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TEZEPELUMAB- EKKO (TEZSPIRE) FOR SEVERE ASTHMA

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ABBREVIATIONS

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAER	annualized rate of asthma exacerbations
ACQ	Asthma Control Questionnaire
ADA	anti-drug antibodies
AEs	adverse events
ASD	Asthma Symptom Diary
ATS	American Thoracic Society
AQLQ	Asthma Quality of Life Questionnaire
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
COPD	chronic obstructive pulmonary disease
CRSwNP	chronic rhinosinusitis with nasal polyps
CTS	Canadian Thoracic Society
DUR	Drug Utilization Review
EAACI	European Academy of Allergy and Clinical Immunology
ERS	European Respiratory Society
EIB	exercise-induced bronchoconstriction
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
ICER	Institute for Clinical and Economic Review
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
IV	intravenously
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonists
LTRA	leukotriene receptor antagonist
MRHD	maximum recommended human dose
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Care Excellence
NO	nitric oxide
NSAIDs	nonsteroidal anti-inflammatory drugs
OCS	oral corticosteroids
PA	prior authorization
QoL	quality of life
RCTs	randomized controlled trials
SABA	short-acting $beta_2$ agonist
SAMA	short-acting muscarinic antagonists
SubQ	subcutaneously
SRs	systematic reviews
Th2	T helper 2
TSLP	thymic stromal lymphopoietin

1.0 INTRODUCTION

Asthma is a heterogeneous, respiratory disease usually characterized by chronic inflammation that causes breathing difficulties due to narrowing of the respiratory airways.[1-4] Asthma severity varies from mild to severe depending on the frequency of respiratory symptoms (eg, wheezing, dyspnea, chest tightness) and exacerbations.[5] Although severe asthma constitutes fewer than 5–10% of all asthma diagnoses, it represents a disproportionate fraction of healthcare expenditures among asthma patients, and is a cause of reduced quality of life (QoL) and higher rates of hospitalization and death.[2,3,6,7] Asthma is comprised of different phenotypes, with the majority of patients with severe asthma expressing the type 2 inflammatory phenotype (eg, allergic asthma or eosinophilic asthma).[1,3,8]

Tezepelumab (Tezspire) was approved by the U.S. Food and Drug Administration (FDA) in December 2021 as add-on maintenance treatment for **severe** asthma in patients ≥ 12 years of age.[9] Based on the decreased annual exacerbation rate observed in the phase IIb randomized controlled trial (RCT), PATHWAY,[10] tezepelumab was granted a "breakthrough therapy" designation by the FDA in 2018 for patients affected by severe asthma *without* an eosinophilic phenotype.[11] Tezepelumab is a first-in-class human monoclonal antibody for asthma that prevents thymic stromal lymphopoietin (TSLP) from binding to its heterodimeric receptor,[9] impacting type 2 inflammation at the outset of the inflammatory pathway and other asthma pathways (eg, neutrophilic).[3,4,12,13] There are 5 other monoclonal antibodies approved as add-on maintenance treatment for asthma with a type 2 inflammatory phenotype (allergic or eosinophilic asthma): benralizumab (Fasenra), mepolizumab (Nucala), reslizumab (Cinqair), dupilumab (Dupixent), and omalizumab (Xolair).[1,2] These agents affect different signaling pathways (eg, IL-4, IL-5, IgE) within the type 2 inflammatory cascade to reduce the levels of inflammatory modulators (eg, cytokines, eosinophils) that promote asthma pathogenesis.[2,14]

Utah Medicaid has prior authorization (PA) criteria in place for all 6 of these agents, including tezepelumab. **Table 1** outlines the FDA approved indication for tezepelumab and directions for use per the product labeling.

The purpose of this report is to provide evidence on the safety and efficacy of tezepelumab to assist the Utah Medicaid Drug Utilization Review (DUR) Board in assuring safe and appropriate use.

Table 1. Tezepelumab (Tezspire) FDA Approved Indication and Directions for Use[9]

FDA-Approved Indication	Add-on maintenance therapy of patients ≥ 12 years with severe asthma Limitation on use: NOT for alleviation of acute bronchospasm or status asthmaticus
Dosing/ Administration Information	210 mg administered subcutaneously once every 4 weeks Intended to be administered by a healthcare provider
Dosage Form and Storage	• Supplied as 210 mg/ 1.91 mL solution in a single-dose vial or pre-filled syringe • Refrigerate (36°F to 46°F) in original carton to protect from light. May be stored at room temperature (68°F to 77°F) for a maximum of 30 days, if necessary. After removal from refrigeration, it should be used within 30 days or discarded

2.0 METHODS

A systematic literature search for randomized controlled trials (RCTs) or systematic reviews (SRs) of RCTs addressing the efficacy and safety of tezepelumab was conducted in Ovid MEDLINE and Embase using free-text terms and controlled vocabulary. Additionally, a search for relevant studies, including unpublished trials, was conducted in ClinicalTrials.gov. The search strategies are provided in **Appendix A.**

Information concerning product prescribing (ie, product labeling or package inserts) was obtained from the manufacturer's website. Additionally, clinical practice guidelines, expert statements, or reviews addressing the management of severe asthma with biologic treatments were searched on the following websites:

- National Asthma Education and Prevention Program (NAEPP): https://www.nhlbi.nih.gov/science/national-asthma-education-and-prevention-program-naepp
- American Academy of Allergy, Asthma, and Immunology (AAAAI): https://www.aaaai.org/Allergist-Resources/Statements-Practice-Parameters
- Global Initiative for Asthma (GINA): https://ginasthma.org/
- Canadian Thoracic Society (CTS): https://cts-sct.ca/guideline-library/
- European Respiratory Society/ American Thoracic Society (ERS/ ATS): https://www.ersnet.org/guidelines/ https://www.thoracic.org/statements/index.php
- The European Academy of Allergy and Clinical Immunology (EAACI): https://www.eaaci.org/
- National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/guidance
- Institute for Clinical and Economic Review (ICER): https://icer.org/

Reference lists of identified studies and clinical practice guidelines were also screened for relevant studies. **Appendix B** includes a list of practice guidelines that were used in the preparation of this report.

3.0 SEVERE ASTHMA OVERVIEW

Asthma is a complex heterogeneous disease, with various underlying pathological mechanisms.[8] This heterogeneity is captured by classification into asthma phenotypes based on identifiable characteristics (eg, "demographic, clinical and/or pathophysiological").[1,8] Some frequently used asthma phenotypes include eosinophilic asthma, allergic asthma, non-allergic asthma, asthma with persistent airflow limitation, adult-onset (late-onset) asthma, and asthma with obesity.[1,8,14] Phenotype-specific therapies are available for patients with moderate to severe asthma, but a strong association between asthma phenotypes and response to treatment or clinical presentation has not been discovered.[1,8]

Terms related to severe asthma include uncontrolled asthma, and difficult-to-treat asthma. Severe asthma should be distinguished from these other classifications to help select an appropriate treatment strategy. Definitions of these terms, according to the Global Initiative for Asthma (GINA) (2021), are as follows:

- *Uncontrolled asthma:* inadequate symptom control (eg, regular reliever use, awakening at night due to asthma) and/or recurrent exacerbations (≥ 2 within 12 months) that necessitates oral corticosteroid (OCS) therapy or severe exacerbations (≥ 1 within 12 months) that requires hospitalization.[6,8]

- *Difficult-to-treat asthma:* uncontrolled symptoms despite medium- or high-dose inhaled corticosteroid (ICS) in combination with a second controller (generally a long-acting beta$_2$ agonist [LABA]) or with an OCS, or needs a high-dose ICS-LABA to maintain symptom control and decrease the risk of exacerbations.[6,8] Difficult-to-treat asthma includes other factors such as incorrect inhaler technique and inadequate adherence.[6,8]
- *Severe asthma:* subgroup of difficult-to-treat asthma in which patients experience uncontrolled asthma regardless of adherence to an optimized high-dose ICS-LABA and appropriate management of modifiable factors (eg, inhaler technique, comorbidities, smoking).[6,8] Severe asthma is also defined as asthma that intensifies after a reduction in the dose from high-dose therapy.[6,8]

The European Respiratory Society/American Thoracic Society (ERS/ATS) (2020) describes severe asthma (after the asthma diagnosis is confirmed and comorbidities are controlled) as "asthma that requires treatment with high-dose ICS […] plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy".[15]

It is estimated that approximately 17% of asthmatic adults experience difficult-to-treat asthma and 3.7% of those adults experience severe asthma.[1,6,8] Severe asthma contributes to a significant symptomatic burden (eg, frequent wheezing, chest tightness, dyspnea) that causes a reduced QoL due to sleep disturbances, difficulty with physical activity, and daily limitations in the ability to work or function.[8] Additionally, severe asthma is associated with high healthcare expenses due to the frequent doctor visits, hospitalizations, multi-pharmacologic regimens, and adverse effects from OCS therapy.[8] An economic analysis study from the United Kingdom demonstrated that healthcare expenses (per patient) of those with severe asthma surpassed those with type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD).[8] In addition, a Canadian study showed that severe uncontrolled asthma approximately contributed to more than 60% of total asthma expenditures.[8]

3.1 Severe Asthma Phenotypes

There are two different categories of severe asthma inflammatory phenotypes: non-type 2 (eg, non-eosinophilic) and type 2 (eg, eosinophilic, allergic), also referred to as low-T2 and high-T2, respectively.[6,16] GINA recommends that patients with severe asthma be evaluated by a specialist.[8] After an established diagnosis of severe asthma, a specialist, preferably located in a multidisciplinary asthma clinic, should perform a phenotypic assessment during high-dose ICS treatment or at the lowest achievable OCS dose (type 2 inflammatory biomarkers tend to be suppressed by OCS therapy).[8] **Type 2 inflammation is generally identified by one or more of the following indicators at the initial assessment:** increased blood eosinophils (≥ 150 cells/µL), increased fractional exhaled nitric oxide (FeNO) concentrations (≥ 20 ppb), sputum eosinophils (≥ 2%), signs of allergen-driven asthma, or the need for maintenance OCS.[8] Whereas the **non-type 2 phenotype** is usually associated with an older age of onset, smoking, obesity, corticosteroid resistance, and either paucigranulocytic (ie, sputum levels of eosinophils and neutrophils are within the normal range) or elevated neutrophil sputum levels (eg, neutrophilic).[16-19]

The 2020 European Academy of Allergy and Clinical Immunology (EAACI) guideline provides the following definitions for patients that have eosinophilic asthma or allergic asthma according to the included SRs that were used to inform their recommendations:

- *Eosinophilic asthma:* Patients with a sputum eosinophil count of > 1% OR a blood eosinophil count of ≥ 150 cells/µL, OR a FeNO of ≥ 20 ppb[2]
- *Allergic asthma:* Patients that are symptomatic in response to a perennial aeroallergen AND serum IgE levels of 30–1300 IU/mL, uncontrolled on an ICS and/or other controller therapy[2]

An estimated 50–70% of asthmatics have the type 2 inflammatory phenotype, with higher percentages expected in patients with severe asthma.[3,20-22] Type 2 inflammation is caused by a subset of $CD4^+$ T cells referred to as T helper 2 (Th2) cells that release cytokines such as interleukins (IL) (eg, IL-4, IL-5, and IL-13) in reaction to the presence of allergens, and triggers type 2 immunity via the adaptive immune system in the respiratory airways, resulting in increased levels of immunoglobulin E (IgE) and eosinophils.[1,8,16,23] Additionally, type 2 inflammation may be stimulated via the innate immune system by bacteria, viruses, and irritants that promote the production of alarmins (eg, IL-33, IL-25, and thymic stromal lymphopoietin [TSLP]) by respiratory epithelial cells.[1,8,16] Upstream cytokine "master regulators" such as TSLP control $CD4^+$ T cell maturation into Th2 cells and the production of type 2 cytokines (eg, IL-4, IL-5, IL-13).[14,16,22,23] Eosinophil differentiation, development, aggregation, initiation, and survival is promoted by IL-5.[1,14,16,24] Synthesis of allergen-specific IgE is stimulated by IL-4 and IL-13,[14] causing "airway hyperresponsiveness, smooth muscle hypertrophy, and airway remodeling."[1,16] Additionally, IL-13 increases nitric oxide (NO), mucus via goblet cells, and contraction of respiratory smooth muscle.[1,14] Thus, TSLP modulation has widespread effects on the type 2 inflammation pathway. TSLP is also involved in other non-type 2 processes associated with asthma such as promoting neutrophil-mediated airway inflammation, or stimulating changes in structural cells of the airway.[4,25]

