = 211)¹⁶ demonstrated benralizumab was no different in improving quality of life compared to placebo as measured by the proportion of subjects achieving a minimally important change of 0.5 points on the AQLQ at 12 weeks (43% vs. 32% respectively; calculated RR 1.34; 95% CI, 0.94 to 1.90); low QoE.¹

Exacerbations

- Data from 4 add-on efficacy RCTs (N = 2,233)^{15,16,18,19} were pooled to assess exacerbation rates. The analysis showed benralizumab was more effective than placebo in lowering the annualized rate of exacerbations (pooled IRR 0.59; 95% CI, 0.47 to 0.79 for every 4 week dose; IRR 0.55; 95% CI, 0.43 to 0.67 for every 8 week dose; absolute rates NR); moderate QoE.¹
- Pooled data from 2 add-on efficacy RCTs (N = 1,537)^{15,17} showed benralizumab was more effective over placebo in reducing annualized rate of exacerbations requiring ED or hospital visits only for the 4 week dose, findings for the 8 week dose were too heterogenous to pool (pooled IRR, 0.67; 95% CI, 0.38 to 0.96 for every 4-week dose; absolute rates NR); low QoE.¹

Corticosteroid Use

- In 1 steroid-sparing RCT (N = 220)²¹ benralizumab was more effective compared to placebo for reducing the proportion of participants with a 50% reduction in their maintenance oral corticosteroid dose at 28 weeks of follow-up (calculated RR 1.79; 95% CI, 1.28 to 2.50 for every 4 week dose; calculated RR 1.76; 95% CI, 1.26 to 2.47 for every 8 week dose); moderate QoE.¹

Overall Adverse Effects and Serious Adverse Effects

- Pooled analysis of the 7 RCTs listed in **Table 3** (N = 2,897) revealed fewer AEs occurred among participants allocated to benralizumab versus placebo (pooled RR, 0.94; 95% CI, 0.90 to 0.98); high QoE.¹ Pooled analysis of the 7 RCTs also showed fewer serious adverse events (SAEs) occurred among participants allocated to benralizumab versus placebo (pooled RR, 0.76; 95% CI, 0.61 to 0.96) based on moderate QoE (downgraded for imprecision due to the rarity of observed events).¹

Mortality

- Six of the 7 studies also reported mortality; however, events were rare (12 deaths of 2,008 total participants across studies [0.60%]); thus, estimates of treatment effect were imprecise.¹

Table 3. Randomized Controlled Trials of Benralizumab in Patients with Asthma¹

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bleecker et al. ¹⁵ SIROCCO Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none"> Subjects aged 12 to 75 Treatment with medium- to high-dose ICS and LABA At least 2 exacerbations requiring systemic steroids in prior year ACQ score \geq 1.5 Subjects with allergic asthma (67%) and non-allergic asthma (33%) 	<ul style="list-style-type: none"> Benralizumab 30 mg SC every 4 wks (n = 399) Benralizumab 30 mg SC every 8 wks (n = 398) Placebo (n = 407) <p>Continued stable doses of other asthma controllers, SABA rescue for symptoms</p>	<p>At 48 weeks:</p> <ul style="list-style-type: none"> Symptom control QoL Adverse events Mortality <p>(Annualized exacerbation rate)</p>
Ferguson et al. ¹⁶ BISE Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none"> Subjects aged 18 to 75 Low- to medium-dose ICS with or without other controller medications Evidence of uncontrolled symptoms Subjects with allergic (30%) and non-allergic asthma (70%) 	<ul style="list-style-type: none"> Benralizumab 30 mg SC every 4 wks (n = 106) Placebo (n = 105) <p>Controller ICS converted to standardized doses, LABAs withdrawn at enrollment, SABA rescue for symptoms</p>	<p>At 12 weeks:</p> <ul style="list-style-type: none"> Symptom control QoL Exacerbations Adverse events Mortality <p>(FEV₁ change)</p>
FitzGerald et al. ¹⁷ CALIMA Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none"> Subjects aged 12 to 75 Treatment with medium- to high-dose ICS and LABA At least 2 exacerbations requiring systemic steroids in prior year ACQ score \geq 1.5 Subjects with allergic (56%) and non-allergic asthma (44%) 	<ul style="list-style-type: none"> Benralizumab 30 mg SC every 4 wks (n = 425) Benralizumab 30 mg SC every 8 wks (n = 441) Placebo (n = 440) <p>Continued stable doses of other asthma controllers, SABA rescue for symptoms</p>	<p>At 56 weeks:</p> <ul style="list-style-type: none"> Symptom control QoL Exacerbations Adverse events Mortality <p>(Annualized exacerbation rate in subgroup with eosinophils > 300/μL)</p>
Harrison et al., 2020 ¹⁸ ANDHI Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none"> Subjects aged 18 to 75 Treatment with high-dose ICS plus another asthma controller Blood eosinophil count at least 150/μL \geq 2 exacerbations in prior year ACQ score \geq 1.5 	<ul style="list-style-type: none"> Benralizumab 30 mg SC every 4 wks first 3 doses, then every 8 wks (n = 427) Placebo (n = 229) <p>Continued stable doses of other asthma controllers</p>	<p>At 24 weeks:</p> <ul style="list-style-type: none"> Symptom control Exacerbations Adverse events Mortality <p>(Annualized exacerbation rate)</p>

<p>Nair et al.²¹ ZONDA Phase 3 RCT of add-on therapy with steroid tapering Moderate</p>	<ul style="list-style-type: none"> • Subjects aged 18 to 75 • Blood eosinophil count at least 150/μL • Medium- to high-dose ICS and LABA • Oral steroids for at least 6 months 	<ul style="list-style-type: none"> • Benralizumab 30 mg SC every 4 wks (n = 72) • Benralizumab 30 mg SC every 8 wks (n = 73) • Placebo (n = 75) <p>Oral steroids adjusted to lowest possible dose to control symptoms before randomization, oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms</p>	<p>At 28 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations • Steroid use • Adverse events • Mortality <p>(Percentage reduction in steroid dose with asthma control maintained)</p>
<p>Panettieri et al.²⁰ SOLANA Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Subjects aged 18 to 75 • Eosinophilic severe asthma requiring ICS/OCS and LABA • ≥ 2 exacerbations requiring OCS in prior year ACQ score ≥ 1.5 	<ul style="list-style-type: none"> • Benralizumab 30 mg SC every 4 wks (n = 118) • Placebo (n = 115) <p>Co-interventions NR</p>	<p>At 8 to 12 wks</p> <ul style="list-style-type: none"> • Symptom control • Adverse events <p>(Change in pre-bronchodilator FEV₁)</p>
<p>Park et al.¹⁹ Phase 2a RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Subjects aged 20 to 75 • Eosinophilic asthma • Medium- to high-dose ICS and LABA • 2 to 6 exacerbations requiring systemic steroids in past year • ACQ score ≥ 1.5 	<ul style="list-style-type: none"> • Benralizumab 20 mg SC every 4 wks first 3 doses, then every 8 wks (n = 25) • Placebo (n = 26) <p>Continued stable doses ICS and LABA</p>	<p>At 52 wks</p> <ul style="list-style-type: none"> • Symptom control • Exacerbations • Adverse events • Mortality <p>(Annualized exacerbation rate)</p>
<p>Abbreviations. ACQ = Asthma Control Questionnaire; FEV₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wks = weeks</p>			

