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Class Review with New Drug Evaluations: Monoclonal Antibodies for Asthma

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Purpose for Class Review:
To review evaluate the place in therapy for 2 new monoclonal antibodies approved for severe asthma, mepolizumab and reslizumab, in addition to the evidence and guideline recommendations for omalizumab.

Research Questions:
1. Does mepolizumab or reslizumab have superior efficacy to placebo and are they more effective than alternative drugs in clinically relevant outcomes for the treatment of severe asthma?
2. Is mepolizumab or reslizumab safer than currently utilized drugs in the treatment of severe asthma?

Conclusions:
- Moderate quality evidence over 32 weeks supports the efficacy of mepolizumab 100 mg administered subcutaneously (SC) every 4 weeks in reducing about one clinically significant asthma exacerbation (an exacerbation that requires use of systemic corticosteroids, an emergency department visit, and/or hospitalization) in patients with severe eosinophilic asthma (broadly defined as peripheral blood count ≥300 cells/µL in past year or ≥150 cells/µL immediately before trial initiation) compared to placebo. This statistically significant difference amounted to about a 50% relative reduction with mepolizumab. All patients received standard of care for severe asthma (i.e., high dose inhaled corticosteroid [ICS], long-acting beta-agonist [LABA] and a rescue short-acting bronchodilator).
- Low quality evidence suggests mepolizumab 100 mg SC every 4 weeks may also reduce the rate of exacerbations that require hospitalization or emergency department visits compared with placebo, with a relative risk reduction of 61% (95% CI, 17 to 82%; p=0.02).
- Low quality evidence suggests mepolizumab may be associated with a statistically significant and clinically meaningful improvement in quality of life. The difference in total St. George's Respiratory Questionnaire scores from baseline between mepolizumab and placebo was -7.0 points (95% CI, -10.2 to -3.8). Low quality evidence also suggests mepolizumab may be associated with a statistically significantly symptom improvement. The difference in total Asthma Control Questionnaire (ACQ) scores from baseline between mepolizumab and placebo was -0.44 points (95% CI, -0.61 to -0.23); however, this difference did not exceed the minimal clinically important difference of 0.5 points.
- Low quality evidence also suggests mepolizumab may decrease chronic daily doses of oral corticosteroids (OCS). Mepolizumab resulted in 50% or greater reduction of OCS dose in 54% of patients versus 33% with placebo (OR 2.26; 95% CI, 1.10-4.65; p=0.03). However, there was no statistically significant difference in the number of patients able to discontinue chronic OCS use between the 2 groups.
- There is insufficient evidence to differentiate differences in efficacy between mepolizumab and other monoclonal antibodies approved for severe asthma.

- Safety data from Phase 3 trials and 2 long-term safety studies for mepolizumab reveal no major safety concerns at 1 to 3.5 years of treatment. Adverse events of interest for mepolizumab are similar to other monoclonal antibodies and include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity.
- The mepolizumab and placebo groups had similar frequencies of serious adverse events, with the majority of events related to asthma exacerbations. However, patients 12 to 17 years of age, elderly patients, and non-white racial groups were underrepresented in clinical trials. Therefore, the safety of mepolizumab in these populations is unclear.
- There is insufficient evidence to differentiate differences in safety between mepolizumab and other monoclonal antibodies for severe asthma of any phenotype.
- Moderate quality evidence over 52 weeks supports the efficacy of reslizumab 3 mg/kg intravenous (IV) infusion every 4 weeks in reducing the number of patients experiencing at least one asthma exacerbation in adults (≥18 years) with severe eosinophilic asthma (broadly defined as peripheral blood count ≥400 cells/µL) compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an absolute risk reduction (ARR) of 18% and a number-needed-to-treat (NNT) of 5 over 52 weeks. An exacerbation was defined as an event that required use of systemic corticosteroids, a 2-fold increase in the dose of either inhaled corticosteroid (ICS) or oral corticosteroids (OCS) for 3 or more days, an emergency department (ED) visit, and/or hospitalization or unscheduled physician's office visit. All patients received standard of care for severe asthma (i.e., high dose ICS, long-acting beta-agonist [LABA] and a rescue short-acting bronchodilator).
- Low quality evidence suggests reslizumab 3 mg/kg IV every 4 weeks does not reduce the rate of exacerbations that require hospitalization or ED visits compared with placebo (RR 0.66; 95% CI 0.38 to 1.16).
- Moderate quality evidence suggests reslizumab is associated a clinically meaningful improvement in quality life, defined as a 0.5 point reduction or more in the Asthma Control Questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ).
- There are insufficient data to support reslizumab use in pediatric patients under 18 years of age. Although the sample size was small, there was an increase in asthma exacerbation rates among adolescents. Reslizumab should not be used in this patient population until evidence of benefit is clear.
- Reslizumab is associated with similar frequencies of serious adverse events as placebo, with the majority of events related to asthma exacerbations. However, pediatric and elderly patients, U.S. patients, and non-white racial groups were underrepresented in clinical trials. Therefore, the safety of reslizumab in these populations is unclear.
- There is insufficient evidence to differentiate differences in efficacy or safety between reslizumab and other monoclonal antibodies for severe asthma of any phenotype.
- Overall, there is moderate quality evidence that omalizumab is more effective than placebo in reducing exacerbations and hospitalizations as adjunctive therapy to standard therapy in IgE-mediated moderate to severe asthma. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma. Limited evidence is available in children.
- Although distinctly different, there is no evidence to support using omalizumab in combination with either reslizumab or mepolizumab.

Recommendations:

- Designate mepolizumab and reslizumab as a non-preferred drug subject to Prior Authorization (PA) criteria in **Appendix 2**.

Background:

An estimated 22 million Americans have asthma, which affects people of all ages and can have a significant impact on quality of life and daily functioning.[1] Only 5-10% of people with asthma have severe asthma but they account for about 50% of all healthcare costs associated with asthma. [1] Severe asthma is characterized by daily symptoms, awakening most nights due to symptoms and significant limitations in normal activities.[1,2] The European Respiratory Society

(ERS)/American Thoracic Society (ATS) defines severe asthma as asthma that (1) requires treatment with high dose ICS plus a second controller (e.g., LABA) during the previous year and/or use OCS for 50% or more of the previous year or (2) remains uncontrolled despite this therapy.[3] However, chronic use of OCS may result in other complications, including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, diabetes, and increased risk for infections. [1]

Clinical trials may further define patients with severe asthma as those whose asthma worsens when high dose ICS or OCS are tapered but do not otherwise meet criteria for uncontrolled asthma and patients with evidence of any one of the 4 following criteria for uncontrolled asthma who are currently on high dose ICS therapy: (1) poor symptom control (ACQ score consistently greater than 1.5 or Asthma Control Test [ACT] score less than 20; (2) frequent severe exacerbations that have required use of OCS for more than 3 days on 2 separate occasions in the previous year; (3) serious exacerbations that resulted in at least 1 hospitalization in the previous year; or (4) airflow limitation (pre-bronchodilator forced expiratory volume in 1 second (FEV_1) less than 80% of the normal predicted volume with a reduced FEV_1/Forced Vital Capacity (FVC) defined as less than the lower limit of normal.[3] However, uncontrolled asthma is multifactorial, and issues such as incorrect diagnosis, comorbidities and nonadherence to prescribed therapy, and psychosocial issues are major causes for treatment failure.[2] The Global Initiative for Asthma (GINA) guidelines recommend patients with severe asthma, despite correct inhaler use and adherence to standard of care, be seen by an asthma specialist.[4] These patients should be seen 1 to 3 months after starting specific treatment for eosinophilic severe asthma, and every 3–12 months thereafter.[4] All patients should be seen within 1 week after an exacerbation.[4]