In severe asthma, the type 2 inflammatory phenotype may be uncontrolled with high-dose ICS therapy plus an additional controller medication.[8] OCS therapy may provide benefit but it is often associated with serious adverse effects, especially when used long-term at high doses (eg, osteoporosis, pneumonia, cataracts, adrenal suppression, diabetes, weight gain, cardiovascular disease).[8,22] OCS-related serious adverse effects encourage the use of alternative therapies.[8] Following the advances in understanding the type 2 inflammatory pathway, targeted biologic therapies against specific inflammatory mediators (eg, IgE, IL-5, IL-4, IL-13, TSLP) were developed.[1,14]

The effects of concurrent steroid use should be considered when evaluating the presence of non-type 2 asthma due to the potential for biomarker suppression below thresholds to define type 2.[16] Non-type 2 asthma is generally unresponsive to traditional treatment options such as corticosteroids and the previously approved biologics that target specific ILs involved in the type 2 inflammatory pathway.[18] Existing therapies that are beneficial for non-type 2 inflammation focus on generalized approaches such as trigger avoidance, smoking cessation, and weight reduction.[18] Currently, no established biomarkers are used to identify non-type 2 asthma, but neutrophilic asthma (a subtype of non-type 2) has been associated with ≥ 50% sputum neutrophils in the absence of elevated type 2 biomarkers.[18]

4.0 TREATMENT OF SEVERE ASTHMA

The goals of long-term asthma treatment are to achieve adequate symptom control, and decrease the risk of exacerbations, permanent airflow obstruction, asthma-related deaths, and medication adverse effects.[1,8] The management of asthma involves a continuous cycle to *assess* (eg, symptoms, risk factors, inhaler technique, adherence), *adjust* (eg, treatment, education, non-pharmacologic therapies), and *review* (eg, exacerbations, adverse effects, lung function).[1,8] To individualize care, evaluation of

comorbidities, inhaler technique, adherence, and patient/family preferences and goals should be discussed for each patient.[5,8] Treatment for asthma in general consists of pharmacologic agents (eg, ICS, LABA), modification of risk factors and comorbidities, and nonpharmacological interventions (eg, smoking cessation, physical activity, and avoiding known allergens, pollution, and nonsteroidal anti-inflammatory drugs [NSAIDs]).[5,8] The majority of asthma patients (up to 70−80%) use their inhaler incorrectly, highlighting the importance of skills training on correct inhaler technique for the self-management of asthma.[8]

GINA provides a stepwise treatment approach for asthma management and a framework for managing difficult-to-treat and severe asthma.[8] There are three different categories of therapy; relievers, containing rapid-onset bronchodilators for acute exacerbations, controllers, and add-on treatments.[5,8] Step-wise therapy for asthma in patients ≥ 12, as recommended by the 2021 GINA guideline is outlined in **Table 2**. Add-on treatments, including monoclonal antibodies are typically reserved for patients with difficult-to-treat or severe asthma (ie, step 5).[5,8]

Appendix C includes the low, medium, and high daily doses of ICSs for all age groups, and the stepwise treatment approach for initial asthma management in pediatrics aged 6 to 11 per the 2021 GINA guideline.[8]

Table 2. Global Initiative for Asthma (GINA) 2021 Stepwise Treatment Approach for Initial Asthma Management in Patients ≥ 12 years of age[8]

GINA Track	GINA Steps	Reliever	Symptom Duration	Preferred Controller
Track 1[a]	*Step 1 and Step 2*	PRN low dose ICS-formoterol **(Preferred)**	Symptoms occur < 4 to 5 days per week	PRN low dose ICS-formoterol
	Step 3		Symptoms occur majority of the time, **or** awakening with asthma ≥ 1 per week	Low dose ICS-formoterol
	Step 4		Symptoms occur daily, **or** awakening with asthma ≥ 1 time per week, **and** low pulmonary function[b]	Medium-dose ICS-formoterol
	Step 5		No symptom duration is specified	• Add-on LAMA • Consider high-dose ICS-formoterol • Consult for phenotypic evaluation and consider add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL4R) • Oral corticosteroids
Track 2[a]	*Step 1*	PRN SABA **(Alternative)**	Symptoms occur < 2 times per month	Administer ICS when SABA is used
	Step 2		Symptoms occur ≥ 2 times per month, but < 4 to 5 days per week	Low dose ICS
	Step 3		Symptoms occur majority of the time, **or** awakening with asthma ≥ 1 per week	Low dose ICS-LABA
	Step 4		Symptoms occur daily, **or** awakening with asthma ≥ 1 time per week, **and** low pulmonary function[b]	Medium- or high-dose ICS-LABA
	Step 5		No symptom duration is specified	• Add-on LAMA • Consider high-dose ICS-formoterol • Consult for phenotypic evaluation and consider add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL4R) • Oral corticosteroids

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL4R, anti-interleukin 4 receptor treatment; anti-IL5/5R, anti-interleukin 5/5 receptor treatment; ICS, inhaled corticosteroids; ICS-LABA, fixed-dose combination of inhaled corticosteroids and long-acting beta$_2$ agonis; IL, interleukin; OCS, oral corticosteroids; PRN, as-needed; SABA, short-acting beta$_2$ agonist

[a] *Track 1 is preferred over Track 2 by the 2021 GINA guideline due to a demonstrated lower risk of serious exacerbations with as-needed low dose ICS-formoterol reliever compared to as-needed SABA reliever. Track 2 is an alternative if Track 1 is not feasible, or is not favored by a patient with no previous exacerbations on their current therapeutic regimen. Treatment may be individualized by switching between tracks based on the patient's needs or may be stepped up or down within a track using the same reliever. Patient adherence to daily controller therapy should be evaluated before initiating a treatment regimen with a SABA reliever (Track 2).*

[b] *Patients presenting with highly uncontrolled asthma may additionally require a short-duration of OCS treatment*

5.0 GUIDELINE RECOMMENDATIONS FOR SEVERE ASTHMA

For patients with *uncontrolled asthma,* GINA (2021) recommends optimizing therapy including adding non-biologics or increasing doses of ICS-LABA.[8] However, once severe asthma is diagnosed biologics can be started rather than prioritizing add-on non-biologics.[8] But prior to starting biologics for severe asthma, GINA recommends consideration of a 3–6 month trial of an increased ICS dose, objectively evaluating adherence (eg, monitoring electronic inhaler, medication records), and adding-on precise treatment for type 2-related comorbidities (eg, add-on intranasal corticosteroids for chronic rhinosinusitis and/or nasal polyposis; topical steroids or non-steroidal treatments for atopic dermatitis).[8] GINA (2021) recommends add-on targeted biologic therapies should be considered, based on availability and cost, for patients experiencing exacerbations or uncontrolled symptoms despite high-dose ICS-LABA use, and who have allergic or eosinophilic biomarkers or require maintenance OCS therapy.[8] It is recommended to test for and treat parasitic infections prior to treatment initiation, if applicable.[8] If biologics are unavailable for a patient with severe asthma, then add-on non-biologics are to be considered.[8]

Several practice guidelines and published articles have stated a need for head-to-head comparisons among the biologic therapies for asthma, especially when a patient is eligible for more than one biologic.[2,8,14] **Treatment guidelines do not yet incorporate tezepelumab.** GINA (2021) states that biologic treatment selection is based on phenotypes (eg, eosinophilic), and other factors such as predictors of asthma response (eg, blood eosinophil levels, age of onset, FeNO levels), insurance coverage, affordability, other type 2 related comorbidities (eg, atopic dermatitis, nasal polyps), dosing frequency, administration route (subQ or IV), and patient preference.[8] There is no established response "class effect" among biologics that target the same pathway (eg, IL-5), indicating that patients with an inadequate response to one anti-IL-5 agent may switch to another anti-IL-5 agent and respond well.[1,2]

Table 3 provides an overview of the guideline recommendations for the treatment of severe asthma, with a focus on biologic therapies.

Table 3. Guideline Recommendations for Biological Therapies for the Treatment of Severe Asthma

Professional Organization and Guideline	Guideline Recommendations

Global Initiative for Asthma (**GINA**)
 	
Global Strategy for Asthma Management and Prevention, 2021[8]
	Severe Asthma Treatment Algorithm (page 105 of guideline)
	<u>Adults and pediatrics ≥ 12 years of age:</u>
	• Refer for phenotypic assessment
	  ○ If type 2 inflammation biomarkers are present (eg, blood or sputum eosinophils, FeNO, allergy driven) or other type 2 indicators present (eg, OCS-dependence or asthma that is allergy driven):
	  ▪ Verify adherence
	  ▪ Increase the ICS dose for 3–6 months
	  ▪ Add specific treatment for clinical type 2 phenotypes (eg, AERD, chronic rhinosinusitis, atopic dermatitis)
	  ▪ Add-on **biologic therapies** (eg, anti-IgE, anti-IL5/5R, anti-IL4R) if **eosinophilic or allergic biomarkers are present or if asthma is OCS-dependent**

Table 3. Guideline Recommendations for Biological Therapies for the Treatment of Severe Asthma

Professional Organization and Guideline	Guideline Recommendations
	• If biologics are not available/affordable, consider adding on additional non-biologic therapies: LABA, LAMA, LTRA, low dose azithromycin (adults), tiotropium (≥ 6 years of age) ○ If type 2 inflammation is not evident: ▪ Trial add-on of LAMA or low dose azithromycin (adults) ▪ Add low dose OCS (≤ 7.5 mg/day prednisone equivalent; adults only), but consider the potential adverse effects ▪ Consider bronchial thermoplasty (+ registry) <u>Pediatrics 6–11 years of age:</u> • Refer for phenotypic assessment and consider add-on treatment (eg, tiotropium, anti-IgE, anti-IL5, anti-IL4R)
European Respiratory Society/ American Thoracic Society (**ERS/ATS**) Management of Severe Asthma: A European Respiratory Society/ American Thoracic Society Guideline, 2020[15]	• Adults with severe uncontrolled asthma with an **eosinophilic phenotype** and those with severe **corticosteroid-dependent asthma**, an **anti-IL5 treatment is recommended** (Conditional recommendation, low evidence quality) • A blood eosinophil threshold of ≥ 150 cells/µL is recommended to direct the initiation of anti-IL5 treatment in adults with severe asthma with previous exacerbations (Conditional recommendation, low evidence quality) • **Irrespective of eosinophil concentrations, dupilumab** is recommended for adults with **severe eosinophilic asthma** and those with severe **corticosteroid-dependent asthma** (Conditional recommendation, low evidence quality) • A blood eosinophil threshold of ≥ 260 cells/µL and a FeNO of ≥ 19.5 ppb is recommended to detect patients > 12 years of age with severe allergic asthma expected to have a better benefit from **anti-IgE** therapy (Conditional recommendation, low evidence quality) • Adding-on tiotropium is recommended for severe asthmatic patients (adults and pediatrics) uncontrolled on GINA step 4–5 or NAEPP step 5 treatments (Strong recommendation, moderate evidence quality)
European Academy of Allergy and Clinical Immunology (**EAACI**) EAACI Biologicals Guidelines–Recommendations for severe asthma, 2020[2]	• **Benralizumab** as add-on therapy for **uncontrolled severe eosinophilic asthma** (baseline blood eosinophil > 300 cells/µL or > 150 cells/µL for OCS-dependent) ○ <u>Adults:</u> recommended even with optimal controlled treatment (high-dose ICS-LABA) to reduce severe exacerbations (strong recommendation), reduce or withdraw OCS for blood eosinophils >150 cells/µL (strong recommendation), improve QoL (conditional recommendation), better asthma control (conditional recommendation), or increase pulmonary function (conditional recommendation) ○ <u>Pediatrics (12–17 years of age):</u> recommended even with optimal controlled treatment (high-dose ICS-LABA) to reduce severe exacerbations, improve QoL, better asthma control, or increase pulmonary function (conditional recommendation for all outcomes) • ***Safety:*** ○ <u>Adults and pediatrics 12–17 years of age:</u> benralizumab showed a favorable safety profile but patients should be routinely "screened for parasitic infections in endemic areas" (conditional recommendation) • **Dupilumab** as add-on therapy for **uncontrolled severe eosinophilic asthma** (type 2 inflammation characterized by elevated blood eosinophils [>150] and/or elevated FeNO> 20) ○ <u>Adults and pediatrics (12–17 years of age):</u> recommended even with optimal controlled treatment (medium/high-dose ICS + 2 additional controllers, including

Table 3. Guideline Recommendations for Biological Therapies for the Treatment of Severe Asthma