Dupilumab Compared to Placebo

Four industry-sponsored, multicenter RCTS evaluated dupilumab compared to placebo.²²⁻²⁵ Two RCTs were conducted in multiple countries among children and adults aged 12 years and older,^{22,25} 1 RCT was conducted in multiple countries among adults aged 18 years and older,²³ and 1 RCT²⁴ was conducted in the United States (US) among adults aged 18 years and older. The 2 Wenzel et al. trials were phase 2 RCTs, and the LIBERTY ASTHMA VENTURE and LIBERTY ASTHMA QUEST were phase 3 trials. The dupilumab studies are summarized in **Table 4**.

Study inclusion and exclusion criteria were similar across the 4 trials.¹ All were conducted among participants who had asthma for at least 12 months that was not well controlled with ICS, or LABAs, or both, and excluded participants with chronic obstructive pulmonary disease or other lung diseases, and current smokers.¹ LIBERTY ASTHMA VENTURE and LIBERTY ASTHMA QUEST enrolled participants without respect to baseline level of eosinophils, but reported findings overall and for the subgroups of participants with baseline eosinophils less than 150, 150 to 300, and greater than 300 cells per μ L.¹ Wenzel et al. 2016 enrolled

participants without regard to baseline eosinophils but defined the primary endpoint for the subgroup with baseline eosinophils greater than 300 cells per μL .¹ Wenzel et al. 2013 enrolled only participants with baseline eosinophils greater than 300 cells per μL .¹

Symptom Control

- Data from 2 add-on efficacy RCTs (N = 2,367)^{23,25} and 2 steroid-sparing RCTs (N = 314)^{22,24} were pooled to evaluate symptom control. Dupilumab was more effective compared to placebo for improving symptom control as measured by difference in mean change from baseline on the ACQ (pooled estimate, -0.28; 95% CI, -0.37 to -0.19 for add-on efficacy trials at 24 weeks and pooled estimate, -0.55; 95% CI, -0.79 to -0.31 for steroid-sparing RCTs at 12 to 24 weeks); moderate QoE.¹
- In 1 add-on efficacy RCT (N = 465)²³ dupilumab was more effective than placebo for improving symptom control as measured by the proportion of participants achieving a MCID (0.5 points) on the ACQ (RR, 1.22; 95% CI, 1.06 to 1.40); moderate QoE.¹

Quality of Life

- In 2 add-on efficacy RCTs (N = 2,367)^{23,25} dupilumab was more effective than placebo for improving quality of life as measured by difference in mean change from baseline on the AQLQ (pooled estimate, 0.23; 95% CI, 0.08 to 0.38 at 24 weeks); moderate QoE.¹ However, the pooled analysis at 24 weeks did not render a mean reduction that achieved a MCID for the AQLQ (0.5 points).¹
- Data from 1 add-on efficacy RCT (N = 465)²³ showed dupilumab was more effective than placebo for improving quality of life as measured by proportion of participants achieving an MCID (0.5 points) on the AQLQ (RR 1.81; 95% CI, 1.28 to 2.57 for 200-mg dose; RR 1.27; 95% CI, 1.05 to 1.53 for 300-mg dose); moderate QoE.¹

Exacerbations

- In 1 add-on efficacy RCTs (N = 465)²³ dupilumab 300 mg was more effective than placebo for reducing the annualized rate of severe exacerbations at 24 weeks (relative risk reduction 70.5; 95% CI 45.4 to 84.1), moderate QoE.¹
- Data from 1 add-on efficacy RCT (N = 1,902)²⁵ demonstrated dupilumab was more effective than placebo in lowering the rate of exacerbations requiring ED visit or hospitalization (IRR 0.53; 95% CI, 0.25 to 0.82); low QoE.¹

Corticosteroids

- 1 steroid-sparing RCT (N = 314)²² showed dupilumab was more effective compared to placebo at reducing the use of maintenance corticosteroids as measured by 50% or greater reduction in corticosteroid dose (calculated RR 1.49; 9% CI 1.22 to 1.83), moderate QoE.¹

Overall Adverse Effects and Serious Adverse Effects

- Data pooled from the 4 RCTs in **Table 4** (N = 2,367) revealed no significant difference between dupilumab and placebo in rates of overall AEs (pooled RR 0.99; 95% CI, 0.95 to 1.03); high QoE.¹ Data from 4 RCTs also showed no significant difference between dupilumab and placebo in SAEs (pooled RR, 1.05; 95% CI, 0.80 to 1.38); moderate QoE.¹

Mortality

- Only 1 study reported mortality; no deaths were reported in either the dupilumab or placebo group.¹