Clinically relevant outcomes for severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of OCS; 3) improved quality of life; and 4) improved symptom management. Four 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 ACQ is a 5- or 7-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[5] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 the minimally clinical important difference. [5] The Asthma Quality of Life Questionnaire (AQLQ) is a 32-item quality-of-life instrument that assesses both physical and emotional impact of disease.[6] Scores range from 1 (severely impaired) to 7 (not impaired at all), with higher scores indicating better quality of life. [6] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument. [6] The St. George's Respiratory Questionnaire (SGRQ) is a 50-item quality-of-life tool for patients with obstructive airway disease.[7] The questionnaire is composed of 2 parts. Part 1 assesses symptoms and part 2 assesses limitation of activities and its social and psychological impact. [7] Scores range from 0 to 100, with higher scores indicating more limitations. [7] A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment. [7] Lastly, the ACT is a tool used to identify patients with poorly controlled asthma.[8] The test contains 5 items that assess the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control. [8] Scores range from 5 (poor control of asthma) to 25 (complete control of asthma). [8] An ACT score greater than 19 indicates well-controlled asthma, with a change of 3 points the minimally clinical important difference over time. [8]

Omalizumab is a monoclonal antibody that has been available for over a decade to help manage severe allergic asthma with use of other asthma controllers (e.g., ICS, LABA, etc.).[9] Omalizumab is also approved for the treatment of chronic idiopathic urticaria, a condition that is not funded by the Oregon Health Plan (OHP). Mepolizumab and reslizumab are humanized monoclonal antibodies recently approved to manage severe asthma. These agents are approved and studied in patients with severe asthma and eosinophilic phenotype, though this phenotype has not been clearly defined outside of these trials and a consensus has not been developed to identify this phenotype in a clinically useful way.[10–12] Eosinophilic asthma is found in patients with both non-severe and severe disease and is often associated with response to corticosteroids.[13,14]However, some patients with eosinophilic asthma may not sufficiently respond to OCS .[13,14] Persistence of eosinophils in the airways despite ICS therapy has been associated with severe asthma, and higher airway and blood eosinophil counts have been

associated with increased risk for asthma exacerbations.[14–16] Mepolizumab and reslizumab bind to interleukin-5 (IL-5), which decreases IL-5 signaling and decreases eosinophils in the blood and tissue.[17] They were studied as add on therapy for patients inadequately controlled on traditional controller medications, which may include inhaled corticosteroids, long-acting inhaled beta-agonists, mast cell stabilizers and leukotriene modifiers. Reslizumab was studied in patients with asthma with sputum eosinophil count ≥3%. However, in clinical trials blood eosinophil was used a surrogate to sputum eosinophilia because it is more accessible.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Table 1. Indications and Dosing

Drug Name	Indications	Strength/Route	Dose and Frequency
Cinqair (reslizumab)[18]	Add-on for severe eosinophilic asthma (≥18 y/o)	Intravenous infusion	3 mg/kg every 4 weeks
Nucala (mepolizumab)[17]	Add-on for severe eosinophilic asthma (≥12y/o)	Subcutaneous Injection	100 mg SubQ every 4 weeks
Xolair (omalizumab)[9]	Moderate-to-severe persistent and uncontrolled asthma (≥12 y/o) Chronic idiopathic urticarial (≥12 y/o)	Subcutaneous Injection	150 to 375 mg SubQ every 2 or 4 weeks

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Boxed Warnings and Risk Evaluation Mitigation Strategies. For drugs recently approved, the manufacturer's summary prescribing information is provided.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A Cochrane systematic review evaluated the use of omalizumab compared to placebo or conventional therapy for the treatment for asthma in adults and children.[19] A total of 25 RCTs were included in the review. Studies including participants on subcutaneous omalizumab with moderate or severe asthma who were on background ICS therapy demonstrated a significant reduction (moderate quality evidence) in asthma exacerbations (OR 055; 95% CI 0.42 to 0.60; n=3261) and hospitalizations (OR 0.16; 95% CI 0.06 to 0.42; n=1824). Little effect on exacerbations was seen when only participants with severe asthma were included (OR 1.00; 95% CI 0.50 to 1.99). Participants were also more likely to be able to withdraw their ICS compared to those treated with placebo (OR 2.50; 95% CI 2.00 to 3.13). However, there was no significant difference between omalizumab and placebo in the number of participants who were able to withdraw from oral corticosteroid therapy (OR 1.18; 95% CI 0.53 to 2.63). There were fewer serious adverse events reported in the omalizumab group compared to placebo (OR 0.72; 95% CI 0.57 to 0.91) but more injection site reactions. Overall, omalizumab was found to be more effective in reducing exacerbations and hospitalizations as adjunctive therapy to inhaled steroids and during steroid tapering. Effects were less profound when only participants with severe disease were included and evidence remains insufficient for the treatment of severe, oral corticosteroid dependent asthma. Limited evidence is available in children.

Another systematic review and economic evaluation was performed by the Health Technology Assessment program of the National Institute for Health Research on omalizumab for the treatment of severe persistent allergic asthma.[20] Studies with omalizumab as add-on therapy to standard care compared with standard therapy alone in adults and children were included. Eleven RCTs and 15 observational trials were included. Studies had variable inclusion criteria but most required ICS background therapy. In adults and adolescents aged 12 years and older, omalizumab reduced the rate of clinically significant exacerbations (RR 0.74; 95% CI 0.55 to 1.00) but did not reach statistical significance, and severe exacerbations (RR 0.50; 95% CI 0.32 to 0.78). There was insufficient evidence that omalizumab reduced the use of oral corticosteroids. Only one trial in children demonstrated a decrease in clinically significant exacerbations (RR 0.67; 95% CI 0.44 to 0.995). Evidence on the safety of omalizumab in children was limited. There is no direct evidence comparing omalizumab to oral corticosteroids as add-on therapy.

Lastly, omalizumab treatment for adults and children with allergic asthma was reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH) in the form of a rapid response.[21] Consistent with previous reviews, the authors found that the evidence suggests omalizumab decreases asthma exacerbations and hospitalizations in adults and adolescents with moderate to severe allergic asthma inadequately controlled by standard therapy with less evidence in children. In addition, omalizumab was found to improve asthma symptoms and be associated with a reduction in inhaled corticosteroid use compared to placebo. A meta-analysis was not done, but rather existing evidence was summarized. They also summarized economic evaluations. Evaluations in the UK and Japan did not find omalizumab to be cost-effective as add-on to standard of care while evaluations by the Dutch and Spanish did find it to be cost effective.