Professional Organization and Guideline	Guideline Recommendations

	OCS) to reduce severe exacerbations (strong recommendation), improve QoL (conditional recommendation), better asthma control (conditional recommendation), increase pulmonary function (strong recommendation), or reduce the use of rescue medication (conditional recommendation)
	• ***Safety:***
	  ○ Adults and pediatrics 12–17 years of age: dupilumab demonstrated a favorable safety profile but "long-term data (up to 2 years) are extrapolated from atopic dermatitis studies and careful reporting of all drug-related adverse events is recommended" (conditional recommendation)
	
	• **Mepolizumab** as add-on therapy for **uncontrolled severe eosinophilic asthma** (blood eosinophil ≥ 300 cells/µL in the past 1 year or ≥ 150 cells/µL at initiation)
	  ○ Adults: recommended even with optimal controlled treatment to reduce severe exacerbations (strong recommendation), reduce or withdraw OCS (strong recommendation), improve QoL (conditional recommendation), better asthma control (conditional recommendation), or increase pulmonary function (conditional recommendation)
	  ○ Pediatrics (12–17 years of age): recommended even with optimal controlled treatment to reduce severe exacerbations, reduce or withdraw OCS, improve QoL, better asthma control, or increase pulmonary function (conditional recommendation for all outcomes)
	• ***Safety:***
	  ○ Adults and pediatrics 12–17 years of age: long-term safety data (up to 5 years) of mepolizumab demonstrated a favorable safety profile but patients should be routinely "screened for parasitic infections in endemic areas" (conditional recommendation)
	
	• **Omalizumab** as add-on therapy for **uncontrolled moderate-to-severe allergic asthma** (total IgE concentrations of 30–700 IU/mL [US] and 30–1,500 IU/mL [EU] ± 1 perennial aeroallergen)
	  ○ Adults and pediatrics (12–17 years of age): recommended even with optimal controlled treatment to reduce severe exacerbations (strong recommendation), improve QoL (conditional recommendation), better asthma control (conditional recommendation), reduce ICS use (conditional recommendation), or reduce the use of rescue medication (conditional recommendation)
	  ○ Pediatrics (6–11 years of age): recommended even with optimal controlled treatment to reduce severe exacerbations, improve QoL, better asthma control, reduce ICS use (conditional recommendation for all outcomes)
	• ***Safety:***
	  ○ Adults and pediatrics (≥ 6 years of age): long-term safety data (> 10 years) of omalizumab demonstrated a favorable safety profile but patients should be monitored for signs of anaphylaxis 60 minutes after each administration for the first 3 doses (conditional recommendation)
	  ○ Pediatrics (6–11 years of age): omalizumab may decrease viral-induced exacerbations (conditional recommendation). Serum IgE concentration does not have an effect on the response (conditional recommendation)

Table 3. Guideline Recommendations for Biological Therapies for the Treatment of Severe Asthma

Professional Organization and Guideline	Guideline Recommendations

	• **Reslizumab** as add-on therapy for **uncontrolled severe eosinophilic asthma** (≥1 blood eosinophil level of ≥ 400 cells/µL during a 2–4 weeks of screening period)
	  ○ Adults: recommended even with optimal controlled treatment (at least a medium-dose ICS ± another controller medication, including OCS) to reduce severe exacerbations (strong recommendation), improve QoL (conditional recommendation), better asthma control (conditional recommendation), or increase pulmonary function (conditional recommendation)
	• ***Safety:***
	  ○ Adults: reslizumab demonstrated a favorable safety profile but patients should be routinely "screened for parasitic infections in endemic areas" and monitored for 30 minutes after IV administration for signs of anaphylaxis (conditional recommendation)

National Heart, Lung, and Blood Institute/ National Asthma Education and Prevention Program (**NHLBI/NAEPP**)
 	
2020 Focused Update to the Asthma Management Guidelines, 2020[26] [a]
	Adults and pediatrics ≥ 12 years of age:[b]
	• Step 4 Care: Severe Persistent Asthma
	  ○ Preferred treatment: medium-dose ICS-formoterol every day and PRN
	• Step 5 Care: Severe Persistent Asthma
	  ○ Preferred treatment: medium- or high-dose ICS-LABA + LAMA every day and PRN SABA
	• Step 6: Severe Persistent Asthma
	  ○ Preferred treatment: high-dose ICS-LABA every day + OCS + PRN SABA
	• Add-on **biologic therapies** (eg, anti-IgE, anti-IL5/5R, anti-IL4/IL13) may be considered in **step 5 or 6**
	Pediatrics (5–11 years of age):[b]
	• Step 3 Care: Severe Persistent Asthma
	  ○ Preferred treatment: low-dose ICS-formoterol every day and PRN
	• Step 4 Care: Severe Persistent Asthma
	  ○ Preferred treatment: medium-dose ICS-formoterol every day and PRN
	• Step 5 Care: Severe Persistent Asthma
	  ○ Preferred treatment: high-dose ICS-LABA every day and PRN SABA
	• Step 6 Care: Severe Persistent Asthma
	  ○ Preferred treatment: high-dose ICS-LABA every day + OCS and PRN SABA
	• Add-on ***omalizumab*** may be considered in **step 5 or 6**[c]

Abbreviations: AERD, aspirin-exacerbated respiratory disease; anti-IgE, anti-immunoglobulin E; anti-IL4R, anti-interleukin 4 receptor treatment; anti-IL5/5R, anti-interleukin 5/5 receptor treatment; ATS, American Thoracic Society; EAACI, European Academy of Allergy and Clinical Immunology; ERS, European Respiratory Society; EU, European Union; FeNO, exhaled nitric oxide fraction; GINA, Global Initiative for Asthma; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IU, international units; IV, intravenous; LABA, long-acting beta$_2$ agonist; LTRA, leukotriene receptor antagonist; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung, and Blood Institute; OCS, oral corticosteroids; ppb, parts per billion; PRN, as-needed; SABA, short-acting beta$_2$ agonist; QoL, quality of life; US, United States

[a] This guideline does not contain specific recommendations for the use of biologic therapies because the included studies (within AHRQ systematic reviews) did not evaluate them.

[b] Asthma severity was determined from the 2007 asthma guideline since the 2020 guideline is an update[26,27]

[c] At the time of publication, omalizumab was the only FDA-approved biologic for this age range

Recommendation strength (GRADE approach for ERS/ATS and EAACI guidelines)[2,15]

- *Conditional/weak: "trade-offs are uncertain, either because of low quality of evidence or because evidence suggests that desirable and undesirable effects are closely balanced"[1]*

Table 3. Guideline Recommendations for Biological Therapies for the Treatment of Severe Asthma

Professional Organization and Guideline	Guideline Recommendations

- *Strong: "desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not"[1]*

Quality of evidence (GRADE approach for ERS/ATS and EAACI guidelines)[2,15]

- *Very low: "any estimate of effect is very uncertain"[1]*
- *Low: "further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate"[1]*
- *Moderate: "further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate"[1]*
- *High: "further research is very unlikely to change the confidence in the estimate of effect"[1]*

Although the most recent clinical practice guidelines predate FDA approval for tezepelumab, some guidelines provide guidance on the place in therapy for the other biologics (eg, omalizumab, mepolizumab, dupilumab) used in the treatment of asthma. This information is provided in **Appendix D**, along with information pertaining to asthma management during the COVID-19 pandemic.

6.0 BIOLOGIC TREATMENTS FOR ASTHMA

The 6 biologic agents for the treatment of asthma (tezepelumab, benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab) are monoclonal antibodies created by recombinant DNA technology.[9,24,28-31] Numerous cell types (eg, eosinophils, mast cells, lymphocytes) and mediators (eg, histamine, cytokines including ILs and TSLP) are associated with the pathogenesis of respiratory inflammation in asthma.[9,24,28,29,31] Tezepelumab is the first agent within the biologic treatments for asthma that blocks TSLP binding to its receptor,[9] thereby reducing blood eosinophils, IgE, FeNO, and downstream ILs such as IL-5 and IL-13.[9] Omalizumab prevents binding of IgE to the IgE receptor (FcεRI) located on mast cells, basophils, and dendritic cells, inhibiting IgE-mediated inflammation as observed by decreased blood eosinophils, IL-4, IL-5, and IL-13.[30] Mepolizumab and reslizumab bind to circulating IL-5 preventing its attachment to the alpha subunit on the IL-5 receptor, whereas benralizumab directly attaches to the alpha subunit of the IL-5 receptor located on eosinophils among others (eg, basophils),[28] thereby decreasing eosinophil production and survival.[24,31] Additionally, benralizumab causes apoptosis of eosinophils.[8,28] Dupilumab blocks the alpha subunit of the IL-4 receptor, thereby preventing IL-4 and IL-13 inflammatory effects.[29] According to the product labeling, the mechanism of action in asthma has not been definitively determined for tezepelumab, benralizumab, dupilumab, mepolizumab, and reslizumab.[9,24,28,29,31]

These biologic agents for the treatment of asthma differ in several respects, including age of approved use, asthma severity and phenotype, and route/frequency of administration. They are similar in that they are all approved for use in adults.[9,24,28-31] With the exception of reslizumab, these agents are also approved for pediatric use: in patients 6 years of age and older for dupilumab, mepolizumab, and omalizumab; and 12 years of age and older for tezepelumab and benralizumab. [9,24,28-31] Most agents are approved for severe asthma, with dupilumab and omalizumab additionally approved for moderate asthma.[9,24,28-31] Agents approved prior to tezepelumab generally have indications that are specific to type 2 phenotypes (allergic or eosinophilic) and/or clinical scenario (severe asthma that is OCS dependent).[9,24,28-31] All products are administered subcutaneously (subQ), except reslizumab which is administered intravenously (IV).[9,24,28-31] Tezepelumab and reslizumab should be administered by a

healthcare provider in a health care setting,[9,31] while the other biologics can be self-administered.[24,28-30] The dosing frequency is every 2 weeks for dupilumab and omalizumab; every 4 weeks for tezepelumab, mepolizumab, omalizumab, and reslizumab; and every 8 weeks for benralizumab.[9,24,28-31]

Some of the products are approved for additional non-asthma indications. Dupilumab is approved for moderate-to-severe atopic dermatitis that is uncontrolled with topical prescription agents (or when these cannot be used).[29] Dupilumab and mepolizumab are approved as add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adults, and mepolizumab is approved for eosinophilic granulomatosis with polyangiitis (EPGA) and treatment of persistent (≥ 6 months) hypereosinophilic syndrome (HES) without a recognizable non-hematologic secondary cause.[24,29] Omalizumab is approved for adults as add-on maintenance treatment of nasal polyps, uncontrolled with nasal corticosteroids, and for adults or adolescents (≥ 12 years) with chronic spontaneous urticaria (CSU).[30]

Several ongoing clinical trials are evaluating tezepelumab for non-asthmatic indications such as CRSwNP, COPD, CSU, and eosinophilic esophagitis (EOE).[12] For the treatment of EOE, it was granted Orphan Drug designation by the FDA in October 2021.[12] Previously, tezepelumab was studied for the treatment of atopic dermatitis but failed to meet the targeted primary efficacy endpoint compared to placebo; thus, the indication for the treatment of atopic dermatitis has been abandoned.[32,33]

Table 4 provides an overview of FDA-approved indications, formulations, dosing recommendations, and other relevant prescribing information for the biological therapies for asthma.