Table 4. Randomized Controlled Trials of Dupilumab in Patients with Asthma¹

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Rabe et al. ²² LIBERTY ASTHMA VENTURE Phase 3 RCT of add-on therapy with steroid tapering Moderate	<ul style="list-style-type: none"> Subjects aged 12 and older Treatment with systemic glucocorticoids in prior 6 months High-dose inhaled glucocorticoid, up to 2 controllers in prior 3 months No minimum requirement for eosinophils but 80% had atopic medical history 	<ul style="list-style-type: none"> Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 103) Placebo (n = 107) <p>Glucocorticoid dose (prednisone or prednisolone) with dose reduced every 4 wks during weeks 4 to 20. Background asthma controllers at stable dose and SABA as needed.</p>	<p>At 24 weeks:</p> <ul style="list-style-type: none"> Symptom control Steroid use Adverse events Mortality <p>(Percentage reduction in oral glucocorticoid dose while asthma control was maintained)</p>
Wenzel et al., 2016 ²³ No trial name Phase 2b trial of effectiveness of add-on therapy Moderate	<ul style="list-style-type: none"> Subjects aged 18 and older Treatment with medium- to high-dose ICS and LABA with a stable dose for 1 month or longer ACQ-5 total score 1.5 or higher 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma in prior year No minimum requirement for eosinophils but primary endpoint defined based on subgroup with $\geq 300/\mu\text{L}$ 	<ul style="list-style-type: none"> Dupilumab 200 mg SC every 2 or 4 wks, 400-mg loading dose (n = 150) Dupilumab 300 mg SC every 2 or 4 wks, 600-mg loading dose (n = 157) Placebo (n = 158) <p>High-dose ICS and LABA use in 1 of 3 approved combinations.</p>	<p>At 24 weeks:</p> <ul style="list-style-type: none"> Symptom control QoL Exacerbations Adverse events Mortality <p>(Change from baseline in FEV₁ at week 12 in subpopulation of patients with baseline eosinophil count of $\geq 300/\mu\text{L}$)</p>
Wenzel et al, 2013 ²⁴ No trial name Phase 2a trial of add-on therapy with LABA discontinuation and steroid tapering Moderate	<ul style="list-style-type: none"> Subjects aged 18 to 65 years Asthma not well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs ACQ-5 ≥ 1.5 and ≤ 3.0 Eosinophils $\geq 300/\mu\text{L}$ At least 1 asthma exacerbation within prior 2 years resulting in 	<ul style="list-style-type: none"> Dupilumab 300 mg SC every 1 wk (n = 52) Placebo (n = 52) <p>Combination therapy with ICS and LABAs, ICS dose based on pretrial doses for 4 wks.</p>	<p>At 12 weeks:</p> <ul style="list-style-type: none"> Symptom control Exacerbations Adverse events Mortality <p>(Occurrence of asthma exacerbation)</p>

	treatment with 1 or more systemic steroid or hospitalization or an emergency care visit	Discontinuation of LABA at week 4 and tapering of ICS during weeks 6 through 9.	
Castro et al. ²⁵ LIBERTY ASTHMA QUEST Phase 3 RCT of effectiveness of add-on therapy Moderate	<ul style="list-style-type: none"> • Subjects aged 12 and older • Treatment with medium- to high-dose ICS plus up to 2 additional controllers • Worsening asthma in prior year that led to hospitalization • Emergency medical care, or treatment with systemic steroids for ≥3 days • ACQ score ≥ 1.5 • No minimum requirement for eosinophils but 82% had atopic medical history 	<ul style="list-style-type: none"> • Dupilumab 200 mg SC every 2 wks, loading dose 400 mg (n = 631) • Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 633) • Placebo (n = 638) • High-dose ICS; continued stable dose asthma-controller medicines; LABA, long-acting muscarinic antagonists, LTRAs, and methylxanthines; SABA as necessary for symptom relief. 	<p>At 52 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations • Adverse events • Mortality <p>(Annualized rate of severe asthma exacerbations)</p>
Abbreviations. ACQ = Asthma Control Questionnaire; FEV ₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonist OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonist; SC = subcutaneous; wk(s) = week(s)			

Mepolizumab Compared to Placebo

Three phase 3 industry-sponsored RCTs (SIRIUS,²⁶ MENSA,²⁷ and MUSCA²⁸) evaluated mepolizumab compared to placebo.¹ All trials were international, multicenter studies conducted between the years 2012 and 2016. MENSA and MUSCA enrolled with participants aged 12 to 75 with eosinophilic asthma on high-dose ICS with at least 2 exacerbations requiring systemic steroids in the prior year.^{27,28} SIRIUS enrolled participants aged 18 to 82 and required participants to have a 6-month history of maintenance systemic steroids in addition to treatment with high-dose ICS and another controller medication.²⁶ MENSA and MUSCA were designed to assess the efficacy of a 100-mg dosage of mepolizumab as add-on therapy compared to placebo without a steroid taper.^{27,28} SIRIUS was designed to assess the efficacy of add-on mepolizumab (100 mg) compared to placebo during a steroid-tapering cointervention in both study groups.²⁶ All participants in SIRIUS continued treatment with high-dose ICS and an additional controller medication (LABA, LTRA, or theophylline) throughout the study.²⁶ The risk of bias of these trials was rated as moderate for extensive manufacturer involvement in study design, execution, and reporting.¹ A summary of these trials is presented in **Table 5**.

Symptom control

- Pooled data from the 2 add-on efficacy RCTs (N = 941)^{27,28} showed mepolizumab was more effective than placebo in improving symptom control as measured by difference in mean change from baseline on ACQ at 24 to 32 weeks follow-up (mean difference (MD) -0.43, 95% CI, -0.59 to -0.27, P=0.001); moderate QoE.¹

Quality of Life

- No studies reported specific measures assessing quality of life with mepolizumab administration in patients with asthma.¹

Exacerbations

- MUSCA and MENSA both reported exacerbation outcomes at 32 and 24 weeks, respectively, but MENSA did not provide enough information to conduct a pooled analysis.¹ MUSCA showed participants allocated to mepolizumab had a significantly lower annualized exacerbation rate (IRR, 0.42; 95% CI, 0.31 to 0.56; moderate QoE) and a lower rate of exacerbations requiring an ED visit or hospitalization (IRR 0.32; 95% CI, 0.12 to 0.90; low QoE) compared to placebo.¹ MENSA also reported a lower annualized exacerbation rate among persons allocated to mepolizumab compared to placebo (0.83 vs. 1.74; calculated IRR 0.48; moderate QoE) and a lower annualized rate of exacerbations requiring an ED visit or hospitalization (0.03 vs. 0.10, 69% decrease; 95% CI, 9% to 89% decrease; low QoE).¹

Corticosteroid use

- In 1 steroid-sparing RCT (N = 135)²⁸, mepolizumab was more effective compared to placebo in reduction of corticosteroid use as measured by the proportion of participants able to reduce oral steroid doses by 50% or more (54% vs. 33%; RR 1.61; 95% CI, 1.07 to 2.41); low QoE.¹

Overall Adverse Effects

- Data pooled from the 3 RCTs in **Table 5** (N = 556) demonstrated fewer AEs occurred among participants allocated to mepolizumab versus placebo (pooled RR 0.93; 95% CI, 0.88 to 0.99); high QoE.¹

Serious Adverse Effects

- Pooled analyses of the MENSA and MUSCA trials also observed fewer SAEs in the mepolizumab group compared to placebo (pooled RR 0.63; 95% CI, 0.41 to 0.97).¹ SIRIUS was not included in this pooled analysis because the findings introduced substantial heterogeneity for reasons that could not be explained based on study or population characteristics.¹ In SIRIUS, 1 of 69 (1.4%) people experienced SAEs in the mepolizumab group compared to 12 of 66 (18.2%) in the placebo group (calculated RR, 0.07; 95% CI, 0.01 to 0.60).¹

Mortality

- Of the 3 studies evaluating mepolizumab, only MUSCA reported mortality; no deaths were reported in either the treatment or placebo group.¹