In addition to asthma, omalizumab is also FDA approved for the treatment of chronic idiopathic urticaria (CIU). CADTH also conducted a systematic review evaluating the beneficial and harmful effects of omalizumab or the treatment of CIU in adults and adolescents who remain symptomatic despite H_1 anthistamine treatment.[22] The review included 3 RCTs that compared omalizumab to placebo in 978 adult and adolescent patients with CIU refractory to antihistamines. The primary outcomes were improvement in the Weekly Itch Severity Score (ITSS) and the Uticaria Activity Score over 7 days (UAS7). These have been validated for use in CIU and were considered clinically relevant by the authors. All 3 trials showed improvements in CIU symptoms as measured by both the UAS7 and WISS. Results were not pooled, but one major trial showed an improvement in UAS7 of -10.02 (95% CI -13.17 to -6.86) with omalizumab 300 mg compared to placebo and in WISS of -4.52 (95% CI -5.97 to -3.08) at week 12. The authors found these results to be clinically significant based on published minimal clinically important differences for these outcomes. The 150 mg dose in trials failed to show a clinically significant response compared to placebo. Omalizumab also appeared to significantly improve quality of life. However, outcomes assessed after the 16-week treatment free follow up period showed that the majority of efficacy outcomes did not maintain statistically improvements compared to placebo. Due to the chronic nature of the disease, it remains possible that long-term

therapy is necessary; however, there are no data on the efficacy and safety of re-treatment or to define the optimal interval between treatment courses. Patients receiving omalizumab were more likely to experience adverse effects overall, and headaches in particular than those in placebo.

Guidelines:
2014 guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) recommends that "omalizumab treatment should only be initiated in specialist centers with experience of evaluation and management of patients with severe and difficult asthma."[23] They also recommend omalizumab is only used in patients on high-dose ICS and LABA who have impaired lung function, are symptomatic with frequent asthma attacks, and have allergy as an important cause of their asthma.

Guidelines from The National Institute for Health and Clinical Excellence (NICE) from 2013 recommend omalizumab similarly as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimized standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (Defined as 4 or more courses in the previous year).[24] This recommendation is consistent with the guidelines from the National Heart, Lung and Blood Institute (NHLBI) asthma guidelines.

Mepolizumab NEW DRUG EVALUATION**:**

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The FDA approved mepolizumab based on data from 3 short-term, GSK-sponsored, placebo-controlled, international trials (Studies 97, 88, and 75).[16] Most study sites occurred outside North America and non-white racial groups were uniformly underrepresented in the trials. Applicability of the trials was further limited by extensive inclusion and exclusion criteria and limited duration of study in a relatively few number patients. However, the studies evaluated clinically relevant endpoints and had an overall low or unclear risk of bias for the domains assessed (see Table 1). In all 3 trials, mepolizumab was compared with placebo and all patients received standard of care for severe asthma, which included high dose ICS, a LABA (or other long-acting controller), and a rescue bronchodilator.

The FDA-approved dose of 100 mg SC every 4 weeks is supported by the data and corresponds to the lowest tested intravenous (IV) dose of 75 mg that provided meaningful reduction of exacerbations versus placebo.[16] Statistically significant reductions in asthma exacerbation rates were seen in 2 exacerbation studies for all mepolizumab doses but with no significant dose-response beyond the 75 mg IV dose, and no significant difference between the mepolizumab 75 mg IV dose and 100 mg SC dose.[16] Overall rates of exacerbations requiring ED visits or hospitalizations were low across all treatment groups in all studies (approximately 1 in every 5 to 10 exacerbations required ED visits or hospitalization).[16] However, exacerbations that did require an ED visit or hospitalization occurred less frequently in groups assigned to mepolizumab compared to the placebo groups.[16] The benefit of mepolizumab on asthma exacerbations was demonstrated in Studies 97 and 88, in which patients were selected based on a previous history of exacerbation and presence of an eosinophilic phenotype.[16] Study 97 used one or more criteria to identify the eosinophil phenotype.[16] However, analysis of the various criteria used to screen patients for enrollment found that number of asthma exacerbations in the prior year and peripheral blood eosinophil threshold (≥300 cells/µL in past year or ≥150 cells/µL at baseline) were the criteria that best selected for patients that showed benefit in asthma exacerbations.[16] In Study 75 (OCS reduction study), the same blood eosinophil threshold was prospectively used to screen patients for enrollment.[16]

Study 97 was a 52-week, multicenter, double-blind, phase 2, placebo-controlled, dose-ranging study of IV mepolizumab every 4 weeks in which the key phenotypic characteristics of the target population for the drug were investigated.[10] Patients recruited were on chronic high-dose ICS therapy with an additional controller agent with or without maintenance OCS. [10] Patients had a history of 2 or more exacerbations per year and eosinophilic airway inflammation, defined by serum eosinophil count (≥300 cells/μL), sputum eosinophils (≥3%), exhaled nitric oxide concentration (≥50 ppb) or loss of asthma control after 25% or more reduction in regular maintenance ICS or OCS dose. [10] The primary outcome was the annualized rate of asthma exacerbations. [10] Quality-of-life and asthma control were assessed by the AQLQ and ACQ questionnaires, respectively, as secondary outcomes.[11] The rate of clinically significant exacerbations (reported as per patient per year) for mepolizumab 75 mg IV every 4 weeks was 1.24 compared to 2.40 for the placebo group, a difference of -1.16 asthma exacerbations (rate ratio [RR] 0.52; 95% CI, 0.39 to 0.69; p<0.001). The rate of exacerbations that resulted in ED visits or hospitalization was reduced by 0.26 exacerbations for the 75 mg IV dose compared to placebo (RR 0.40; 95% CI, 0.19 to 0.81). However, no significant difference in total ACQ scores (Mean Difference [MD] -0.16 (95% CI, -0.39 to 0.07) or total AQLQ scores (MD –0.08 (95% CI, –0.16 to 0.32) were found.

Study 88 was a 32-week, multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled exacerbation study of SC (100 mg) and IV (75 mg) mepolizumab every 4 weeks in patients with severe asthma, most of whom did not yet require daily OCS.[11] The key characteristics used to identify eligible patients included a blood eosinophil count (≥150 cells/μL at screening or ≥300 cells/μL in the past 12 months), number of previous exacerbations (≥2), and high-dose ICS use plus an additional controller with or without OCS. [11] The primary outcome was the annualized rate of asthma exacerbations.[12] Quality-of-life and asthma control were assessed by the SGRQ and ACQ-5 questionnaires, respectively, as secondary outcomes. [11] The IV and SC groups had statistically significant 47% (95% CI, 28 to 60%) and 53% (95% CI, 36 to 65%) relative reductions in the mean rate of exacerbations, respectively, compared with placebo. [11] The SC group also experienced a statistically significant mean reduction in the rate of exacerbations requiring hospitalization or ED visits when compared with placebo (61%; 95% CI, 17 to 82%; p=0.02) but the IV group did not. [11] Both the IV and SC mepolizumab groups had statistically significant and clinically meaningful[7] improved total SGRQ scores versus placebo, with differences of –6.4 (95% CI, –9.7 to –3.2) and –7.0 (95% CI, –10.2 to –3.8), respectively. [11] Both the IV and SC mepolizumab groups also had statistically significantly improved ACQ scores versus placebo, with differences of –0.42 (95% CI, –0.61 to –0.23) and –0.44 (95% CI, –0.61 to –0.23), respectively; [11] however, these differences did not exceed the minimal clinically important difference of 0.5 points.[5]