Table 4. FDA-Approved Biological Treatments for Asthma

Generic Name Brand Name and Preparation (Approval Year)	**FDA-Approved Indication for Asthma**	**Age**	**Mechanism of Action**	**Recommended Dosage for Asthma**	**Other FDA-Approved Indications**
Tezepelumab-ekko[9 a, b] Tezspire • 210 mg/1.91 mL single-dose vial • 210 mg/ 1.91 mL pre-filled syringe (2021)	Add-on maintenance treatment for **severe** asthma Limitation of use: not for the alleviation of acute bronchospasm or status asthmaticus	≥ 12 years	Anti-TSLP	210 mg SQ Q4W	None
Benralizumab[28 b, c] Fasenra • 30 mg/mL pre-filled syringe • 30 mg/mL autoinjector pen (2017)	Add-on maintenance treatment for **severe** asthma with an **eosinophilic phenotype** Limitation of use: not for the treatment of other eosinophilic conditions; not for the alleviation of acute bronchospasm or status asthmaticus	≥ 12 years	Anti-IL-5Rα	30 mg SQ Q4W for the first 3 doses, then Q8W	None
Dupilumab[29 b, c] Dupixent • 300 mg/2 mL; 200 mg/1.4 mL pre-filled pen • 300 mg/2 mL; 200 mg/1.14 mL; 100 mg/0.67 mL pre-filled syringe (2017)	Add-on maintenance treatment for **moderate-to-severe** asthma with an **eosinophilic phenotype** or **oral corticosteroid dependent asthma** Limitation of use: not for the alleviation of acute bronchospasm or status asthmaticus	≥ 6 years	Anti-IL-4Rα	**Adults and children ≥12 years:** 400 mg (two 200 mg injections)SQ initially, then 200 mg SQ Q2W **OR** 600 mg[d] (two 300 mg injections) SQ initially, then 300 mg Q2W **Children 6 to 11 years old:** weight-based dose • 15 to <30 kg: 100 mg SQ Q2W **OR** 300 mg SQ Q4W • ≥30 kg: 200 mg SQ Q2W	Moderate-to-severe AD that is uncontrolled by topical prescription treatment (or when these options cannot be used) (≥ 6 years of age) Add-on maintenance treatment of CRSwNP (adults)

Table 4. FDA-Approved Biological Treatments for Asthma

Generic Name Brand Name and Preparation (Approval Year)	**FDA-Approved Indication for Asthma**	**Age**	**Mechanism of Action**	**Recommended Dosage for Asthma**	**Other FDA-Approved Indications**
Mepolizumab[24] [b, c] Nucala • 100 mg/mL pre-filled autoinjector • 100 mg/mL; 40 mg/0.4 mL pre-filled syringe • 100 mg lyophilized powder for reconstitution (2015)	Add-on maintenance treatment for **severe** asthma with an **eosinophilic phenotype** Limitation of use: not for the alleviation of acute bronchospasm or status asthmaticus	≥ 6 years	Anti-IL-5	**Adults and children ≥12 years:** 100 mg SQ Q4W **Children 6 to 11 years old:** 40 mg SQ Q4W	Add-on maintenance treatment of CRSwNP (adults) Treatment of EGPA (adults) Treatment of persistent (≥6 months) HES without a recognizable non-hematologic secondary cause (≥12 years of age)
Omalizumab[30] [b, e] Xolair • 150 mg/mL; 75 mg/0.5 mL pre-filled syringe • 150 mg lyophilized powder for reconstitution (2003)	**Moderate-to-severe persistent asthma** that is uncontrolled by ICSs with a **perennial aeroallergen** sensitivity as indicated by a positive skin test or in vitro reaction Limitation of use: not for the alleviation of acute bronchospasm or status asthmaticus; other allergic conditions or other types of urticaria	≥ 6 years	Anti-IgE	75 to 367 mg SQ Q2W or Q4W[f]. Dose and dosing frequency are determined by pretreatment total IgE levels (IU/mL) and body weight (kg). Refer to dose recommendations in Tables 1 and 2 of the PI	Add-on maintenance treatment of nasal polyps, uncontrolled with nasal corticosteroids (adults) Symptomatic CSU despite H1 antihistamine therapy (≥12 years of age)
Reslizumab[31] [a] Cinqair • 100 mg/10 mL solution in single-use vials (2016)	Add-on maintenance treatment for **severe** asthma with an **eosinophilic phenotype** Limitation of use: Not for the treatment of other eosinophilic conditions; not for the alleviation of acute bronchospasm or status asthmaticus	≥ 18 years	Anti-IL-5	3 mg/kg **IV** Q4W infused over 20 to 50 minutes	None

Table 4. FDA-Approved Biological Treatments for Asthma

Generic Name Brand Name and Preparation (Approval Year)	**FDA-Approved Indication for Asthma**	**Age**	**Mechanism of Action**	**Recommended Dosage for Asthma**	**Other FDA-Approved Indications**

Abbreviations: AD, atopic dermatitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; CSU, chronic spontaneous urticaria; EGPA, eosinophilic granulomatosis with polyangiitis; FDA, U.S. Food and Drug Administration; HES, hypereosinophilic syndrome; ICS, inhaled corticosteroids; IL, interleukin; IL-4Rα, interleukin-4 receptor alpha; IL-5Rα, interleukin-5 receptor alpha; IgE, immunoglobulin E; IV, intravenously; PI, package insert; Q, every; subQ, subcutaneously; TSLP, thymic stromal lymphopoietin; W, weeks

[a] *Should be administered by a healthcare provider*

[b] *Recommended subQ sites: thigh, abdomen, upper arm (by healthcare provider or caregiver only). Rotate injection sites.*

[c] *Intended to be used under the guidance of a healthcare provider, may be administered by the patient or caregiver.*

[d] *This dosage regimen is recommended for patients with oral corticosteroid dependent asthma or with comorbid chronic rhinosinusitis with nasal polyposis*

[e] *Treatment should be started in a healthcare setting and the healthcare provider may determine if self-administration of the pre-filled syringe is appropriate*

[f] *Limit injections to ≤150 mg per site, doses of > 150 mg should be divide among more than one injection site*

6.1 Initiation, Switching, and Discontinuation of Biologics for Asthma

6.1.1 Initiation and Re-evaluation

According to the 2021 GINA guideline, an initial trial of at least 4 months should be considered to determine the effectiveness of biologic therapies.[8] The patient's response to a biologic treatment should be reviewed after 3–4 months, and every 3–6 months thereafter, including review of asthma control, pulmonary function, type 2-related comorbidities (eg, nasal polyposis, atopic dermatitis), other asthma-related pharmacologic agents, and patient gratification.[8] A trial extension of 6 to 12 months may be considered in patients with an uncertain response.[8]

EAACI (2020) recommends a review of treatment response after 4–6 months due to the high price of biologics; however, authors highlight the lack of validated standards for a favorable response.[2] Tailored predefined objectives are recommended based on the patient's desires for asthma control.[2]

6.1.2 Switching

If no response has been achieved after the initial trial period of 4 months, switching to a different biologic therapy should be considered, if appropriate.[8] According to the EAACI guideline, in patients that have produced neutralizing anti-drug antibodies (ADAs) to an asthma biologic, switching to an alternative biologic with a different mechanism of action or administration route which targets the same proinflammatory mediator (eg, anti-IL5), or a biologic that affects a separate pathway may be considered.[2]

6.1.3 Discontinuation

According to the 2021 GINA guideline, patients with a favorable response to add-on biological therapy should not discontinue the biologic for at least 1 year after treatment initiation.[8] Discontinuation should only be considered in situations where asthma control is maintained on medium-dose ICS therapy, "and (for allergic asthma) there is no further exposure to a previous well-documented allergic trigger."[8] Based on limited evidence evaluating the discontinuation of biologic treatment among patients with severe asthma, most individuals experience worsening symptoms and/or exacerbations after withdrawal of biologic therapies.[8]

7.0 TEZEPELUMAB CLINICAL TRIALS

No systematic reviews (SRs) were identified for tezepelumab that included phase 3 randomized controlled trials (RCTs). However, 2 pivotal phase 3 RCTs for tezepelumab were identified: NAVIGATOR and SOURCE.[34,35] Both trials compared tezepelumab to placebo among patients with severe asthma.[34,35] The results from SOURCE are unpublished and the information below is based on data from ClinicalTrials.gov., a conference abstract, and a 2021 ICER report on tezepelumab.[3,36,37] Patients from NAVIGATOR and SOURCE had the opportunity to enroll in an ongoing long-term extension study, DESTINATION.[38,39] No results have been reported for DESTINATION yet.

Details are also provided for the phase IIb dose-finding trial, PATHWAY[10] since tezepelumab was granted "breakthrough therapy" designation by the FDA from evidence demonstrated by this trial.[11] According to the study protocols, NAVIGATOR and PATHWAY allowed the continuation of background asthma

treatments such as medium- or high-dose ICS use with or without a LABA and other controllers for maintenance (eg, LAMA, LTRA, theophylline, OCS) during the duration of the trials.[9] This information is unknown for the unpublished SOURCE trial.

7.1 Study Population Among the Pivotal Clinical Trials

Table 5 summarizes the key inclusion criteria of the patients that were enrolled in the pivotal clinical trials for tezepelumab. Patients that had previously received biologic therapies were allowed into the trials as long as the last dose was administered > 4 months or > 5 half-lives (whichever was longer) prior to screening or the first visit.[10,13,34-36]

Appendix E includes additional inclusion and exclusion criteria.

Table 5. Overview of the Patient Population in Pivotal Tezepelumab Clinical Trials

RCT	Select Inclusion Criteria						
	Age	*Diagnosis*	*ICS dose*	*Other Controller Use*	*Number of Exacerbations*	*Prebronchodilator FEV_1*	*Postbronchodilator FEV_1 reversibility*
NAVIGATOR[34]	12–80 years	Severe asthma[a]	*Medium*- or high-dose ICS	≥ 1 additional controller (ie, LABA, LTRA)	≥ 2 within the previous 12 months	<80% of normal predicted value (<90% for those aged 12–17 years)	≥ 12% and ≥ 200 mL
PATHWAY[10]	18–75 years	Severe asthma[a]		LABA	≥ 2 **OR** ≥ 1 severe exacerbation that required hospitalization within the previous 12 months	≥ 40% but ≤ 80% of normal predicted value	
SOURCE[35,36]	18–80 years	Severe **OCS-dependent** asthma	High-dose ICS	LABA with or without other controllers	≥ 1 within the previous 12 months	<80% of normal predicted value	

Abbreviations: FEV_1, forced expiratory volume in 1 second; LABA, long-acting $beta_2$ agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; RCT, randomized controlled trial

[a] Trial investigators labeled patients with "severe asthma" but patients with uncontrolled asthma on medium-dose ICS were permitted to enroll, which varies slightly from the definition of severe asthma according to the GINA and ERS/ATS guidelines. However, it also fails to meet the GINA definition of moderate asthma which is adequately controlled with a low- or medium-dose ICS-LABA.

7.2 Outcome/Questionnaire Definitions from Pivotal Clinical Trials

The effect of tezepelumab versus placebo on the annualized rate of asthma exacerbations (AAER) over the study duration among the entire study population was the primary outcome in the NAVIGATOR and PATHWAY trials, while it was the secondary outcome in SOURCE.[10,34,36,40] Unlike the other trials, the primary outcome for SOURCE was assessing the effect of tezepelumab compared to placebo for changes

in daily OCS maintenance therapy among adults with severe OCS-dependent asthma.[35,36] The effect of tezepelumab on AAER was further evaluated in predefined subgroups (eg, baseline eosinophil thresholds, allergic status) in NAVIGATOR and PATHWAY.[10,34]

The clinical trials for tezepelumab evaluated patient report outcomes (PRO) as secondary endpoints. The patient-reported Asthma Control Questionnaire – six question version (ACQ-6) was used to evaluate asthma symptom control; the total score ranges from 0 (no impairment) to 6 (maximum impairment), with lower scores implying better asthma control (≤ 0.75 is well-controlled).[34,41] ACQ-6 scores ≥ 1.5 suggest uncontrolled asthma.[34,41] The Asthma Quality of Life Questionnaire standardized for those aged ≥ 12 years (AQLQ[S]+12) is a patient-response questionnaire that includes 4 domains ("symptoms, activity limitations, emotional function, and environmental stimuli") designed to measure the QoL of individuals 12 years of age and older with asthma on a 7-point Likert scale (1 [maximum impairment] to 7 [no impairment]).[34] Higher AQLQ[S]+12 total scores suggest a better QoL.[34,42]

Table 6 summarizes the outcomes evaluated in the pivotal clinical trials for tezepelumab.