Table 5. Randomized Controlled Trials of Mepolizumab in Patients with Asthma¹

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bel et al. ²⁶ SIRIUS Phase 3 RCT of add-on therapy with steroid tapering Moderate	<ul style="list-style-type: none"> Aged 12 to 75 Eosinophilic asthma Maintenance systemic steroids, high-dose ICS and controller medication (LABA, LTRA, or theophylline) 	<ul style="list-style-type: none"> Mepolizumab 100 mg SC every 4 wks (n = 69) Placebo (n = 66) <p>Oral steroids adjusted to lowest possible dose to control symptoms before randomization; oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms.</p>	<p>At 24 weeks:</p> <ul style="list-style-type: none"> Symptom control QoL Exacerbations Steroid use <p>At 32 weeks:</p> <ul style="list-style-type: none"> Adverse events Mortality <p>(Percentage reduction in steroid dose with asthma control maintained)</p>

<p>Ortega et al.²⁷ MENSA Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 18 to 82 • Eosinophilic asthma • High-dose ICS and controller medication, at least 2 exacerbations requiring systemic steroids in prior year 	<ul style="list-style-type: none"> • Mepolizumab 100 mg SC every 4 wks (n = 194) • Placebo (n = 191) <p>Continued stable doses of other asthma controllers, SABA rescue for symptoms.</p>	<p>At 32 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations <p>At 40 weeks:</p> <ul style="list-style-type: none"> • Adverse Events • Mortality <p>(Annualized exacerbation rate)</p>
<p>Chupp et al.²⁸ MUSCA Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 12 to 75 • Eosinophilic asthma • High-dose ICS and controller medication • At least 2 exacerbations requiring systemic steroids in prior year 	<ul style="list-style-type: none"> • Mepolizumab 100 mg SC every 4 wks (n = 276) • Placebo (n = 280) <p>Continued stable doses of other asthma controllers, SABA rescue for symptoms.</p>	<p>At 24 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations • Adverse events • Mortality <p>(HRQOL mean change)</p>
<p>Abbreviations. ACQ = Asthma Control Questionnaire; FEV₁ = forced expiratory volume in 1 second; HRQOL = health-related quality of life; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wk(s) = week(s)</p>			

Reslizumab Compared to Placebo

Seven industry-sponsored studies (published in 5 articles) evaluated reslizumab compared to placebo.²⁹⁻³³ Six studies were phase 3 RCTs while the Castro et al.³⁰ trial was a phase 2 trial. Corren et al.³³ was conducted in the US among adults aged 18 to 65, and Castro et al.³² was conducted in the US and Canada among adults aged 18 to 75. The remaining 5 RCTs were conducted at multiple sites in multiple countries among participants aged 12 to 75 or participants aged 12 and older. The risk of bias as rated as moderate for all studies because of extensive manufacturer involvement in study design, execution, and reporting.¹ Study details are presented in **Table 6**.

Study inclusion and exclusion criteria were similar; all studies were conducted with participants who had asthma that was poorly controlled by at least a medium-dose ICS or a high-dose of ICS.¹ Six of the studies enrolled participants based on higher baseline blood eosinophils (e.g., more than 300 or 400 cells per μL).¹ Corren et al.³³ did not enroll participants based on baseline blood eosinophils, and 80% of those enrolled had levels less than 400 cells per μL . Six of the studies were add-on therapy efficacy trials that assessed 110 mg SC or 3 mg per kg IV of reslizumab every 4 weeks compared to placebo.¹ The FDA-approved dose of reslizumab is 3 mg per kg IV, and a 110-mg SC dose approximates a dose of 1 mg per kg IV for a 70-kg person.¹ One of the studies reported in Bernstein et al.²⁹ assessed 110 mg SC of reslizumab every 4 weeks as add on-therapy during a steroid-tapering co-intervention. This study included participants with oral corticosteroid-dependent severe asthma who required an average daily maintenance dose of oral corticosteroids (5 to 40 mg of prednisone or equivalent) during the 3 months before study entry; participants had their oral steroid doses optimized during the run-in period to the lowest possible dosage to maintain asthma control.²⁹

Symptom control

- Pooled data from 5 add-on efficacy RCTs (N = 1,766)²⁹⁻³³ showed reslizumab was more effective than placebo for improving symptom control as measured by difference in mean change from baseline in ACQ at 15 to 16 weeks (pooled estimate, -0.25; 95% CI, -0.33 to -0.17); moderate QoE.¹
- Pooled data from 5 add-on efficacy RCTs (N = 1,766)³⁰⁻³⁴ demonstrated reslizumab was more effective than placebo as measured by the proportion of participants achieving an MCID (0.5 points) on the ACQ at 15 to 52 weeks (range of pooled RRs, 1.24 to 1.28); high QoE.¹

Quality of life

- Pooled data from 4 add-on efficacy RCTs (N = 1,632)^{29,31,32} showed reslizumab was more effective over placebo for improving quality of life as measured by difference in mean change from baseline on the AQLQ at 15 to 52 weeks (range of pooled estimates, 0.24 to 0.21); moderate QoE.¹
- Pooled data from 3 add-on efficacy RCTs (N = 1,164)^{31,32} demonstrated reslizumab was more effective than placebo for improving quality of life as measured by the proportion of participants achieving an MCID (0.5 points) on the AQLQ at 16 to 52 weeks (range of pooled RRs, 1.14 to 1.35); high QoE.¹

Exacerbations

- Pooled data from 3 add-on efficacy RCTs (N = 1,421)^{29,32} showed reslizumab was more effective compared to placebo for reducing the annualized rate of exacerbations (pooled IRR, 0.53; 95% CI, 0.36 to 0.71 in add-on efficacy trials at 52 weeks; absolute rates NR); high QoE.¹
- Pooled data from 3 add-on efficacy RCTs (N = 1,421)^{30,32} demonstrated no difference between reslizumab and as measured by annualized rate of exacerbations requiring ED or hospital visit (pooled IRR, 0.73; 95% CI, 0.36 to 1.09; absolute rates NR); low QoE.¹

Corticosteroid Use

- 1 steroid-sparing RCT (N = 177)³⁰ demonstrated no difference between reslizumab and placebo in reducing corticosteroid use as measured by percentage change in oral maintenance steroid dose (difference in mean percentage dose change, -17.8; 95% CI, -39.0 to 3.5); low QoE.¹

Overall Adverse Effects and Serious Adverse Effects

- Data pooled from the 7 RCTs presented in **Table 5** (N = 2,411) showed no difference between reslizumab and placebo in overall AEs (pooled RR, 0.92; 95% CI, 0.84 to 1.00); high QoE.¹ Data pooled from 7 RCTs showed no difference between reslizumab and placebo in overall SAEs (pooled RR, 0.94; 95% CI, 0.68 to 1.31); moderate QoE.¹