Study 75 was a 24-week, multicenter, randomized, double-blind, phase 3, placebo-controlled study designed to investigate whether SC mepolizumab 100 mg every 4 weeks would allow patients on chronic OCS for severe eosinophilic asthma to reduce their OCS dose without loss of asthma control.[12] Eligible patients were on an OCS for at least 6 months equal to 5 to 35 mg daily of prednisone or its equivalent) and had presence of eosinophilic inflammation (blood eosinophil level ≥300 cells/μL anytime during the preceding 12 months before screening or 150 cells/μL at screening). [12] The primary outcome was reduction in OCS dose. [12] Quality-of-life and asthma control were assessed by the SGRQ and ACQ questionnaires, respectively, as secondary outcomes. [12] Before randomization, patient's OCS doses were tapered to the lowest effective dose that did not result in a clinically meaningful increase of 0.5 points in ACQ scores. These doses were used as a baseline measure from which dose reductions were made over a 16-week period. After 20 weeks on mepolizumab or placebo, 14% on mepolizumab completely stopped OCS compared to 8% on placebo and 23% of patients on mepolizumab had a 90-100% reduction in OCS compared to 11% on placebo. Overall, 36% of patients on mepolizumab had no reduction in OCS dose, developed uncontrolled asthma or withdrew from treatment, compared to 56% on placebo. The proportion of patients who had a reduction in OCS dose of 50% or more after 20 weeks was greater in patients on mepolizumab versus placebo (54% vs. 33%, respectively; odd ratio [OR] 2.26; 95% CI, 1.10 to 4.65; p=0.03; number-needed-to-treat = 5). Similarly, the proportion of patients who had a reduction in OCS dose equivalent to 5 mg or less daily of prednisone was greater in patients on mepolizumab versus placebo (54% vs. 32%, respectively; OR 2.45; 95% CI, 1.12 to 5.37; p=0.02; number-needed-to-treat = 5). Clinically meaningful improvements in asthma control (ACQ -0.52 points; 95% CI, -0.87 to -0.17; p=0.004) and quality-of-life (SGRQ -5.8 points; 95% CI, -10.6 to -1.0; p=0.02) were also noted in patients who received mepolizumab versus placebo.

Mepolizumab has not been studied against other monoclonal antibodies for comparative efficacy in severe asthma. It is also unknown whether the efficacy demonstrated in these trials would be sustained long-term. The trials included only 28 patients 12 to 17 years of age and only 38 patients at least 65 years of age.[16] The number of young and elderly patients was insufficient to determine whether this population would respond differently to mepolizumab.

Clinical Safety:

The safety of mepolizumab can be assessed over a time frame of 1 to 3.5 years from Studies 97, 88, and 75, and the ongoing safety extension Studies 61 and 66, where patients from the Studies 97, 88 and 75 were enrolled.[16] Adverse events of interest for monoclonal antibodies include allergic reactions, local injection site reactions, serious cardiac events, infections, malignancy, and immunogenicity. The mepolizumab and placebo groups had similar frequencies of serious adverse events (SAEs), with the majority of SAEs related to asthma exacerbation. [16] In patients who received at least 1 dose of study drug, discontinuation rates were low (about 1 to 3%). Common adverse events leading to early withdrawal were worsening of asthma, fatigue, and headache (<1% for each). [16]

Treatment groups had similar safety profiles, with the exception of injection site reaction (8% with mepolizumab 100 mg SC vs. 3% with placebo). Other common adverse reactions found with mepolizumab 100 mg SC are noted in **Table 1**.[17]

Table 2. Adverse Reactions with Mepolizumab with ≥3% Incidence and More Common than Placebo. [17]

Adverse Reaction	Mepolizumab 100 mg SC (n=263)	Placebo (n=257)
Headache	19%	18%
Injection site reaction	8%	3%
Back pain	5%	4%
Fatigue	5%	4%
Influenza	3%	2%
Urinary tract infection	3%	2%
Upper abdominal pain	3%	2%
Pruritus	3%	2%
Eczema	3%	<1%
Muscle spams	3%	<1%

The studies did not report any cases of anaphylaxis. [16] Non-anaphylactic allergic reactions occurred in 2% of less of all patients, with similar rates similar between mepolizumab and placebo groups. [16] Once case was a Type 4 delayed hypersensitivity reaction. [16]

Study 97 had a numerical imbalance in the number of serious cardiac events with 7 events in the mepolizumab group and only 1 patient in the placebo group. [16] All but one patient had cardiovascular risk factors at baseline; this finding was not seen in subsequent studies 88 and 75 or in the ongoing safety extension studies, with a 3% overall frequency of cardiac events in both mepolizumab and placebo groups. [16]

The mepolizumab and placebo groups had similar frequencies of infections, including serious infections and opportunistic infections (57% and 58%, respectively). [16] However, 2 patients treated with mepolizumab 100 mg SC had serious herpes zoster infection compared to none in placebo groups. Therefore, prescribing information recommend the varicella vaccination, when appropriate, before starting mepolizumab. [16] The overall risk of infections will be clarified with long-term use of mepolizumab.

The FDA considers the risk of malignancy with mepolizumab to be lower than for other monoclonal antibodies because IL-5 inhibition is unlikely to induce general immunosuppression. In the controlled severe asthma studies, treatment groups had similar frequencies of benign or malignant neoplasms ranging from 0% to 2%. Three cases of malignancies were reported in the placebo groups and 2 cases were reported in mepolizumab groups. No reports of lymphoma or lymphoproliferative cancers occurred, which can suggest general immunosuppression. [16] The overall risk of malignancy will be clarified with long-term use of mepolizumab.

Clinical trials included only 28 patients 12 to 17 years of age and older and only 38 patients at least 65 years of age. [16] The number of elderly patients was insufficient to determine whether this population would respond differently to mepolizumab. The risk of helminth infection is unknown because patients with, or at risk for, parasitic infections were excluded.

Table 3: Pharmacology and Pharmacokinetic Properties: [17]

Parameter	
Mechanism of Action	The mechanism of action has not been firmly established. Mepolizumab is an antagonist of IL-5, the cytokine predominantly responsible for the eosinophil production, recruitment, activation, and survival. By binding to IL-5, mepolizumab blocks IL-5 from binding to the alpha chain of the IL-5 receptor complex expressed on the cell surface of eosinophils. This inhibition of IL-5 signaling reduces eosinophil production and survival.
Distribution and Protein Binding	Vd 3.6 L in 70 kg individual
Metabolism	Proteolytic enzymes widely distributed in the body
Half-Life	16 to 22 days
Elimination	Clearance 0.28 L daily in 70 kg individual

Abbreviations: IL-5 = interleukin 5; kg = kilograms; L = liters; Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hospitalizations due to exacerbations
2) Emergency Department visits due to exacerbations
3) Quality of life
4) Asthma symptoms
5) Reduction/elimination in systemic corticosteroid use
6) Serious adverse events
7) Discontinuations due to adverse events

Primary Study Endpoints:
1) Studies 97 and 88: The rate of clinically significant asthma exacerbations, which were defined as worsening of asthma requiring use of OCS for ≥3days, hospital admission, or an ED visit.
2) Study 75: Percentage reduction in daily OCS dose during weeks 20 to 24 as compared to baseline.

Table 4. Clinical Efficacy Evidence Table.