Table 6. Summary of Outcomes Evaluated Across the Pivotal Tezepelumab Clinical Trials

	Outcomes			
RCT	*Primary Outcome*	*Key Secondary Outcomes*[a]		
NAVIGATOR[34]	AAER (events per patient-year) measured at 52 weeks[b]	Change in baseline prebronchodilator FEV_1 at week 52	ACQ-6	AQLQ[S]+12
PATHWAY[10]				
SOURCE[36]	Percent reduction in the daily OCS maintenance dose while maintaining asthma control at 48 weeks	AAER (events per patient-years)		

Abbreviations: AAER, annualized asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire, six-question version; AQLQ[S]+12, Asthma Quality of Life Questionnaire standardized for those aged ≥ 12 years; FEV_1, forced expiratory volume in 1 second; OCS, oral corticosteroids; RCT, randomized controlled trial

[a] *Not a comprehensive list of all evaluated secondary outcomes. Please refer to the specific study for additional secondary outcomes.*

[b] *Also evaluated based on predetermined subgroups of baseline blood eosinophil levels and allergic status*

7.3 NAVIGATOR

NAVIGATOR was a 52-week, multicenter, randomized, double-blind, placebo-controlled trial conducted by Menzies-Gow et al (2021) evaluating the efficacy and safety of tezepelumab in **adolescents and adults with severe asthma** (see Table 5 enrollment parameters).[34]

Among the total study population (N=1059), the mean age was 49.5 years, with 36.5% and 62.2% of patients reporting as male and Caucasian, respectively.[34] Participants were randomized in a 1:1 ratio to either tezepelumab (N=528) 210 mg subQ every 4 weeks, or matching placebo (N=531), both added to standard care.[34] Across both study arms, approximately 74% of patients had elevated blood eosinophil concentrations (≥ 150 cells/µL) and approximately 26% had low blood eosinophil concentrations (< 150 cells/µL).[34,40]

Tezepelumab significantly reduced exacerbations relative to placebo in the total study population, as well as those with a blood eosinophil concentration < 300 cells/µL (rate ratio of the annualized rate of asthma exacerbations [AAER] = 0.44 and 0.59, respectively; for both outcomes *p<0.001*) over 52 weeks.[34] Among those with a positive or negative allergic test for any perennial allergens at baseline, tezepelumab produced greater reductions in the AAER than placebo.[34] Additionally, compared to placebo, tezepelumab significantly improved the key secondary outcomes of prebronchodilator FEV_1, and scores on questionnaires for asthma control (ACQ-6), and patient-reported QoL (AQLQ[S]+12).[34]

Overall, tezepelumab demonstrated a similar safety profile to placebo, including for the incidence of adverse events (AEs) of serious infections (8.7% in either arm) and cancer (0.8% in either arm).[34] The most frequently reported AEs among either treatment group, but occurring numerically more often in the placebo arm, were nasopharyngitis, upper respiratory tract infection (URTI), headache, and worsening asthma.[34] As expected, injection-site reactions occurred more frequently in the tezepelumab arm compared to placebo (3.6% vs 2.6%, respectively) but "no treatment-related anaphylactic reactions or cases of Guillain-Barre syndrome were reported".[34] Two deaths occurred in the placebo arm during the study duration, and no deaths occurred during tezepelumab treatment.[34] Anti-drug antibodies (ADAs) were detected in both treatment groups, with one individual from each group positive for neutralizing antibodies.[34]

7.4 SOURCE

SOURCE was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial assessing the effect of tezepelumab compared to placebo for changes in daily OCS maintenance therapy in **adults with severe, OCS-dependent asthma** (see Table 5 for enrollment parameters).[35] This trial is not yet fully published. At baseline, approximately 74% of the study population in both treatment groups had a blood eosinophil concentration of ≥ 150 cells/ µL.[40]

The study included a 48-week treatment period, consisting of a 4-week induction period, followed by 36 weeks of an OCS reduced-dose phase, and an 8 week maintenance period.[35] Before randomization, during the 8-week OCS optimization period, the lowest effective dose of OCS required to maintain symptom control was determined for each patient.[35] This optimized lowest effective OCS dose was considered the baseline OCS dose.[35] During the trial, after randomization, the OCS dose could have been further decreased as frequently as every 4 weeks.[35] During the 8 week maintenance period which followed the 36 week OCS taper period, patients continued on the OCS dose that was achieved at the completion of the reduction period.[35] For situations in which a patient experienced an exacerbation during the maintenance period, an increased OCS dose may be used or the same OCS dose was maintained.[35]

According to data reported on ClinicalTrials.gov., the mean age of the total study population (N=150) was 53.4 years, with 37.3% comprising of males and 84% of patients reporting as Caucasian.[36] Participants were randomized in a 1:1 ratio to either tezepelumab (N=74) 210 mg subQ every 4 weeks, or matching placebo (N=76).[35] The primary efficacy outcome was to evaluate the effect of tezepelumab versus placebo on decreasing the daily OCS maintenance dose, categorized by percent reduction (≥ 90%, ≥ 75% to <90%, ≥ 50% to <75%, >0% to <50%, and no modification or any escalation in OCS dose), while preserving asthma control from baseline to week 48.[35]

For the primary efficacy outcome, a cumulative odds ratio of 1.28 (95% CI 0.69 to 2.35) was reported, indicating tezepelumab was not statistically different from placebo in terms of decreasing the daily requirement of OCS therapy while maintaining asthma control.[36] Nevertheless, numerically more patients maintained asthma control in the category of ≥90 to ≤100% reduction with tezepelumab than placebo (54.1% vs 46.1%, respectively).[36] For OCS daily dose reductions of <75% to no change, or for those that required an increase in OCS therapy, tezepelumab numerically produced similar or worse results compared to placebo.[36] Patients with a baseline eosinophil count at or exceeding 150 cells/µL or 300 cells/µL had significantly increased odds of reducing their OCS dose with tezepelumab compared to placebo.[37] In contrast, the point estimate for cumulative odds of a reduction in OCS dose in patients with a baseline eosinophil count below those eosinophil thresholds favored placebo over tezepelumab, although statistically significant differences were not observed.[37] For the key secondary endpoint, the AAER was numerically lower in the tezepelumab arm compared to placebo (1.38 vs 2.00, respectively), but it was not statistically significant (rate ratio= 0.69; 95% CI 0.44 to 1.09).[3,37]

Tezepelumab demonstrated a similar safety profile to previous clinical trials (NAVIGATOR). The most common AEs reported in either treatment group were nasopharyngitis, URTI, worsening asthma, bacterial bronchitis, and headache.[36] No deaths occurred among the patients receiving placebo.[36] However, one death occurred in the tezepelumab-treated group, but the cause of death has yet to be reported.[36]

7.5 PATHWAY

PATHWAY was a 52-week, phase 2, multicenter, randomized, double-blind, placebo-controlled trial conducted by Corren et al (2017) evaluating the efficacy and safety of three different doses of tezepelumab versus placebo in **adults with severe asthma** inadequately controlled on medium-to high-dose ICS plus a LABA (see Table 5 for enrollment parameters).[10]

Among the study population (N=550), the mean age was 51.6 years, with 34.4% male and 91.6% of patients reporting as Caucasian.[3,10] Multiple doses of tezepelumab were studied (low-to high-dose); the medium dose (210 mg subQ every 4 weeks) is the FDA-approved regimen.[9,10] At baseline, approximately 80% of the patients in the medium dose category had blood eosinophil concentrations ≥ 150 cells/µL compared to 76% in the placebo group.[40]

For the purposes of this report, the efficacy and safety results pertaining to this study are reported with a focus on the FDA-approved dosing regimen. Regarding the primary efficacy outcome, the asthma exacerbation rate was significantly reduced among medium-dose tezepelumab-treated patients compared to placebo-treated patients at week 52 (0.20 vs 0.72, respectively); the benefit on exacerbation rate favoring tezepelumab was consistently observed regardless of baseline eosinophil concentration or allergic status.[10] Patients also experienced fewer exacerbations resulting in hospitalization or emergency department visits with tezepelumab than placebo.[3] Additionally, tezepelumab improved the prebronchodilator FEV_1 and scores on questionnaires for asthma control (ACQ-6), and patient-reported QoL (AQLQ[S]+12).[10]

The adverse effect profile across the 3 tezepelumab dosing regimens was similar to placebo.[10] The most common AEs reported among any treatment group were bronchitis, nasopharyngitis, headache, and worsening asthma.[10] One death occurred due to a stroke in a 74 year old woman receiving 70 mg of tezepelumab, whereas no deaths were reported in any other treatment groups.[10] One incident of

Guillain-Barre syndrome was reported, which occurred in the medium-dose tezepelumab regimen and resulted in treatment discontinuation.[10] Similar to other tezepelumab trials, non-neutralizing ADAs were detected after baseline in each study arm (ie, all tezepelumab groups and placebo).[10]

7.6 Summary of Pivotal Tezepelumab Randomized Controlled Trials

Table 7 includes a summary of the primary and secondary endpoint results, and pertinent safety information for the pivotal tezepelumab RCTs.

Table 7. Summary of Pivotal Tezepelumab Randomized Controlled Trials

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results	Safety Results
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (Menzies-Gow, 2021, **NAVIGATOR**)[34]	Patients ≥ 12 years of age diagnosed with severe asthma[a] for ≥ 1 year, uncontrolled on *medium*- or high-dose ICS plus at least 1 other controller agent (eg, LABA, LTRA), with or without OCS	TEZ 210 mg SQ Q4W (N=528) vs PBO (N=531) Duration: 52 weeks	Primary endpoint: AAER: events per patient-year during the 52-week study duration Among the entire study population: • **TEZ:** 0.93 (95% CI 0.80 to 1.07) • **PBO:** 2.10 (95% CI 1.84 to 2.39) ○ ***Rate ratio=*** *0.44 (95% CI 0.37 to 0.53; p<0.001)* Pre-defined subgroup analysis: Among those with a blood eosinophil concentration ≤ 300 cells/µL: • **TEZ:** 1.02 (95% CI 0.84 to 1.23) • **PBO:** 1.73 (95% CI 1.46 to 2.05) ○ ***Rate ratio=*** *0.59 (95% CI 0.46 to 0.75; p<0.001)* Among those with a blood eosinophil concentration ≥ 300 cells/µL: • **TEZ:** 0.79 (95% CI NR) • **PBO:** 2.66 (95% CI NR) ○ ***Rate ratio=*** *0.30 (95% CI 0.22 to 0.40; p-value NR)* Among those with a positive test for any perennial allergens: • **TEZ:** 0.85 (95% CI NR) • **PBO:** 2.03 (95% CI NR) ○ ***Rate ratio=*** *0.42 (95% CI 0.33 to 0.53; p-value NR)* Among those with a negative test for any perennial allergens: • **TEZ:** 1.09 (95% CI NR) • **PBO:** 2.21 (95% CI NR)	Most frequently report TEAEs (≥ 4% in any treatment group): • Nasopharyngitis TEZ (21.4%) vs PBO (21.5%) • URTI TEZ (11.2%) vs PBO (16.4%) • Headache TEZ (8.1%) vs PBO (8.5%) • Worsening asthma TEZ (5.1%) vs PBO (11.1%) • Viral bronchitis TEZ (4.7%) vs PBO (6.2%) • Bacterial bronchitis TEZ (4.5%) vs PBO (3.2%) • UTI TEZ (4.2%) vs PBO (4.1%) • Hypertension TEZ (4.4%) vs PBO (4.1%) • Back pain TEZ (4.0%) vs PBO (2.8%) Discontinued treatment due to AEs: TEZ (2.1%) vs PBO (3.6%) Any SAEs:[b] TEZ (9.8%) vs PBO (13.7%) Deaths: 2 deaths occurred, both in PBO arm Selected other AEs of interest: • Injection-site reactions TEZ (3.6%) vs PBO (2.6%) • Positive ADA at or after baseline TEZ (4.9%) vs PBO (8.3%)

Table 7. Summary of Pivotal Tezepelumab Randomized Controlled Trials

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results	Safety Results
			○ ***Rate ratio=*** *0.49 (95% CI 0.36 to 0.67; p-value NR)* Key secondary endpoints: LSM change in prebronchodilator FEV_1: from baseline to week 52 • ***TEZ vs PBO:*** *LSM difference= 0.13 (95% CI 0.08 to 0.18; p-value <0.001)* LSM change in ACQ-6 score: from baseline to week 52 • ***TEZ vs PBO:*** *LSM difference= –0.33 (95% CI –0.46 to –0.20; p-value <0.001)* LSM change in AQLQ[S]+12 score: from baseline to week 52 • ***TEZ vs PBO:*** *LSM difference= 0.34 (95% CI 0.20 to 0.47; p-value <0.001)*	
Phase 3, multicenter, randomized, double-blind, placebo-controlled trial (Wechsler, 2020, **SOURCE**)[35,36 c]	Patients ≥ 18 years of age diagnosed with severe asthma (OCS-dependent) for ≥ 1 year, uncontrolled on high-dose ICS-LABA[d], with or without other controller agents	TEZ 210 mg SQ Q4W (N=74) vs PBO (N=76) Duration: 48 weeks	Primary endpoint: Percent reduction in daily OCS dose, while maintaining asthma control: from baseline to week 48: Among the entire study population: **Cumulative OR= 1.28** (95% CI 0.69 to 2.35; p=0.43) **≥90 to ≤100% reduction:** • **TEZ:** 40 patients (54.1%) • **PBO:** 35 patients (46.1%) **≥75 to <90% reduction:** • **TEZ:** 5 patients (6.8%) • **PBO:** 4 patients (5.3%) **≥50 to < 75% reduction:** • **TEZ:** 10 patients (13.5%) • **PBO:** 14 patients (18.4%) **>0 to <50% reduction:** • **TEZ:** 5 patients (6.8%)	Most frequently report TEAEs (≥ 3% in any treatment group): • Nasopharyngitis TEZ (16.2%) vs PBO (25.0%) • URTI TEZ (12.2%) vs PBO (10.5%) • Worsening asthma TEZ (8.1%) vs PBO (10.5%) • Bacterial bronchitis TEZ (8.1%) vs PBO (9.2%) • Headache TEZ (4.0%) vs PBO (10.5%) • Myalgia TEZ (5.4%) vs PBO (1.3%) • Oral candidiasis