Mortality

- Six of the 7 studies reported mortality. Events were rare (2 deaths out of 2,300 total participants across studies), so estimates of treatment effect were imprecise.¹¹

Table 6. Randomized Controlled Trials of Reslizumab in Patients with Asthma¹

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bernstein et al., 2020 (study 1) ²⁹ No trial name Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none">• Aged 12 and older with uncontrolled severe asthma• Eosinophils \geq 300/μL• At least a medium dose of ICS with 1 or more additional asthma controllers	<ul style="list-style-type: none">• Reslizumab 110 mg SC every 4 wks (n = 236)• Placebo (n = 232) <p>Continued inhaled asthma controller regimen; oral corticosteroids as needed</p>	<p>At 32 or 52 weeks:</p> <ul style="list-style-type: none">• Symptom control• QoL• Exacerbations• Adverse events• Mortality

<p>Bernstein et al., 2020 (study 2)²⁹ No trial name Phase 3 RCT of add-on therapy with steroid tapering Moderate</p>	<ul style="list-style-type: none"> • ACQ score > 1.5 • Aged 12 and older with severe asthma • Eosinophils \geq 300/μL • Daily maintenance oral corticosteroid • High-dose ICS plus another controller 	<ul style="list-style-type: none"> • Reslizumab 110 mg SC every 4 wks (n = 88) • Placebo (n = 89) <p>Continued ICS use; minimal effective oral corticosteroid dose optimized during run-in and continued for first 4 weeks of double-blind treatment, then reduced from weeks 5 to 20, maintained at lowest dose for last 4 weeks</p>	<p>(Frequency of exacerbations)</p> <p>At 24 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Steroid Use • Exacerbations • Adverse events • Mortality <p>(Percentage reduction in daily oral steroid dose)</p>
<p>Castro et al., 2011³⁰ No trial name Phase 2 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 18 to 75 with poorly controlled asthma • Using high-dose ICS with at least 1 other agent • ACQ score > 1.5 • Induced sputum eosinophils \geq 3% 	<ul style="list-style-type: none"> • Reslizumab 3 mg/kg IV every 4 wks (n = 53) • Placebo (n = 53) <p>Continued ICS use</p>	<p>At 15 weeks:</p> <ul style="list-style-type: none"> • Symptom control • Exacerbations • Adverse events <p>(Change in ACQ score)</p>
<p>Bjermer et al., 2016³¹ BREATH-3 Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS • ACQ score > 1.5 • Eosinophils \geq 400/μL 	<ul style="list-style-type: none"> • Reslizumab 3 mg/kg IV every 4 wks (n = 106) • Placebo (n = 105) <p>Continued long-acting bronchodilators, LTRA, or cromolyn</p>	<p>At 16 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Adverse events • Mortality <p>(FEV1 change)</p>
<p>Castro et al., 2015³² BREATH-2 Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS with or without another controller drug • ACQ score > 1.5 • Eosinophils \geq 400/μL 	<ul style="list-style-type: none"> • Reslizumab 3 mg/kg IV every 4 wk (n = 232) • Placebo (n = 232) <p>Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids LTRAs, and cromolyn</p>	<p>At 16 or 52 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations • Adverse events • Mortality <p>(Incidence and rate exacerbations)</p>
<p>Castro et al., 2015³² BREATH-1 Phase 3 RCT of add-on therapy Moderate</p>	<ul style="list-style-type: none"> • Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS with or without another controller 	<ul style="list-style-type: none"> • Reslizumab 3 mg/kg IV every 4 wk (n = 245) • Placebo (n = 244) 	<p>At 16 or 52 weeks:</p> <ul style="list-style-type: none"> • Symptom control • QoL • Exacerbations • Adverse events

	<ul style="list-style-type: none"> • ACQ score > 1.5 • Eosinophils \geq 400/μL 	Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids, LTRAs, and cromolyn	<ul style="list-style-type: none"> • Mortality (Incidence and rate of exacerbations)
Corren et al., 2016 ³³ No trial name Phase 3 RCT of add-on therapy Moderate	<ul style="list-style-type: none"> • Aged 18 to 65 with inadequately controlled asthma • On at least a medium-dose ICS • ACQ score > 1.5 • Allergic asthma (20%) 	<ul style="list-style-type: none"> • Reslizumab 3 mg/kg IV every 4 wk (n = 398) • Placebo (n = 98) Continued LABAs, LTRAs, 5-lipoxygenase inhibitors, or cromolyn; rescue medications as needed	At 16 weeks: <ul style="list-style-type: none"> • Symptom control • Adverse events • Mortality (FEV1 change)
Abbreviations. ACQ = Asthma Control Questionnaire; FEV ₁ = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IV = Intravenous; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wk(s) = week(s)			

Omalizumab Compared to Placebo

Twenty-three RCTs evaluated 1 or more dosing regimens of omalizumab for management of moderate to severe asthma.¹ One RCT used a no-treatment control group, and 2 RCTs used a control group characterized as optimized asthma therapy and best standard-of-care treatment.¹ The rest of the RCTs used placebo comparators.¹ There was strong variation in QoE ratings for outcomes related to omalizumab, ranging from very low to high.¹ Eight studies were evaluated as high risk for bias for various methodological issues, including lack of intervention masking, no description of randomization and allocation concealment or baseline differences among groups, selective outcome reporting, selection bias related to recruitment or unexplained post-randomization exclusions, deviation from intervention protocol, and high attrition.¹

Of the 23 included studies, 15 were entirely sponsored by the manufacturer, 6 had partial funding from the manufacturer, 1 reported no sponsor information, and 1 was funded by a government agency.¹ All but 1 study were multicenter trials.¹ Six studies were phase 4 post marketing RCTs, 4 studies were phase 3 RCTs, 1 study was a phase 2 RCT, and trial phase was not reported in the remaining 12 studies.¹ Six studies were conducted in the US, and the rest were conducted in other countries or globally in multiple countries.¹ Eight studies were conducted among adults, 4 were conducted among participants under age 18 years, and the rest were conducted among participants aged 12 and older.¹

Study entry criteria were reasonably similar across studies. In addition to requiring moderate to severe asthma, most required participants to have allergic asthma, including evidence of a positive skin prick or radioallergosorbent test (RAST) for 1 or more environmental allergens.¹ Most studies were designed to evaluate the efficacy of omalizumab as add-on therapy to existing asthma controller medications and rescue medications as needed. However, 6 RCTs were designed to evaluate the efficacy of omalizumab as add-on therapy during a steroid-tapering cointervention.¹ The specific details for the 23 RCTs are summarized in the DERP report.¹