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Pavord, et al.[10] MC, DB, PC, RCT Phase 3 STUDY 97	1. MEP 75 mg IV Q4 wk 2. MEP 250 mg IV Q4 wk 3. MEP 750 mg IV Q4 wk 4. PBO IV Q4 wk 52 weeks	Demographics: Mean age: 49 y Females: 63% White: 90% Hospitalizations due to asthma in past year: 38% Severe exacerbations in past year: 3.6 Chronic OCS: 30% Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted; or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability -h/o ≥2 asthma exacerbations requiring OCS past 12 months -ICS equiv. to ≥880 mcg fluticasone plus an additional controller -blood eosinophil ≥300 cell/µL or sputum eosinophils ≥3% or FE_{NO} ≥50 ppb or rapid deterioration of asthma control after ≥25% reduction in ICS or OCS dose in past 12 months Key Exclusion Criteria: -current smokers or h/o ≥10 pack years -concurrent respiratory disease -liver disease -pregnancy/lactation	mITT 1. 153 2. 152 3. 156 4. 155 Attrition 1. 0.6% 2. 0% 3. 0% 4. 2.5%	Primary Endpoint: Rate of clinically significant exacerbations per patient per year* 1. 1.24 (SE log 0.12) 2. 1.46 (SE log 0.11) 3. 1.15 (SE log 0.12) 4. 2.40 (SE log 0.11) 1 vs. 4: RR 0.52 (95% CI, 0.39 to 0.69) 2 vs. 4: RR 0.61 (95% CI, 0.46 to 0.81) 3 vs. 4: RR 0.48 (95% CI, 0.36 to 0.64) Key Secondary Endpoints: Rate of hospitalizations or ED visits per patient per year from exacerbation: 1. 0.17 (SE log 0.30) 2. 0.25 (SE log 0.25) 3. 0.22 (SE log 0.26) 4. 0.43 (SE log 0.24) 1 vs. 4: RR 0.40 (95% CI, 0.19 to 0.81) 2 vs 4: RR 0.58 (95% CI, 0.30 to 1.12) 3 vs. 4: RR 0.52 (95% CI, 0.27 to 1.02) Δ ACQ from baseline (0-6): 1. -0.75 (SE log 0.09) 2. -0.87 (SE log 0.09) 3. -0.80 (SE log 0.09) 4. -0.59 (SE log 0.0.9) 1 vs. 4 MD -0.16 (95% CI, -0.39 to 0.07) 2 vs. 4 MD -0.27 (95% CI, -0.51 to 0.04) 3 vs. 4 MD -0.20 (95% CI, -	 NA NA NA NA NS NS NS NS NS	Safety Outcomes (0-56 weeks) D/C due to AE: 1. 3% 2. 5% 3. 6% 4. 4% SAE (includes asthma-related AE): 1. 13% 2. 16% 3. 12% 4. 16% Fatal AE: 1. 0% 2. 1.3% 3. 0.6% 4. 0% Serious Infection: 1. 5% 2. 2% 3. 3% 4. 3% Infusion-related reactions: 1. 5% 2. 8% 3. 12% 4. 6%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1:1:1 by centralized computer-generated, permuted-block schedule. Stratified by chronic OCS. Baseline ACQ and exacerbations requiring hospitalization higher in PBO arm at baseline. Performance bias: (low) MEP and PBO identical in appearance and administered by staff unaware of group assignments. However, staff that prepared study drugs were aware of group assignments. Detection bias: (unclear) statisticians and GSK personnel blinded to data; power assumptions are not referenced; specific statistical tests utilized unclear. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk. **Applicability**: Patient: extensive inclusion criteria may limit applicability of study results. Eosinophil asthma broadly defined w/ multiple criteria. Intervention: IV infusion of MEP was not approved by FDA; 10-fold difference in dose tested but no dose-response observed. Comparator: PBO allows investigators to assess efficacy of MEP, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy. Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 81 centers in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, South Korea, Poland, Romania, Russia, Ukraine, U.K. and U.S.

				0.43 to 0.03)				
2. Ortega, et al.[11] MC, DB, PC, PG, RCT Phase 3 STUDY 88	1. MEP 75 mg IV + PBO SC Q4 wk 2. MEP 100 mg SC + PBO IV Q4 wk 3. PBO IV + SC Q4 wk 32 weeks	Baseline Demographics: Mean age: 50 y Females: 57% White: 78% SGRQ: 46.4 ACQ-5: 2.22 Chronic OCS: 25% Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following tests results: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability -≥2 asthma exacerbations in past 1 year while on ≥880 mcg/d of ICS fluticasone (or equiv.) requiring OCS -≥3 months of additional controller besides ICS -blood eosinophil >150 cell/µL at screening or ≥300 cell/µL in past year Key Exclusion Criteria: -current smokers or h/o ≥10 pack years -concurrent respiratory disease -liver disease -HF (EF<30%; NYHA Class IV; hospitalized in past year) or angina -immunodeficiency (HIV) -monoclonal antibody drug for asthma -pregnancy/lactation	mITT 1. 191 2. 194 3. 191 Attrition 1. NR 2. NR 3. NR (total 0.6%)	Primary Endpoint: Rate of clinically significant asthma exacerbations* 1. 0.93 2. 0.83 3. 1.74 1 vs. 3: RRR 47% (95% CI, 28 to 60%; p<0.001) 2 vs. 3: RRR 53% (95% CI, 36 to 65%; p<0.001) Key Secondary Endpoints: Mean annual rate of asthma exacerbations requiring hospitalization or ED visit: 1. 0.14 2. 0.08 3. 0.20 1 vs. 3: RRR 32% (95% CI, -41 to 67%; p=0.30) 2 vs. 3: RRR 61% (95% CI, 17 to 82%; p=0.02) Δ SGRQ from baseline (0-100): 1. -15.4 (SE 1.2) 2. -16.0 (SE 1.1) 3. -9.0 (SE 1.2) 1 vs. 3: ARR -6.4% (95% CI, -9.7 to -3.2%; p<0.001) 2 vs. 3: ARR -7.0% (95% CI, -10.2 to -3.8; p<0.001) Δ ACQ from baseline (0-6): 1. -0.92 (SE 0.07) 2. -0.94 (SE 0.07) 3. -0.50 (SE 0.07) 1 vs. 3: ARR -0.42% (95% CI, -0.61 to -0.23%; p<0.001) 2 vs. 3: ARR -0.44% (95% CI, -0.63 to -0.25; p<0.001)	NA NA NA NA NA NA NA	Safety Outcomes (0-40 weeks) Any non-asthma AE: 1. 84% 2. 78% 3. 82% Drug-related AE: 1. 17% 2. 20% 3. 16% D/C due to AE: 1. 0% 2. 1% 3. 2% SAE (includes asthma-related AE): 1. 7% 2. 8% 3. 14% Anti-MEP antibodies: 1. 4% 2. 5% 3. 2% Injection-site AE: 1. 3% 2. 9% 3. 3%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1:1 by centralized computer-generated, permuted-block schedule. Performance bias: (low) See Pavord, et al. Detection bias: (low) statisticians and GSK personnel blinded to data. Power assumptions appropriate. Appropriate statistical tests utilized. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear but few dropped out early. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk reduction. **Applicability**: Patient: About 1/4 of patients on chronic OCS and 1/3 were former smokers. Average duration of asthma was about 20 years. Patients remained on ICS and at least one other controller agent. Intervention: SC dose approved and available in U.S.; IV dose was not approved and appeared to be associated with more AEs w/o additional efficacy vs. SC dose. Comparator: See Pavord, et al. Outcomes: composite primary endpoint is clinically relevant but results were nearly all driven by use of ≥3 days of OCS and not hospitalizations or ED visits. Mean dose and duration of OCS for each exacerbation between groups unknown. Short study duration. Setting: 16 countries in Europe (n=270); South and Central America (n=68); USA (n=67); Japan (n=50); Korea (n=45); Canada (n=35); Australia/Russia/Ukraine (n=41).