Table 7. Summary of Pivotal Tezepelumab Randomized Controlled Trials

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results	Safety Results
			• **PBO:** 9 patients (11.8%) **No change or any increase:** • **TEZ:** 14 patients (18.9%) • **PBO:** 14 patients (18.4%) Among those with a blood eosinophil concentration: < 300 cells/µL: **Cumulative OR= 0.70** (95%CI 0.33 to 1.47) *≥ 300 cells/µL: **Cumulative OR= 3.49** (95% CI 1.16 to 10.49)* < 150 cells/µL: **Cumulative OR= 0.40** (95% CI 0.14 to 1.13) *≥ 150 cells/µL: **Cumulative OR= 2.58** (95% CI 1.16 to 5.75)* <u>Key secondary endpoint:</u> <u>AAER:</u> events during the 48-week treatment period • **TEZ:** 1.38 (95% CI 0.98 to 1.95) • **PBO:** 2.00 (95% CI 1.46 to 2.74) ○ **Rate ratio=** 0.69 (95% CI 0.44 to 1.09; p-value NR)[3]	TEZ (5.4%) vs PBO (5.3%) • Viral bronchitis TEZ (5.4%) vs PBO (4.0%) • Fall TEZ (4.0%) vs PBO (1.3%) • Hypertension TEZ (2.7%) vs PBO (7.9%) • Sinusitis TEZ (1.4%) vs PBO (6.6%) • Influenza-like illness TEZ (0%) vs PBO (6.6%) • Nasal polyps TEZ (0%) vs PBO (5.3%) <u>Discontinued treatment due to AEs:</u> NR <u>Any SAEs:</u> TEZ (16.2%) vs PBO (21.1%) <u>Deaths:</u> 1 death occurred in the TEZ arm, cause not reported <u>Selected other AEs of interest:</u> • Positive ADA at or after baseline TEZ (4.1%) vs PBO (2.6%)
Phase 2, multicenter, randomized, double-blind, placebo-controlled trial (Corren, 2017, **PATHWAY**)[10 e]	Patients ≥ 18 years of age diagnosed with severe asthma[a] for ≥ 1 year, uncontrolled on *medium*- or high-dose ICS plus a LABA	**Low dose:** TEZ 70 mg SQ Q4W (N=138) vs **Medium dose:** TEZ 210 mg SQ Q4W (N=137)	<u>Primary endpoint:</u> <u>AAER:</u> events per patient-year during the 52-week study duration Among the ITT population: • **TEZ:** 0.20 (90%CI 0.14 to 0.28)	<u>Most frequently report TEAEs (≥ 5% among TEZ 210 mg and PBO):</u> • Worsening asthma TEZ (19.7%) vs PBO (36.2%) • Nasopharyngitis TEZ (13.9%) vs PBO (11.6%)

Table 7. Summary of Pivotal Tezepelumab Randomized Controlled Trials

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results	Safety Results
		vs **High dose:** 280 mg SQ Q2W (N=137) vs PBO (N=138) Duration: 52 weeks	○ *Percent reduction vs. PBO: 71% (95%CI 54% to 82%; p-value <0.001)* • **PBO:** 0.72 (90% CI 0.61 to 0.86) ○ **Rate ratio=** *0.29 (95%CI 0.16 to 0.51; p-value NR)*[3] Pre-defined subgroup analysis: Among those with a blood eosinophil concentration: <u>≥ 250 cells/µL:</u> • **TEZ:** 0.26 (95%CI 0.16 to 0.42) ○ *Percent reduction vs. PBO: 65% (95%CI 27% to 83%; nominal p-value =0.005)* • **PBO:** 0.78 (95% CI 0.59 to 1.00) <u>< 250 cells/µL:</u> • **TEZ:** 0.14 (95%CI 0.06 to 0.27) ○ *Percent reduction vs. PBO: 79% (95%CI 48% to 92%; nominal p-value <0.001)* • **PBO:** 0.65 (95% CI 0.46 to 0.89) Among those with a <u>High</u> Th2 status[f]: • **TEZ:** 0.25 (95%CI 0.14 to 0.41) ○ *Percent reduction vs. PBO: 62% (95%CI 13% to 83%; nominal p-value =0.021)* • **PBO:** 0.62 (95%CI 0.45 to 0.83) Among those with a <u>Low</u> Th2 status[f]: • **TEZ:** 0.23 (95%CI 0.14 to 0.37) ○ *Percent reduction vs. PBO: 68% (95%CI 38% to 84%; nominal p-value <0.001)*	• Headache TEZ (8.0%) vs PBO (4.3%) • Bronchitis (unclear if bacterial or viral) TEZ (3.6%) vs PBO (5.1%) <u>Discontinued treatment due to AEs:</u> TEZ (1.5%) vs PBO (0.7%) <u>Any SAEs:</u>[c] TEZ (9.5%) vs PBO (13.0%) <u>Deaths:</u> 1 death occurred in the TEZ 70 mg arm from a stroke <u>Selected other AEs of interest:</u> • Injection-site reactions after 1mL injection TEZ (2.9%) vs PBO (3.6%) • Injection-site reactions after 1.5mL injection TEZ (2.9%) vs PBO (2.9%) • Positive ADA after baseline TEZ (0.8%) vs PBO (9.4%)

Table 7. Summary of Pivotal Tezepelumab Randomized Controlled Trials

RCT Design (author, year, trial name)	Population	Intervention	Efficacy Results	Safety Results
			• **PBO:** 0.86 (95%CI 0.64 to 1.13) Key secondary endpoints: LSM change in prebronchodilator FEV_1: from baseline to week 52 • ***TEZ vs PBO:*** *LSM difference= 9.50 (95% CI 3.45 to 15.56; nominal p-value =0.002)* LSM change in ACQ-6 score: from baseline to week 50[g] • ***TEZ vs PBO:*** *LSM difference= –0.29 (95% CI –0.56 to –0.01; p-value =0.039)* LSM change in AQLQ[S]+12 score: from baseline to week 48[g] • **TEZ vs PBO:** LSM difference= 0.20 (95% CI –0.09 to 0.48; p-value =0.185)	

Abbreviations: AAER, annualized rate of asthma exacerbations; ACQ-6, Asthma Control Questionnaire, six-question version; ADA, anti-drug antibody; AEs, adverse events; AQLQ[S]+12, Asthma Quality of Life Questionnaire standardized for those aged ≥ 12 years; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting $beta_2$ agonist; LSM, least-square mean; LTRA, leukotriene receptor antagonist; NR, not reported; OCS, oral corticosteroids; OR, odds ratio; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomized controlled trial; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TEZ, tezepelumab; URTI, upper respiratory tract infection;

Italicized text signifies statistically significant results

[a] *Trial investigators labeled patients with "severe asthma" but patients with uncontrolled asthma on medium-dose ICS were permitted to enroll, which varies slightly from the definition of severe asthma according to the GINA and ERS/ATS guidelines. However, it also fails to meet the GINA definition of moderate asthma which is adequately controlled with a low- or medium-dose ICS-LABA. Please refer to* ***Appendix E*** *for additional inclusion and exclusion criteria.*

[b] *"A serious adverse event was defined as an event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, was an important medical event, or resulted in a congenital anomaly or birth defect (in the offspring of the parent)".*[10]

[c] *Efficacy and safety results were reported according to the ClincialTrials.gov website (NCT03406078) and a 2021 conference abstract*[37] *since results are not yet published in medical literature*

[d] *Patients taking a medium-dose ICS were required to be escalated to a high dose for ≥ 3 months prior to screening*

[e] *Only reported the efficacy and safety results of the medium-dose tezepelumab regimen (210 mg subcutaneously every 4 weeks) since that is the FDA-approved dose*

[f] *High Th2 status defined as an IgE >100 IU/mL AND eosinophil levels ≥ 140 cells/µL; Low Th2 status defined as an IgE ≤ 100 IU/mL OR eosinophil levels < 140 cells/µL*

[g] *A programming issue prevented patients from completing the questionnaire at week 52 causing a lower completion rate compared to week 48 and 50.*

8.0 PHARMACOKINETICS AND SPECIAL POPULATIONS

8.1 Pharmacokinetics

Based on the FDA-approved dosing schedule (every 4 weeks), tezepelumab obtains steady-state concentrations after 12 weeks, with an estimated elimination half-life of 26 days.[9] Tezepelumab has an estimated absolute bioavailability of 77%, with no clinically meaningful differences in bioavailability between various injection sites (eg, thigh, abdomen, upper arm).[9] No race, sex, or age specific changes in pharmacokinetic parameters have occurred with tezepelumab.[9] Additionally, dose adjustments are not necessary for patients with an increased body weight, although they may have decreased drug exposure.[9] Other asthma-related medications (eg, ICS, leukotriene receptor antagonist [LTRA], OCS) do not seem to interact with tezepelumab, but there is a lack of evidence from conventional drug interaction trials.[9]

8.2 Pediatrics

The safety and effectiveness of tezepelumab in patients < 12 years of age has not been determined.[9] In the NAVIGATOR trial, which included 82 adolescents (aged 12–17 years), compared to placebo, treatment with tezepelumab tended to improve the AAER (rate ratio=0.70; 95% CI 0.34 to 1.46) and FEV_1 (least-square mean [LSM] change= 0.17; 95%CI –0.01 to 0.35), although both results were not statistically significant.[9] According to the package insert for tezepelumab, the safety and pharmacodynamic profile in pediatric patients is considered similar to the overall study population.[9]

8.3 Older Adults

In older adults, the effectiveness and safety of tezepelumab seems to be similar to younger individuals according to the PATHWAY and NAVIGATOR trials, which included a combined number of 119 patients ≥ 65 years of age.[9]

8.4 Considerations for Pregnancy/Lactation

The potential risk associated with the use of tezepelumab during pregnancy is unclear (ie, unknown risk of major birth defects or miscarriage).[9] Fetal risks may be higher during the 3rd trimester when placental transfer of monoclonal antibodies occurs to a greater degree.[9] Although placenta transfer of tezepelumab was observed during a study in pregnant cynomolgus monkeys, there were no fetal harms observed after intravenous administration of tezepelumab during pregnancy at a drug exposure dose "up to 168 times the exposure at the maximum recommended human dose (MRHD)".[9]

The risks and benefits of potential treatment-related harms compared to suboptimal asthma management must be weighed.[9] There are serious known risks to the mother and/or embryo/fetus that are associated with poorly or moderately controlled asthma such as "increased risk of preeclampsia and prematurity, low birth weight, and small for gestational age in the neonate".[9]

A lack of data exists on the presence of tezepelumab in human milk; however, it has been shown to be excreted into the milk of cynomolgus monkeys after receiving tezepelumab during pregnancy.[9] The maternal and/or fetal benefits of breastfeeding should be evaluated, along with the clinical necessity for tezepelumab and the associated potential side effects.[9]

8.5 Renal/Hepatic Impairment

No significant clearance differences were observed in mild or moderate renal impairment compared to those with adequate renal function, so renal dose adjustments are not recommended.[9] Tezepelumab has not been studied in severe renal impairment (estimated creatinine clearance < 30 mL/minute). Hepatic impairment is not expected to influence tezepelumab clearance because it is not metabolized by liver-specific enzymes, instead it is metabolized by proteolytic enzymes distributed throughout the body.[9]

9.0 SAFETY

Below is a summary of commonly reported adverse events (AEs), and warnings and precautions as reported in the prescribing information.