Symptom control

- Pooled data from 3 add-on efficacy RCTs in adults (N = 721) showed omalizumab was more effective over placebo in symptom control as measured by difference in mean change in days with asthma symptoms over 1 to 2 weeks (pooled estimate, -0.48 days; 95% CI, -0.74 to -0.23); high QoE.¹
- Pooled data from 2 add-on efficacy RCTs in adults (N = 691) revealed omalizumab had a larger improvement in mean change from baseline on the ACT compared with placebo (pooled estimate, 0.52; 95% CI, 0.14 to 0.91); low QoE.¹

Quality of Life

Across the add-on efficacy trials and the trials that included steroid-tapering, omalizumab was more effective than placebo for improving quality of life as measured by the AQLQ mean change from baseline (moderate QoE), and MCID response on the AQLQ (high QoE).¹ However, in 2 trials of add-on efficacy with steroid-tapering in children ages 6 to 11, there was no difference in change in quality of life as measured by the Pediatric AQLQ (PAQLQ) mean change from baseline in 1 trial (low QoE) and no difference as measured by a large MID response in the PAQLQ in another trial (low QoE).¹

- Four add-on efficacy RCTs (N = 1,791) showed omalizumab was more effective compared to placebo in improving quality of life as measured by the AQLQ mean change from baseline, but data suitable for pooling was not available.¹ Across the 4 RCTs, the mean improvement from baseline in the AQLQ score was larger for participants allocated to omalizumab compared to placebo or control (range, 0.29 to 1.19); moderate QoE.¹
- Three add-on efficacy RCTs (N = 1,662) demonstrated omalizumab was more effective compared to placebo as measured by the proportion of respondents achieving an MCID (0.5 points) on the AQLQ at 28 to 46 weeks (pooled RRs range, 1.15; 95% CI 1.07 to 1.23); high QoE.¹
- One steroid-sparing RCT (N = 627) showed no difference between omalizumab versus placebo as measured by difference in mean change from baseline on the PAQLQ: 0.04; 95% CI, NR; low QoE.¹
- In 1 steroid-sparing RCT (N = 334), there was no difference in proportion of participants achieving a large MCID (1.5 points) on the PAQLQ (RRs, 1.45 to 1.67 across trial phases but measures of variance did not exclude a null effect); low QoE.¹

Exacerbations

- Data from 12 add-on efficacy RCTs (N = 3,646) and 4 steroid-sparing RCTs (N = 2,032) revealed omalizumab was more effective over placebo for reducing the incidence of exacerbations in adults (pooled RR, 0.71; 95% CI, 0.61 to 0.82 for add-on efficacy trials; range of pooled RRs, 0.55 to 0.67 across trial phases in steroid-sparing RCTs; absolute rates NR); high QoE.¹
- Data from 3 add-on efficacy RCTs (N = 1,309) showed omalizumab was more effective compared with placebo in adults as measured by the incidence or rate of exacerbations requiring ED or hospital visits (RRs and IRRs range from 0.23 to 0.66 across studies; absolute rates NR); moderate QoE.¹

Corticosteroid Use

- Three steroid-sparing RCTs in adults (N = 1,317) showed omalizumab was more effective than placebo as measured by the proportion of participants who reduced their maintenance inhaled steroid dose by 50% or more (pooled RRs range, 1.39 to 1.40 across various steroid trial phases: steroid-stable, steroid-reduction, and extension); high QoE.¹

Overall Adverse Effects

- 17 RCTs (N = 23,751) reported no difference in AEs at 16 to 60 weeks of follow-up between omalizumab versus placebo (pooled RR, 1.00; 95% CI, 0.97 to 1.03); high QoE.¹

Serious Adverse Effects

- 16 RCTs (N = 23,561) reported fewer SAEs occurred among participants allocated to omalizumab versus placebo (pooled RR, 0.76; 95% CI, 0.59 to 0.99); moderate QoE.¹

Mortality

- Nine studies reported mortality outcomes. In 5 studies, no deaths occurred in either study group, and in the remaining 4 studies, deaths were very rare (6 deaths out of 1,738 participants).⁵

New Indications

Mepolizumab

Mepolizumab received FDA-approval in September 2020 for an expanded indication for the treatment of adult and pediatric patients aged 12 years and older with HES with a duration of 6 months or greater without an identifiable non-hematologic secondary cause.² The recommended mepolizumab dose for HES is 300 mg (given as 3 separate 100 mg injections) SC every 4 weeks, this dose is significantly higher than recommended dosing in asthma patients.² Hypereosinophilic syndromes are rare disorders marked by the overproduction of eosinophils which cause damage to multiple organs.³⁴ Hypereosinophilia has generally been defined as a peripheral blood eosinophil count greater than 1,500 cells per μL .³⁵ The goal of treatment for patients with HES is the long-term reduction of blood and tissue eosinophil levels to reverse and prevent end-organ damage.³⁴ With the exception of patients with imatinib-sensitive HES variants (including those associated with the FIP1-like-1-platelet-derived growth factor receptor alpha fusion gene [FIP1L1-PDGFR α]), the standard of care consists of glucocorticoids and cytotoxic/immunosuppressive therapy.³⁴ First-line therapy for all patients with the FIP1L1-PDGFR α mutation is the tyrosine kinase inhibitor, imatinib mesylate.³⁵

The evidence for the expanded mepolizumab indication was provided from 1 trial conducted in 104 adult and adolescent patients aged 12 years and older with FIP1L1-PDGFR α -negative HES.³⁴ Patients with non-hematologic secondary HES or FIP1L1-PDGFR α kinase-positive HES were excluded from the trial.³⁴ The study was a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients entering the trial had experienced at least 2 HES flares within the previous 12 months and a blood eosinophil count of 1,000 cells per μL or higher during screening.³⁴ Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy.³⁴ Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy.³⁴ Subjects received 300 mg of mepolizumab or placebo subcutaneously once every 4 weeks.

The primary endpoint was the proportion of patients who experienced a flare during the 32-week treatment period.³⁴ An HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase oral steroids or increase/add immunosuppressive HES therapy.³⁴ Over the 32-week treatment period, the incidence of HES flare over the treatment period was 56% (30 of 54 subjects) for the placebo group and 28% (15 of 54 subjects) for the group treated with mepolizumab (OR 0.28; 95% CI 0.12 to 0.64; $P = 0.002$).³⁴ Difference was observed between mepolizumab and placebo arms in the time to first HES flare. The risk of first HES flare over the treatment period was 66% lower for patients treated with mepolizumab compared with placebo (26.3% vs. 52.7%; hazard ratio: 0.34; 95% CI 0.18, 0.67, $P = 0.002$).³⁴ Similar proportions of patients in the mepolizumab and placebo groups experienced on-treatment adverse events (89 versus 87 percent, respectively).³⁴ The higher mepolizumab dose was well tolerated in the HES trial and no additional mepolizumab adverse reactions were identified than those reported in the severe asthma trials.²

As of July 2021, mepolizumab is also FDA-approved as add-on treatment for adults with chronic sinusitis with nasal polyps who have an inadequate response to nasal corticosteroids.