3. Bel, et al.[12] MC, DB, PC, PG, RCT Phase 3 STUDY 75	1. MEP 100 mg SC Q4 wk 2. PBO SC Q4 wk 4 Phases: Optimization: taper OCS to lowest effective dose Induction: post-randomization (weeks 0-4) Reduction: reduce OCS by 1.25-10 mg/d Q4 wk (weeks 4-20) Maintenance: no change in OCS dose (weeks 20-24)	Baseline Demographics: Mean age: 50 y Females: 55 % White: 95% Hospitalizations due to asthma in past year: 17% Severe exacerbations in past year: 3.1 Key Inclusion Criteria: -age ≥12 y and wt ≥45 kg -chronic (≥6 months) OCS equiv. to 5-35 mg/d of prednisone -blood eosinophil >150 cell/µL at screening or ≥300 cell/µL in past year -ICS equiv. to ≥880 mcg fluticasone except ≥440 mcg adolescents <18 y -≥3 months of additional controller besides ICS -asthma w/ FEV_1 <80% predicted for adults; FEV_1 <90% predicted or FEV_1/FVC <0.8 for adolescents <18 y -≥1 of the following tests results: FEV_1 w/ >12% reversibility; + methacholine challenge; or ≥20% FEV_1 variability Key Exclusion Criteria: See Ortega, et al.	mITT 1. 69 2. 66 Attrition 1. 0% 2. 0%	Primary Endpoint: % reduction of daily OCS dose from baseline to weeks 20-24 (MEP vs. PBO): 90 to 100%: 23% vs. 11% 75 to <90%: 17% vs. 8% 50 to <75%: 13% vs. 15% >0 to <50%: 10% vs. 11% OR 2.39 (95% CI, 1.25-4.56; p=0.008) Key Secondary Endpoints (weeks 20-24): ≥50% reduction of OCS dose: 1. 54% 2. 33% OR 2.26 (95% CI, 1.10-4.65; p=0.03) Reduction of daily OCS dose to ≤5 mg: 1. 54% 2. 32% OR 2.45 (95% CI, 1.12-5.37; p=0.02) Off OCS: 1. 14% 2. 8% OR 1.67 (95% CI, 0.49-5.75; p=0.41)	NA 21/5 22/5 NS	Safety Outcomes (0-32 weeks) Any non-asthma AE: 1. 83% 2. 91% Drug-related AE: 1. 30% 2. 18% D/C due to AE: 1. 4% 2. 5% SAE (includes asthma-related AE): 1. 1% 2. 18% Anti-MEP antibodies: 1. NR 2. NR (4% total cohort) Injection-site AE: 1. 6% 2. 3%	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: (low) randomized 1:1 by centralized computer-generated, permuted-block schedule, stratified by country. Baseline SGRQ lower and OCS dose higher in PBO arm than MEP arm. Performance bias: (low) See Ortega, et al. Detection bias: (low) See Ortega, et al. Attrition bias: (high) imputation of missing data unclear; mITT performed but 26% of subjects in run-in optimization phase did not get randomized. Reporting bias: (unclear) See Ortega, et al. **Applicability**: Patient: Patients remained on maintenance asthma drug regimen used prior to study, including ICS and ≥1 other controller agent. Intervention: FDA-approved dose and formulation studied. Comparator: See Pavord, et al. Outcomes: Mean daily OCS doses at weeks 20-24 were 10.5 mg and 8.6 mg for PBO and MEP, respectively; median doses were 10.0 and 3.1 mg, respectively. Only 40% had >75% reduction in OCD dose vs. 19% with PBO. No difference in more moderate dose reductions. Short study duration. Setting: 38 sites in Germany (n=8); France (5); Czech Republic (5); U.S. (5); U.K. (4); Australia (3); Canada (3); Netherlands (2), Poland (2); and Mexico (1).

Abbreviations [alphabetical order]: ACQ = 5-item Asthma Control Questionnaire (scale 0-6); AQLQ = 32-item Asthma Quality of Life Questionnaire (scale 1-7); ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; EF = ejection fraction; FDA = U.S. Food and Drug Administration; FE_{NO} = exhaled nitric oxide concentration; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HF = heart failure; h/o = history of; ICS = inhaled corticosteroid; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; MEP = mepolizumab; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; NYHA = New York Heart Association; OCS = oral corticosteroid; OR = odds ratio; PC = placebo-controlled; PBO = placebo; PC20 = provocative concentration of inhaled methacholine needed to reduce FEV1 by 20%; PEF = peak expiratory flow; PG = parallel group; PP = per protocol; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SC = subcutaneous; SE = standard error; SGRQ = St. George's Respiratory Questionnaire; wk = weeks; wt = weight; y = years; µL = microliters.

*Worsening of asthma which requires use of systemic corticosteroids (IV or oral steroid for ≥3 days or a single IM dose; for subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for ≥3 days) and/or hospitalization and/or emergency department visits

Reslizumab NEW DRUG EVALUATION:

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Reslizumab was approved by the FDA based on 3 phase 3 studies (3081, 3082, and 3083).[25] Study 3081 was a lung function study and studies 3082 and 3083 were exacerbation studies. Patients were required to have a blood eosinophil count ≥400 cells/µl. This cutoff is based on data suggesting that a blood eosinophil count of at least 400 cells/µl had a high positive predictive value for the presence of sputum eosinophils of 3% or greater. However, this threshold is not definitive nor widely accepted.[25] The studied dose was 3 mg/kg IV every 4 weeks. However, the FDA notes that dose-ranging data are not as robust for reslizumab, and only a single dose was studied in all phase 3 studies.[25] Study sites were in North America (including the U.S.), South America, Asia and Europe. In the 3 primary studies (3081, 3082, 3083), only 20% of sites were within the US. Studies included patients with mean asthma duration of around 20 years or more with a mean of 2 exacerbations in the previous year.[25] All patients were on standard of care treatment based on disease severity, including ICS and LABA with inadequate control based on an ACQ score of ≥1.5.[25]

Study 3081 was a dose-ranging lung function study over 16 weeks. It remains unpublished and cannot be adequately assessed for quality. It included patients taking medium- to high-dose ICS with or without another controller with inadequate control based on an ACQ score of ≥1.5.[25] This was the only study investigating more than one dose of reslizumab (0.3 mg/kg and 3 mg/kg IV). Overall, both groups had a significant improvement in FEV1 from baseline compared to placebo (0.127, 0.238, and 0.286 L for placebo, 0.3 mg/kg and 3 mg/kg, respectively). Both doses demonstrated improvement in FEV1 but the treatment effect was modestly greater in the 3.0 mg/kg treatment group (FEV1 of 0.159 L) compared to the 0.3 mg/kg group (FEV1 of 0.111 L), both demonstrated efficacy. Both doses demonstrated improvements in the ACQ and AQLQ. A dose-dependent reduction of blood eosinophil count was seen with the higher dose (92%) compared to the lower dose (68%) and placebo (14%), but whether this endpoint translates into clinical outcomes remains unknown.[25] An additional study was designed to evaluate for an interaction between change from baseline in FEV1 and baseline eosinophil count and no significant interaction was found.[25] Additionally, an FDA exploratory analysis of studies 3082 and 3083 found no relationship between blood eosinophil count and exacerbation benefit.[25]