9.1 Adverse Events

A pooled population from PATHWAY and NAVIGATOR determined the safety profile of tezepelumab.[9] The most common AEs (with an incidence ≥ 3%) in these clinical trials were pharyngitis, arthralgia, and back pain. The incidence was 4% for each of these AEs in the treatment arm and 3% in the placebo arm.[9] Injection-site reactions (eg, erythema, swelling, pain) occurred more frequently in tezepelumab-treated patients than those receiving placebo (3.3% vs 2.7%, respectively).[9]

9.2 Immunogenicity

Similar to other biologic proteins, immunogenicity may develop during treatment with tezepelumab (ie, ADAs, as well as neutralizing antibodies).[9] Among clinical trials, ADAs were detected in 5% of the tezepelumab-treated patients at any time during the 48 to 52-week study duration.[9] Of the 5% that produced ADAs, 2% produced treatment-emergent antibodies and <1% produced neutralizing antibodies.[9]

9.3 Warnings and Precautions

Product labeling for tezepelumab includes the following warnings and precautions:

- **Contraindication:** Hypersensitivity to active substance or any product components.[9]
- **Hypersensitivity reactions:** Hypersensitivity reactions (eg, rash, allergic conjunctivitis) may occur within hours or days after administration of tezepelumab.[9] Risks and benefits should be evaluated to determine discontinuing or continuing treatment in the event of a hypersensitivity reaction.[9]
- **Abrupt reduction in corticosteroid dosage is not advised:** When systemic or inhaled corticosteroid dose reduction is medically indicated, corticosteroids should be gradually reduced to prevent withdrawal symptoms and/or manifestation of symptoms from conditions formerly suppressed by corticosteroid treatment.[9] Thus, corticosteroids should not be abruptly stopped when starting tezepelumab.[9]
- **Parasitic (Helminth) infections:** Patients should be treated for pre-existing helminth infections prior to starting tezepelumab.[9] Tezepelumab should be discontinued until the infection is cleared in patients that developed a parasitic infection that is unresponsive to anti-parasitic therapy.[9]

- **Live attenuated vaccines:** The administration of live attenuated vaccines should be avoided during the use of tezepelumab.[9]
- **Limitation of use:** Tezepelumab is not indicated for the treatment of acute asthma/exacerbations, acute bronchospasm, or status asthmaticus.[9]

10.0 UTAH MEDICAID UTILIZATION DATA

Since tezepelumab was FDA-approved in December 2021, there are not yet any pharmacy or medical claims among the Utah Medicaid fee-for-service population up through March 2022.

11.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION CRITERIA

Utah Medicaid currently has prior authorization (PA) criteria in place for tezepelumab (Tezspire), and the other 5 add-on biologics (benralizumab, mepolizumab, reslizumab, dupilumab, and omalizumab). The PA criteria were last updated in February 2022. **Appendix F** includes the PA request form for these anti-asthmatic monoclonal antibodies. The approach listed below is generally consistent with the current PA form for asthma biologics, but additional details specific to tezepelumab are provided.

A. Considerations related to patient eligibility for tezepelumab:

Indication considerations:

1. Patients should be *12 years of age and older* based on the FDA-approved indication.
    a. The safety and effectiveness has not yet been determined for patients < 12 years of age.[9] Of the major clinical trials for approval of tezepelumab, only NAVIGATOR enrolled adolescents (12–17 years of age).[34]
2. Patients should have a diagnosis of *severe asthma,* consistent with the FDA-approved indication.
    a. Criteria for patient inclusion in the pivotal tezepelumab trials differ slightly from clinical guideline definitions of severe asthma.
        i. The key tezepelumab trials (NAVIGATOR and PATHWAY) did not require all patients to be on high-dose ICS at baseline. Instead, the trials required patients to meet both of the following criteria (1 and 2):
            1. Receiving *medium*- to high-dose ICS in combination with either of the following:
                a. A LABA (PATHWAY)
                b. 1+ other controller medication(s) (NAVIGATOR)
            2. Asthma was "uncontrolled", defined as either of the following in the prior 12 months:
                a. 1+ severe asthma exacerbation(s) (PATHWAY)
                b. 2+ exacerbations of any severity (PATHWAY and NAVIGATOR)
        ii. Guidelines have various definitions for severe asthma:
            1. 2021 GINA guideline defines it as any of the following:
                a. Uncontrolled asthma despite "adherence with optimized high-dose ICS-LABA therapy"[8]
                b. Requiring *high* ICS-LABA treatment to maintain symptom control, despite optimization of modifiable factors (eg, inhaler technique, comorbidities, smoking)[6,8]

c. Intensifying symptoms after a reduction from high-dose therapy[6,8]

2. ERS/ATS (2020) defines it as requiring (for control of symptoms) high-dose ICS *and* a second controller medication (and/or systemic corticosteroids)[15]

3. Based on the FDA-approved indication, tezepelumab should be administered as add-on maintenance treatment.[9]

Treatment failure considerations:

1. Patients should be candidates for add-on biologic therapy based on failure to achieve adequate disease control after treatment for an adequate duration with a preferred first-line therapy for severe asthma per an accepted asthma practice guideline, or when such treatments cannot be tolerated after a trial.
    a. For severe asthma, GINA (2021) recommends add-on targeted biologic therapies, based on availability and cost, for patients experiencing exacerbations or uncontrolled symptoms despite *high-dose ICS-LABA use* for patients with allergic or eosinophilic biomarkers, or that require maintenance OCS therapy.[8] This guideline does not yet address tezepelumab use.
    b. NHLBI/NAEPP (2020) recommends that patients with severe asthma receive at least *medium-dose* ICS-formoterol prior to considering an add-on biologic.[26] For patients ages 12 or older, biologics may be considered at step 5 of therapy; the preferred controller therapy at this step is *medium*- or high-dose ICS-LABA with a LAMA.[26] This guideline does not yet address tezepelumab use.
    c. Pivotal tezepelumab trials (NAVIGATOR and PATHWAY) included patients taking a *medium*- or high-dose ICS in combination with a LABA or at least one additional controller agent (eg, LTRA, theophylline, OCS).[10,34]

Concomitant treatment considerations:

1. There is a lack of information regarding the safety and therapeutic utility of tezepelumab in combination with other biologic therapy for the treatment of severe asthma.[43,44]
2. ICER 2018 conclusions/recommendations regarding other biologic therapies for asthma:
    a. ICER (2018) advised that "payers should not deny ongoing coverage of biologic therapy if patients are able to reduce the intensity of their ICS or other long-acting controller medications during treatment with the biologic."[45]

B. Considerations related to provider eligibility to prescribe:

1. Tezepelumab should be prescribed either by a provider specialized in treating severe asthma (eg, pulmonologist, immunologist) or by a provider consulting with a specialist.
    a. GINA (2021) recommends that patients with a confirmed diagnosis of severe asthma be *referred to a specialist or an asthma clinic, if feasible*.[8]

C. Considerations related to mechanism for distribution:

1. Tezepelumab should be administered by a healthcare provider in a health care setting.[9]

D. Re-authorization criteria for tezepelumab:

The DUR board may consider the following guideline recommendations if a re-authorization for tezepelumab is required:

1. Reauthorization for continuation could be required (eg, after 4 months of the initial authorization) for continuation. The provider should attest that the patient has had either a **response OR unclear** response. For patients with an initial unclear response, the provider should attest by 1 year of treatment that the patient has had a response. If the patient has had **no response** (or unclear response) after 4 months of initial treatment, then they should be switched to a different biologic, if appropriate.
    a. The 2021 GINA guideline recommends a trial of at least 4 months for the other add-on biologic agents for the treatment of asthma (benralizumab, mepolizumab, reslizumab, dupilumab, and omalizumab).[8] EAACI (2020) recommends a review of treatment response after 4 to 6 months due to the high price of biologics.[2] Although both guidelines note the absence of well-established criteria for a favorable response,[2,8] the following broad criteria may be considered to evaluate a patient's response to biologic therapy:[8]
        i. Occurrence and severity of exacerbations during the trial period
        ii. Asthma control
        iii. Pulmonary function
        iv. Adverse effects
        v. Treatment severity, including OCS dose, if applicable
        vi. Patient quality of life
    b. A trial extension of 6 to 12 months may be considered in patients with an **unclear response** according to the GINA recommendations.[8] If **no response** has been achieved (rather than a response or uncertain response) after the initial trial period of 4 months, a consideration of switching to a different biologic therapy should be evaluated, if the patient is eligible.[8]
2. GINA (2021) recommends the patient's response to a biologic treatment should be reviewed after 3–4 months, and every 3–6 months thereafter.[8]

E. Considerations with respect to the current PA criteria

1. Documentation of allergen testing and particular thresholds for baseline eosinophil concentrations is not applicable for tezepelumab
    a. Clinical trials for tezepelumab did not require patients to meet certain biological marker thresholds for enrollment.[10,34,40] Moreover, in PATHWAY and NAVIGATOR, tezepelumab demonstrated therapeutic benefit in exacerbation reductions compared to placebo in asthma patients regardless of baseline eosinophil and allergic status.[10,34]
2. As of April 2022, reslizumab (Cinqair), dupilumab (Dupixent), benralizumab (Fasenra), and omalizumab (Xolair) are preferred agents on the Utah Medicaid Preferred Drug List (PDL); whereas mepolizumab (Nucala) and tezepelumab (Tezspire) are non-preferred. As a PDL-non-preferred product, according to the current PA, tezepelumab would be accessible after a 3-month trial and failure of one of the preferred biologics for asthma, or based on medical necessity. Since the indications for all the PDL preferred biologics do not include patients who have a non-type 2 severe asthma phenotype (eg, non-eosinophilic and non-allergic) and are non-OCS dependent, tezepelumab could be considered for this subpopulation without requiring

failure of a PDL-preferred biologic since its indication does not require meeting a type 2-related biologic marker threshold.

a. According to the 2021 ICER report, tezepelumab is the only biologic to have demonstrated efficacy for patients with non-OCS dependent asthma that is neither eosinophilic or allergic asthma.[3] Other biologics approved for the treatment of asthma have only demonstrated efficacy in either eosinophilic or allergic asthma, or among those who are OCS dependent.[24,28-31,40] Refer to **Table 4** on page 13 for the indications of each biologic.

12.0 SUMMARY

Asthma is a complex, heterogeneous respiratory disease usually associated with chronic inflammation.[1-4] Disease severity varies from mild to severe depending on the frequency of respiratory symptoms and exacerbations.[5] Although severe asthma constitutes fewer than 5–10% of all asthma diagnoses, it represents a disproportionate fraction of healthcare expenditures among asthma patients, and is attributed to a reduced quality of life (QoL).[2,3,6,7] There are two different categories of severe asthma inflammatory phenotypes; non-type 2 (eg, non-eosinophilic) and type 2 (eg, eosinophilic, allergic).[6] An estimated 50–70% of asthmatics have the type 2 inflammatory phenotype, with higher percentages expected in patients with severe asthma.[3,20-22]

Tezepelumab (Tezspire) is a first-in-class biological agent that prevents thymic stromal lymphopoietin (TSLP) binding to its receptor,[9] impacting numerous cell types (eg, eosinophils) and mediators (eg, ILs) that contribute to chronic airway inflammation.[3,12,13] Unlike other biologic agents for asthma, tezepelumab targets TSLP which is a mediator at the outset of the inflammatory pathway, thereby affecting downstream proinflammatory pathogenic mechanisms of asthma.[4,9] TSLP is also involved in other non-type 2 processes associated with asthma such as promoting neutrophil-mediated airway inflammation, or stimulating changes in structural cells of the airway.[4,25] Tezepelumab was approved by the U.S. Food and Drug Administration (FDA) in December 2021 as add-on maintenance treatment of **severe** asthma in patients 12 years of age and older, regardless of the presence of biomarkers (eg, eosinophils or allergic positivity).[9] It must be administered by a healthcare provider in a health care setting, and is provided as a subcutaneous (subQ) injection every 4 weeks.[9]

There are 5 other add-on biologic treatments approved for severe asthma (*moderate* to severe asthma for dupilumab and omalizumab) with type 2 inflammatory markers: benralizumab (Fasenra), mepolizumab (Nucala), reslizumab (Cinqair), dupilumab (Dupixent), and omalizumab (Xolair).[1,2] Dupilumab can also be used for moderate to severe asthma dependent on OCS, regardless of the presence of biologic markers (eg, eosinophils).[29] These agents target proinflammatory cytokines and mediators (eg, IL-4, IL-5, IgE) downstream of TSLP.[1,2] Some biologics are approved for a younger age range than tezepelumab (6 years of age and older for dupilumab, mepolizumab, omalizumab).[9,24,29,30] Benralizumab is approved for the same age range as tezepelumab, whereas reslizumab is approved only for adults.[9,28,31]

Monoclonal antibodies are typically reserved for patients with difficult-to-treat or severe asthma.[5,8] The Global Initiative for Asthma (GINA) (2021) recommends add-on targeted biologic therapies should be considered, based on availability and cost, for patients experiencing exacerbations or uncontrolled symptoms despite high-dose ICS-LABA use, and who have allergic or eosinophilic biomarkers or require

maintenance OCS therapy.[8] **Treatment guidelines do not yet incorporate tezepelumab**.[9,12] GINA (2021) states that biologic treatment selection is based on phenotypes (eg, eosinophilic), and other factors such as predictors of asthma response (eg, blood eosinophil levels, age of onset, FeNO levels), insurance coverage, affordability, other type 2 related comorbidities (eg, atopic dermatitis, nasal polyps), dosing frequency, administration route (subQ or IV), and patient preference.[1,8]