Omalizumab

In November 2020, omalizumab received FDA-approval for treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add on maintenance treatment.³ The recommended dose for treatment of nasal polyps is 75 mg to 600 mg SC every 2 or 4 weeks based on serum total IgE level and by body weight.³ In contrast, the asthma dosing for omalizumab is 75 mg to 375 mg SC every 2 or 4 weeks based on serum total IgE level and body weight.³

The safety and efficacy of omalizumab was evaluated in two, randomized, multicenter, double-blind, placebo-controlled clinical trials that enrolled patients with nasal polyps with inadequate response to nasal corticosteroids (POLYP 1, n=138; POLYP 2, n=127).³⁶ Patients received weight-based omalizumab or placebo SC every 2 or 4 weeks, for 24 weeks followed by a 4-week follow-up period.³⁶ All patients received background nasal mometasone therapy during both the treatment period and during a 5-week run-in period.³⁶ Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a nasal polyp score (NPS) of at least 5 with NPS greater than or equal to 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and given a score of 0 to 4 per nostril for a total NPS range of 0 to 8. Scores were based on the following criteria: 0= no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; and 4=large polyps causing complete obstruction of the inferior nasal cavity.³⁶ Patients were furthermore required to have a weekly average of nasal congestion score (NCS) greater than 1 prior to randomization, indicating moderate to severe congestion despite use of nasal mometasone.³⁶ Nasal congestion was measured by a daily assessment on a 0 to 3 point severity scale (0=none, 1=mild, 2=moderate, 3=severe).³⁶ The co-primary endpoints in POLYP 1 and 2 were NPS and average daily NCS at Week 24.³⁶ In POLYP 1 and POLYP 2, the mean changes from baseline at week 24 for omalizumab versus placebo were as follows: NPS, -1.08 versus 0.06 (Difference: -1.14; 95% CI -1.59 to -0.69; P <0.0001) and -0.90 versus -0.31 (Difference: -0.59; 95% CI -1.05 to -0.12; P=0.014); NCS, -0.89 versus -0.35 (Difference: -0.55; 95% CI -0.84 to -0.25; P = 0.0004) and -0.70 versus -0.20 (Difference: -0.50; 95% CI -0.80 to -0.19; P = 0.0017).³⁶ In both trials, patients who received omalizumab had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo.³

New Formulations

Omalizumab

In April 2021, the FDA approved a prefilled syringe for self-administration of omalizumab for treatment of persistent asthma in patients 6 years and older, chronic idiopathic urticaria in patients 12 years and older, and nasal polyps in patients 18 years and older.³ Chronic idiopathic urticaria is not funded by HERC, therefore, claims for this indication are not covered for Oregon Medicaid FFS patients.

Mepolizumab

In September 2019, the FDA approved a new prefilled syringe for self-administration of mepolizumab for treatment of severe eosinophilic asthma in patients 6 years and older, adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), and adults and adolescents aged 12 years and older with HES without an identifiable non-hematologic secondary cause.²

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
montelukast sodium	MONTELUKAST SODIUM	ORAL	TAB CHEW	Y
montelukast sodium	SINGULAIR	ORAL	TAB CHEW	Y
montelukast sodium	MONTELUKAST SODIUM	ORAL	TABLET	Y
montelukast sodium	SINGULAIR	ORAL	TABLET	Y
benralizumab	FASENRA PEN	SUB-Q	AUTO INJCT	N
benralizumab	FASENRA	SUB-Q	SYRINGE	N
mepolizumab	NUCALA	SUB-Q	AUTO INJCT	N
mepolizumab	NUCALA	SUB-Q	SYRINGE	N
mepolizumab	NUCALA	SUB-Q	VIAL	N
montelukast sodium	MONTELUKAST SODIUM	ORAL	GRAN PACK	N
montelukast sodium	SINGULAIR	ORAL	GRAN PACK	N
omalizumab	XOLAIR	SUB-Q	SYRINGE	N
omalizumab	XOLAIR	SUB-Q	VIAL	N
reslizumab	CINQAIR	INTRAVEN	VIAL	N
roflumilast	DALIRESP	ORAL	TABLET	N
zafirlukast	ACCOLATE	ORAL	TABLET	N
zafirlukast	ZAFIRLUKAST	ORAL	TABLET	N
zileuton	ZYFLO	ORAL	TABLET	N
zileuton	ZILEUTON ER	ORAL	TBMP 12HR	N

Appendix 2: Medline Search Strategy

Databases(s): Ovid MEDLINE (R) 1996 to May Week 2, 2021

Ovid MEDLINE(R) In-Process and In-Data-Review Citations 1946 to May Week 12, 2021

1. benralizuamb.mp	303
2. Mepolizumab.mp	704
3. Omalizumab	1769
4. Reslizumab.mp	234
5. Dupilumab.mp	812
6. 1 or 2 or 3 or 4 or 5	3272
7. limit 6 to (english language and humans and yr="2020-current")	351
8. limit to clinical trial or guideline, or meta-analysis or practice guideline or systematic review	37

Appendix 3: Prior Authorization Criteria

Monoclonal Antibodies for Severe Asthma

Goal(s):

- Restrict use of monoclonal antibodies to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria).