Studies 3082 and 3083 were identical phase 3 studies evaluating the frequency of exacerbations over 52 weeks with similar inclusion criteria as study 3081 in addition to requiring at least one exacerbation during the previous year. Use of OCS was permitted.[26] Studies only included the 3 mg/kg dose despite the FDA suggesting inclusion of more than one dose.[25] Pooled data from 3082 and 3083 demonstrated a decrease in the number of patients experiencing at least one asthma exacerbation compared to placebo (32% vs. 50%, respectively; RR 0.64; 95% CI 0.5 to 0.7) with an ARR of 18% and a NNT of 5 over 52 weeks.[26] There was no significant difference in the rate of episodes requiring hospitalizations or ED visits per patient per year between reslizumab and placebo (0.077 vs. 0.12; RR 0.66; 95% CI 0.38 to 1.16).[26] However, ED/hospitalization rates were low across all treatment groups (approximately 1 for every 5-10 exacerbations).[25] There was a significant improvement in patient-reported measures of the ACQ (pooled mean difference -0.25; 95% CI -0.343 to 0.156) and significantly more patients achieved a clinically significant reduction of 0.5 points on the ACQ in the reslizumab group compared to placebo, despite a large placebo effect.[26] Both studies demonstrated an increased change in FEV1 over placebo at week 52 (0.145 L in study 3082 and 0.123 L in study 3083).

Study data did not show a consistent benefit in patients 12 to 17 years of age; therefore, reslizumab is only approved for adults ages 18 years or older.[25] A total of 40 pediatric patients ages 12 to 17 years were included in studies 3081, 3082 and 3083 and the FDA advisory committee did not find the data adequate to support approval. In addition, an increase in asthma exacerbation rates was observed for adolescents, Blacks, and U.S. patients, which could be driven by the small sample size in these subgroups. Further data are needed in these populations.

Clinical Safety:
Overall dropouts and early discontinuations were low. The most common adverse event leading to discontinuation in all groups was worsening asthma. The most common adverse events, those that occurred in more than 5% of patients who received reslizumab, were worsening of asthma symptoms, nasopharyngitis, upper respiratory tract infections, sinusitis, influenza and headache.

Anaphylaxis was reported in 3 patients who received reslizumab. Malignancy also occurred with reslizumab, and a transient increase in creatine phosphokinase (CPK) suggest potential for muscle toxicity. Elevated CPK levels higher than 10-times the upper limit of normal occurred more frequently in the reslizumab arm (0.8%) than the placebo arm (0.4%). Musculoskeletal pain, muscle spasm, myalgia, muscle fatigue and rhabdomyolysis also occurred more with reslizumab than placebo. However, overall differences were small and there was an imbalance in baseline CPK values between the groups.

Table 5: Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	IL-5 antagonist; thereby reducing the production and survival of eosinophils.
Distribution and Protein Binding	Volume of distribution of 5 L, suggesting minimal distribution to the extravascular tissues.
Metabolism	Metabolized by enzymatic proteolysis into small peptides and amino acids.
Half-Life	Approximately 24 days.
Elimination	Clearance approximately 7 mL/hour.

Abbreviations: IL-5 = interleukin 5; L = liters; ml =milliliters

Comparative Clinical Efficacy:
Clinically Relevant Endpoints:
1) Hospitalizations due to exacerbations
2) Emergency Department visits due to exacerbations
3) Quality of life
4) Asthma symptoms
5) Reduction/elimination in systemic corticosteroid use
6) Serious adverse events
7) Discontinuations due to adverse events

Primary Study Endpoint:
1) Frequency of clinical asthma exacerbations per patient during the 52 week treatment period.

Table 6. Clinical Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Castro, et al.[26] MC, DB, PC, RCT Phase 3 Study 3082	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo IV Duration: 52 weeks	Demographics: Mean age: 49 y Females: 62% White: 73% Chronic OCS: 19% LABA use: 85% Mean ACQ: 2.71 Key Inclusion Criteria: Age 12-75 years blood eosinophil ≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 245 2. 244 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.90 2. 1.80 RR 0.50 (95% CI 0.37 to 0.67) Patients with ≥ 1 clinical asthma exacerbation (CAE) 1. 92 (38%) 2. 132 (54%) RR 0.69 (95% CI 0.56 go 0.85) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 184 (76%) 2. 152 (63%) OR 0.5; 95% CI 0.3 to 0.8 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 75% 2. 65% OR 0.6; 95% CI 0.4 to 0.9) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.14 2. 0.21 RR 0.66 (95% CI 0.32 to 1.36) P=0.26	NA 16/6 13/7 10/10 NS	Outcome: D/C due to AE: 1. 4 (1.6%) 2. 8 (3.3%) SAE (includes asthma-related AE): 1. 10% 2. 14%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and had access to all study data and were involved in writing and publishing of the manuscript. **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose due to lack of dose response data. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 15% in the US.

2. Castro, et al.[26] MC, DB, PC, RCT Phase 3 Study 3083	1. RES 3 mg/kg IV Q 4 weeks 2. Placebo Duration: 52 weeks	Demographics: Mean age: 48 y Females: 63% White: 73% Chronic OCS: 12% LABA use: 82% Mean ACQ: 2.59 Key Inclusion Criteria: Age 12-75 years blood eosinophil ≥ 400 cells/ µL; ACQ-7 score ≥1.5, at least medium dose ICS, ≥1 exacerbation in year prior Key Exclusion Criteria: Any clinically meaningful comorbidity, other lung disease, current smoker, any inadequately controlled medical factors (diabetes, GERD), pregnant or nursing females, HIV, drug and alcohol abuse.	ITT: 1. 232 2. 232 Attrition: 1. 0 2. 0	Primary Endpoint: Rate of asthma exacerbations per patient per year* 1. 0.86 2. 2.11 RR 0.41 (95% CI 0.28 to 0.59) Patients with ≥ 1 clinical asthma exacerbation (CAE) 1. 59 (25%) 2. 105 (45%) RR 0.56 (95% CI 0.4 to 0.74) Secondary Endpoints: Proportion of patients achieving a 0.5 point reduction in ACQ score from baseline: 1. 178 (77%) 2. 140 (61%) OR 0.4; 95% CI 0.2 to 0.6 Proportion of patients achieving a 0.5 point reduction in AQLQ score from baseline: 1. 74% 2. 64% OR 0.6; 95% CI 0.4 to 1.0) Rate of CAE requiring hospitalization or ER treatment per patient per year: 1. 0.03 2. 0.05 RR 0.69 (95% CI 0.29 to 1.65)	NA 20/5 16/6 NS NS	Outcome: D/C due to AE: 1. 8 (3.4%) 2. 9 (3.9%) SAE (includes asthma-related AE): 1. 8% 2. 10%	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Performance Bias: (low) patients and investigators remained masked. RES and PBO identical volume and in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear for several dropouts. Appropriate statistical tests used. Reporting Bias: (unclear) Funded by Teva. Teva employees were involved in all steps of study design and data analysis and were involved in writing and publishing **Applicability**: Patient: extensive and elusive exclusion criteria limits applicability of study results. Intervention: FDA suggested that multiple doses of RES studied in phase 3 trials. Unclear on optimal dose. Comparator: PBO allows investigators to assess efficacy of RES, but a direct comparison with other monoclonal antibodies for severe asthma would be helpful to understand place in therapy Outcomes: clinically significant asthma exacerbation defined as a composite of many outcomes but it is unclear what criteria primarily drove the reduction in exacerbations; no clear dose-response observed across doses. Short study duration. Setting: 128 centers in Asia, Australia, North America, South America, South Africa, and Europe. Only 7% in the US.