Length of Authorization:

- Up to 12 months

Requires PA:

- Biologic drugs with indications for asthma (see **Table 2** below) (pharmacy and provider-administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	Maximum Dose
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	Maximum Dose
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	464/28 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved indications and ages

Drug	Eosinophilic Asthma	Moderate to Severe Persistent Asthma	Hypereosinophilic Syndrome (HES)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Atopic Dermatitis (AD)
Dupilumab	≥12 years (or with oral corticosteroid dependent asthma)				≥18 years	≥6 years
Benralizumab	≥12 years					
Reslizumab	≥18 years					
Mepolizumab	≥6 years		≥ 12 years	≥18 years	≥18 years	
Omalizumab		≥6 years			≥18 years	

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the diagnosis an OHP-funded diagnosis? <u>Note:</u> chronic idiopathic urticaria is not an OHP-funded condition	Yes: Go to #4	No: Pass to RPh. Deny; not funded by the OHP.
4. Is the request for an FDA-approved indication and age (Table 2)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria

<p>5. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?</p>	<p>Yes: Go to #6</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>
<p>6. Is the diagnosis Severe Atopic Dermatitis (AD)?</p>	<p>Yes: Go to #7</p>	<p>No: Go to #9</p>
<p>7. Is the medication being prescribed by or in consultation with a dermatologist or a provider who specializes in care of atopic dermatitis?</p>	<p>Yes: Go to #8</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>8. Does the patient have a documented contraindication or failed trial of the following treatments:</p> <ul style="list-style-type: none"> • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) <u>AND</u> • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) <u>AND</u> • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)? 	<p>Yes: Document drug and dates trialed and intolerances (if applicable):</p> <p>1. _____(dates)</p> <p>2. _____(dates)</p> <p>3. _____(dates)</p> <p>Approve for length of treatment; maximum 6 months.</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>

Approval Criteria		
9. Is the request for eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	Yes: Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	No: Go to #10
10. Is the request for the treatment of a patient with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	Yes: Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	No: Go to #11
11. Is the request for treatment of nasal polyps?	Yes: Go to # 12	No: Go to #14
12. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	Yes: Go to # 13	No: Pass to RPh. Deny; medical appropriateness
13. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks ¹)?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness
14. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	Yes: Go to #15	No: Pass to RPh. Deny; medical appropriateness.
15. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	Yes: Go to #16 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	No: Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
16. Has the patient been adherent to current asthma therapy in the past 12 months?	Yes: Go to #17	No: Pass to RPh. Deny; medical appropriateness.
17. Is the patient currently receiving another monoclonal antibody for asthma (e.g., dupilumab, omalizumab, mepolizumab, benralizumab or reslizumab)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #18
18. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	Yes: Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	No: Go to #19
19. If the request is for asthma with an eosinophilic phenotype, can the prescriber provide documentation of severe eosinophilic asthma, confirmed by blood eosinophil count ≥ 300 cells/ μ L in the past 12 months?	Yes: Approve once every 4 to 8 weeks for up to 12 months. Note: Initial benralizumab dose is 30 mg every 4 weeks x 3 doses followed by 30 mg every 8 weeks Document eosinophil count (date):_____	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew therapy for EGPA, nasal polyps, or HES?	Yes: Go to #2	No: Go to #3

Renewal Criteria		
2. Have the patient's symptoms improved with therapy?	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	Yes: Go to #4	No: Go to #5
4. Have the patient's symptoms improved with dupilumab therapy? <ul style="list-style-type: none"> at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR at least a 2 point improvement on the Investigators Global Assessment (IGA) score? 	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness.
5. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness.
6. Has the number of ED visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	Yes: Approve for up to 12 months.	No: Pass to RPh. Deny; medical appropriateness.

- Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016; 4:Cd011993.

P&T Review: 8/21 (DM); 10/20 (KS), 7/19 (DM); 7/18; 7/16
Implementation: 8/19/19, 8/15/18, 8/16

Dupilumab -RETIRE

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis an OHP funded diagnosis?	Yes: Go to #3	No: Pass to RPh. Deny, not funded by the OHP.
3. Is this a request for continuation of therapy?	Yes: Go to Renewal Criteria	No: Go to #4
4. Is the product requested preferred?	Yes: Approve for length of treatment; maximum 1 year.	No: Go to #5

Approval Criteria

<p>5. Will the prescriber consider a change to a preferred product?</p> <p>Message: Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.</p>	<p>Yes: Inform provider of preferred alternatives.</p> <p>Approve for length of treatment; maximum 1 year.</p>	<p>No: Go to # 6</p>
<p>6. Is the medication being prescribed by or in consultation with a dermatologist, otolaryngologist, or allergist who specializes in management of severe asthma?</p>	<p>Yes: Go to # 7</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>7. What is the age of the patient?</p> <ul style="list-style-type: none"> Dupilumab injection is FDA approved for patients 12 years of age and older for management of atopic dermatitis and moderate-to-severe asthma. 	<p>Age 11 years or younger: Pass to RPh. Deny; medical appropriateness.</p>	<p>Ages 12 years and older: Go to #8</p>
<p>8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)?</p>	<p>Yes: Go to #9</p>	<p>No: Go to #10</p>

Approval Criteria

<p>9. Does the patient have a documented contraindication or failed trial of the following treatments:</p> <ul style="list-style-type: none"> • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) <u>AND</u> • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) <u>AND</u> • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)? 	<p>Yes: Document drug and dates trialed and intolerances (if applicable):</p> <p>1. _____(dates)</p> <p>2. _____(dates)</p> <p>3. _____(dates)</p> <p>Approve for length of treatment; maximum 6 months.</p>	<p>No: Pass to RPh. Deny; medical appropriateness</p>
<p>10. Is the claim for moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma?</p>	<p>Yes: Go to #11</p>	<p>No: Go to # 14</p>
<p>11. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?</p>	<p>Yes: Pass to RPh. Deny; medical appropriateness.</p>	<p>No: Go to #12</p>
<p>12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?</p>	<p>Yes: Go to #13</p> <p>Document number of hospitalizations or ED visits in past 12 months: _____ . This is the baseline value to compare to in renewal criteria.</p>	<p>No: Pass to RPh. Deny; medical appropriateness.</p>

Approval Criteria		
13. Has the patient been adherent to current asthma therapy in the past 12 months?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness.
14. Does the patient have chronic rhinosinusitis with nasal polyposis and is the patient an adult? *Use of dupilumab in chronic rhinosinusitis with nasal polyposis is only approved in adults.	Yes: Go to # 15	No: Pass to RPh. Deny; medical appropriateness.
15. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks ¹)?	Yes: Approve for 6 months	No: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to renew dupilumab for atopic dermatitis?	Yes: Go to #2	No: Go to #3
2. Have the patient's symptoms improved with dupilumab therapy? <ul style="list-style-type: none"> at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR at least a 2 point improvement on the Investigators Global Assessment (IGA) score? 	Yes: Approve for 12 months	No: Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. Is the request to renew dupilumab for moderate to severe asthma?	Yes: Go to # 4	No: Go to # 6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness.
5. Has the patient reduced their systemic corticosteroid dose by $\geq 50\%$ compared to baseline?	Yes: Approve for up to 12 months.	No: Pass to RPh. Deny; medical appropriateness.
6. Have the patient's symptoms of chronic rhinosinusitis with polyposis improved?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny; medical appropriateness.

1. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016; 4:Cd011993.

P&T/DUR Review: 9/21 (DM); 9/19 (DM); 7/19 (DM)
 Implementation: TBD: 8/19/19