Abbreviations [alphabetical order]: ACQ = 5-item Asthma Control Questionnaire (scale 0-6); AQLQ = 32-item Asthma Quality of Life Questionnaire (scale 1-7); ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; h/o = history of; ICS = inhaled corticosteroid; ITT = intention to treat; IV = intravenous; LABA = Long Acting Beta Agonist; MC = multi-centered; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not statistically significant; OCS = oral corticosteroid; OR = odds ratio; PC = placebo-controlled; PBO = placebo; PG = parallel group; PP = per protocol; RR = relative risk; RES = reslizumab; RRR = relative risk reduction; SAE = serious adverse event; y = years; µL = microliters.
*Worsening of asthma that resulted in use of systemic corticosteroids in patients not already receiving treatment, or 2-fold increase in the dose of either ICS or OCS for 3 or more days, or the need for emergency department or hospital admission or unscheduled physician's office visit.

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUCALA® safely and effectively. See full prescribing information for NUCALA.

NUCALA (mepolizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

NUCALA is an interleukin-5 antagonist monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. (1)

Limitations of Use:

- Not for treatment of other eosinophilic conditions. (1)
- Not for relief of acute bronchospasm or status asthmaticus. (1)

DOSAGE AND ADMINISTRATION

100 mg administered subcutaneously once every 4 weeks. (2)

- See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection.

DOSAGE FORMS AND STRENGTHS

For injection: 100 mg of lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

History of hypersensitivity to mepolizumab or excipients in the formulation. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of NUCALA. Discontinue NUCALA in the event of a hypersensitivity reaction. (5.1)
- Do not use to treat acute bronchospasm or status asthmaticus. (5.2)
- Herpes zoster infections have occurred in patients receiving NUCALA. Consider varicella vaccination if medically appropriate prior to starting therapy with NUCALA. (5.3)
- Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with NUCALA. Decrease corticosteroids gradually, if appropriate. (5.4)
- Treat patients with pre-existing helminth infections before therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue NUCALA until parasitic infection resolves. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence greater than or equal to 5%) include headache, injection site reaction, back pain, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CINQAIR safely and effectively. See full prescribing information for CINQAIR.

CINQAIR® (reslizumab) injection, for intravenous use
Initial U.S. Approval: 2016

WARNING: ANAPHYLAXIS
See full prescribing information for complete boxed warning.

- **Anaphylaxis occurred with CINQAIR infusion in 0.3% of patients in placebo-controlled studies (5.1)**
- **Patients should be observed for an appropriate period of time after CINQAIR infusion; healthcare professionals should be prepared to manage anaphylaxis that can be life-threatening (5.1)**
- **Discontinue CINQAIR immediately if the patient experiences anaphylaxis (5.1)**

----------INDICATIONS AND USAGE----------

CINQAIR is an interleukin-5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype (1).

Limitations of Use: CINQAIR is **not** indicated for:

- treatment of other eosinophilic conditions (1)
- relief of acute bronchospasm or status asthmaticus (1)

----------DOSAGE AND ADMINISTRATION----------

- CINQAIR is for intravenous infusion only. Do not administer as an intravenous push or bolus (2.1)
- CINQAIR should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis (2.2)
- Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to reslizumab or any of its excipients (4)

----------WARNINGS AND PRECAUTIONS----------

- Malignancy: Malignancies were observed in clinical studies. (5.3)
- Reduction in Corticosteroid Dosage: Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with CINQAIR. Decrease corticosteroids gradually, if appropriate. (5.4)
- Parasitic (Helminth) Infection: Treat patients with pre-existing helminth infections before therapy with CINQAIR. If patients become infected while receiving CINQAIR and do not respond to anti-helminth treatment, discontinue CINQAIR until the parasitic infection resolves. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reaction (incidence greater than or equal to 2%) includes oropharyngeal pain. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 03/2016

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XOLAIR safely and effectively. See full prescribing information for XOLAIR.

XOLAIR® (omalizumab) for injection, for subcutaneous use
Initial U.S. Approval: 2003

WARNING: ANAPHYLAXIS

See full prescribing information for complete boxed warning.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred after the first dose of Xolair but also has occurred beyond 1 year after beginning treatment. Closely observe patients for an appropriate period of time after Xolair administration and be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and have them seek immediate medical care should symptoms occur. (5.1)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1) 12/2015

----------INDICATIONS AND USAGE----------

Xolair is an anti-IgE antibody indicated for:

- Moderate to severe persistent asthma in patients (12 years of age and above) with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (1.1)
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment (1.2)

Limitations of use:

- Not indicated for other allergic conditions or other forms of urticaria. (1.1, 1.2,)
- Not indicated for acute bronchospasm or status asthmaticus. (1.1, 5.3)

----------DOSAGE AND ADMINISTRATION----------

For subcutaneous (SC) administration only. (2.1, 2.2)
Divide doses of more than 150 mg among more than one injection site to limit injections to not more than 150 mg per site. (2.4)

- Asthma: Xolair 150 to 375 mg SC every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See the dose determination charts. (2.1)
- Chronic Idiopathic Urticaria: Xolair 150 or 300 mg SC every 4 weeks. Dosing in CIU is not dependent on serum IgE level or body weight. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- For injection: Lyophilized, sterile powder in a single-use 5mL vial, 150 mg. (3)

----------CONTRAINDICATIONS----------

- Severe hypersensitivity reaction to Xolair or any ingredient of Xolair. (4, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis: Administer only in a healthcare setting prepared to manage anaphylaxis that can be life-threatening and observe patients for an appropriate period of time after administration. (5.1)
- Malignancy: Malignancies have been observed in clinical studies. (5.2)
- Acute Asthma Symptoms: Do not use for the treatment of acute bronchospasm or status asthmaticus. (5.3)
- Corticosteroid Reduction: Do not abruptly discontinue corticosteroids upon initiation of Xolair therapy. (5.4)
- Fever, Arthralgia, and Rash: Stop Xolair if patients develop signs and symptoms similar to serum sickness. (5.6)
- Eosinophilic Conditions: Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.5)

----------ADVERSE REACTIONS----------

- Asthma: The most common adverse reactions (≥1% more frequent in Xolair-treated patients) in clinical studies were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. (6.1)
- Chronic Idiopathic Urticaria: The most common adverse reactions (≥2% Xolair-treated patients and more frequent than in placebo) included the following: nausea, nasopharyngitis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection, arthralgia, headache, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- No formal drug interaction studies have been performed. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2015

Appendix 2: Proposed 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:

- Omalizumab
- Mepolizumab
- Reslizumab

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
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient required at least 2 hospitalizations or 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, aminophylline, theophylline)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9

Approval Criteria		
9. 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 #10
10. If the claim is for mepolizumab or reslizumab, can the prescriber provide documentation of eosinophilic phenotype, confirmed by blood eosinophil count ≥300 cells/μL in the past 12 months?	**Yes:** Approve once every 4 weeks for up to 12 months. Document eosinophil count (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the patient currently taking a maximally-dosed inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, aminophylline, theophylline)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. 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.

P&T Review: *7/16*
Implementation: *TBD*