Three pivotal clinical trials (PATHWAY, NAVIGATOR, and SOURCE) evaluated tezepelumab as add-on biologic treatment for severe asthma. The phase 2 dose-finding trial, PATHWAY suggested positive efficacy and safety of tezepelumab for reducing asthma exacerbation rates when used at 210 mg subQ every 4 weeks.[10] This dose was carried forward to the two pivotal phase 3 randomized controlled trials NAVIGATOR and SOURCE, in which tezepelumab was compared to placebo among patients with severe asthma.[34-36] In both trials, tezepelumab tended to reduce the annualized rate of asthma exacerbations (AAER) over the treatment duration (the primary endpoint of NAVIGATOR and a secondary endpoint of SOURCE) among the overall study population compared to placebo, although statistical significance differed between trials.[34,36] In SOURCE, tezepelumab failed to significantly reduce the daily maintenance oral corticosteroid (OCS) dose versus placebo (the primary endpoint of this study) among OCS-dependent severe asthma patients.[36] In NAVIGATOR and PATHWAY, the benefit on exacerbation rate favoring tezepelumab was consistently observed regardless of baseline eosinophil concentration or allergic status.[10,34] Regarding secondary outcomes, compared to placebo, tezepelumab improved pulmonary function and patient-reported outcomes related to asthma control/symptoms and QoL in NAVIGATOR and PATHWAY.[10,34] Tezepelumab appeared well-tolerated compared to placebo across the 3 studies; treatment-emergent common AEs were pharyngitis, arthralgia, and back pain.[9]

Based on the body of reviewed evidence, including tezepelumab prescribing information, asthma treatment guidelines, and pivotal tezepelumab clinical trials (NAVIGATOR, PATHWAY, and SOURCE), we developed considerations for tezepelumab PA criteria. These criteria include recommendations related to patient eligibility definitions on the basis of meeting the FDA-approved indication (ie, patients with severe asthma, aged 12 years and older), concomitant treatments, and failed first-line requirements for add-on biologic therapy. Additional considerations are made for provider eligibility, tezepelumab distribution, and re-authorization. Regarding the Utah Medicaid PA criteria already in place for anti-asthmatic monoclonal antibodies, we list special considerations for tezepelumab. This includes recommending that despite currently being a non-preferred therapy on the Utah PDL, tezepelumab should be accessible to patients with non-OCS dependent, non-eosinophilic, and non-allergic severe asthma without the requirement of failing a PDL-preferred add-on biologic.

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APPENDIX A - LITERATURE SEARCHES

Embase was searched on March 11, 2022 for information about tezepelumab (**134 results**):
tezepelumab:ti,ab,kw OR tezspire:ti,ab,kw OR medi9929:ti,ab,kw OR amg157:ti,ab,kw

Table 8. Ovid Medline Literature Search Strategy for Systematic Reviews

Database: Ovid MEDLINE ® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to March 14, 2022>
Search strategy (date of search: March 15, 2022)

#	Searches	Results
1	(tezepelumab or Tezspire).ti,ab,kw,kf.	72
2	(MEDI9929 or AMG 157 or AMG157).ti,ab,kw,kf.	8
3	(("thymic stromal lymphopoietin" adj2 (blocker* or antagonist* or inhibitor*)) or (TSLP adj2 (blocker* or antagonist* or inhibitor*))).ti,ab,kw,kf.	26
4	exp Asthma/ or asthma*.ti,ab,kw,kf	191629
5	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. or (Medline or Embase or Pubmed or search).tw. or (systematic-review or meta-analysis).tw,pt.	716972
6	1 or 2 or 3	99
7	4 and 5 and 6	**6**

Table 9. Ovid Medline Literature Search Strategy for Randomized Controlled Trials

Database: Ovid MEDLINE ® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to March 14, 2022>
Search strategy (date of search: March 15, 2022)

#	Searches	Results
1	(tezepelumab or Tezspire).ti,ab,kw,kf.	72
2	(MEDI9929 or AMG 157 or AMG157).ti,ab,kw,kf.	8
3	(("thymic stromal lymphopoietin" adj2 (blocker* or antagonist* or inhibitor*)) or (TSLP adj2 (blocker* or antagonist* or inhibitor*))).ti,ab,kw,kf.	26
4	exp Asthma/ or asthma*.ti,ab,kw,kf	191629
5	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1317732
6	1 or 2 or 3	99
7	4 and 5 and 6	**29**

APPENDIX B – CLINICAL GUIDELINES

Guidelines used for the preparation of this report:

- 2021 **Global Initiative for Asthma (GINA)** Global Strategy for Asthma Management and Prevention[5,8]; and the 2021 pocket guide for severe and difficult-to-treat asthma[6]
- 2021 updated **National Institute for Health and Care Excellence (NICE)** guideline on the diagnosis, monitoring and chronic asthma management[46]
- 2020 **European Respiratory Society/ American Thoracic Society (ERS/ATS)** guideline for the management of severe asthma[15]
- 2020 **European Academy of Allergy and Clinical Immunology (EAACI)** guideline for the use of biologics in severe asthma[2]
- 2020 Focused Updates to the Asthma Management Guidelines: A Report from the **National Asthma Education and Prevention Program (NAEPP)** Coordinating Committee Expert Panel Working Group[26]
- 2020 **NICE** guideline on the management of severe asthma during COVID-19[47]
- 2017 **Canadian Thoracic Society (CTS)** position statement for the management of severe asthma[7]

APPENDIX C – SUPPLEMENTARY TABLES

Table 10. Daily Doses of Inhaled Corticosteroids per the 2021 GINA Guideline[8]

	Low Dose (µg/day)	Medium Dose (µg/day)	High Dose (µg/day)
Adults and Adolescents (≥12 years of age)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	200–500	>500–1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	100	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device– refer to product information		
Mometasone furoate (pMDI, standard particle, HFA)	200–400	200–400	>400
Children (6 to 11 years of age)			
Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle, HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	50	50	NA
Fluticasone propionate (DPI)	50–100	>100–200	>200
Fluticasone propionate (pMDI, standard particle, HFA)	50–100	>100–200	>200
Mometasone furoate (pMDI, standard particle, HFA)	100	100	200

Abbreviations: DPI, dry powder inhaler; HFA, hydrofluoroalkane propellant; NA, not applicable; pMDI, pressurized metered dose inhaler

Table 11. Global Initiative for Asthma (GINA) Stepwise Treatment Approach for Initial Asthma Management in Patients 6 to 11 years of age[8]

GINA Steps	Reliever	Symptom Duration	Preferred Controller	*Other Controller Choices*
Step 1	PRN SABA or low dose ICS-formoterol as MART	Symptoms occur < 2 times per month	Administer low dose ICS when SABA is used	*Low dose ICS every day*
Step 2		Symptoms occur ≥ 2 times per month, but fewer than every day	Low dose ICS every day	*Low dose ICS when SABA is used or LTRA every day*
Step 3		Symptoms occur majority of the time, **or** awakening with asthma ≥ 1 per week	Low-dose ICS-LABA, **or** medium-dose ICS **or** very low-dose[a] ICS-formoterol (MART)	*Low dose ICS plus LTRA*
Step 4		Symptoms occur majority of the time, **or** awakening with asthma ≥ 1 time per week, **and** low pulmonary function[b]	Medium-dose ICS-LABA, **or** low dose[c] ICS-formoterol (MART)	*Tiotropium or LTRA*
Step 5		No symptom duration is specified	Consult for phenotypic evaluation with or without higher dose ICS-LABA **or** consider add-on biologic therapy (eg, anti-IgE, anti-IL-5/5R, anti-IL4R)	*Anti-IL 5 treatment **or** low dose OCS, but adverse effects should be considered*

Abbreviations: anti-IgE, anti-immunoglobulin E; anti-IL5; anti-interleukin 5 treatment; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; ICS-LABA, fixed-dose combination of inhaled corticosteroids and long active beta$_2$ agonists; LTRA, leukotriene receptor antagonists; MART, maintenance and reliever therapy with ICS-formoterol; OCS, oral corticosteroid; PRN, as-needed; SABA, short-acting beta$_2$ agonists

[a] *Very low dose: budesonide-formoterol 100/6 mcg*

[b] *Patients presenting with highly uncontrolled asthma may additionally require a short-duration of OCS treatment*

[c] *Low dose: budesonide-formoterol 200/6 mcg (metered doses)*

APPENDIX D – SUPPLEMENTARY INFORMATION

Asthma Management During the COVID-19 Pandemic

The risk of developing Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infection (ie, coronavirus disease 2019 [COVID-19]), and the risk of COVID-19-related mortality does not seem to be increased for patients with asthma.[8] However, an increased mortality risk from COVID-19 has been observed among the subset of asthma patients that recently required oral corticosteroid (OCS) treatment.[8] Respiratory disease, including moderate to severe asthma, is a risk factor for increased COVID-19 infection severity.[48] Thus, it is vital for patients to maintain symptom control, minimize exacerbations, and prevent the need for OCS use.[8] All patients, including those with active or suspected COVID-19 infection, should continue taking their asthma treatment, including ICS monotherapy or in combination with a LABA, or biologic agents if prescribed for severe asthma to prevent worsening symptoms and reduce the risk of exacerbations.[8,47] According to the 2020 National Institute for Health and Care Excellence (NICE) COVID-19 guideline on severe asthma, there is no evidence that biologic agents for the treatment of asthma suppress the immune response to viruses.[47] Healthcare providers should consider the opportunity for self-administration at home or in-clinic administration of biologic therapies to minimize patient hospital visits.[47]

The 2021 GINA guideline recommends that patients with asthma should receive the COVID-19 vaccine, with consideration of routine precautions including verifying allergies to vaccine ingredients and evaluating the presence of fever or infection.[5,8] For patients on biologic therapies, the 2021 GINA guideline advises that administration of the biologic agent and the COVID-19 vaccine should be given on separate days to better determine associated adverse effects.[8]

Anti-IgE Treatment for Asthma (omalizumab)

Omalizumab is approved for the treatment of **moderate-to-severe allergic asthma** in patients ≥ 6 years of age.[30] According to the 2021 GINA guideline, add-on anti-IgE therapy (omalizumab) is recommended for patients (≥ 6 years of age) that are uncontrolled on Step 4–5 therapy with moderate or severe allergic asthma.[8] GINA (2021) mentions some potential predictors of a favorable asthma response to omalizumab include childhood-onset and history supporting allergen-driven symptoms.[8] Baseline IgE concentrations are not a predictor of asthma response.[8]

ERS/ATS (2020) recommends a blood eosinophil concentration of ≥ 260 cells/µL and FeNO ≥ 19.5 ppb to detect patients (≥ 12 years of age) with severe allergic asthma that are expected to have a better benefit to anti-IgE treatment (conditional recommendation, low quality evidence).[15] The authors state that these biomarker thresholds should be used cautiously to direct treatment since some patients may respond well to omalizumab and may have eosinophil or FeNO concentrations below the suggested thresholds.[15]

EAACI (2020) recommends add-on omalizumab for patients aged ≥ 6 years with moderate-to-severe allergic asthma unresponsive to “optimal controller treatment”.[2] The patient population was characterized as patients with “moderate-to-severe asthma, total IgE level of 30–700 IU/mL with or without one perennial aeroallergen”.[2]

A 2017 position paper by the Canadian Thoracic Society (CTS) suggests omalizumab for patients aged ≥ 6 years with severe asthma that is uncontrolled with a combination high-dose ICS plus at least one additional controller, and has a positive sensitivity test to at least one perennial allergen.[7] Patients 6 to 11 years of age should have a serum IgE concentration between 30–1300 IU/mL, or 30–700 IU/mL for those aged ≥ 12 years.[7] Additionally, omalizumab should be considered for pediatrics that experience worsening symptoms or more frequent exacerbations when decreasing from high-dose ICS therapy.[7]

Anti-IL 5 Treatments for Asthma (mepolizumab, benralizumab, and reslizumab)

The anti-IL 5/5R biologic agents includes mepolizumab, reslizumab (both are IL-5 antagonists) and benralizumab (IL-5 receptor antagonist) are approved for the treatment of **severe eosinophilic asthma**.[8] GINA (2021) recommends these as add-on agents for patients that are uncontrolled on Step 4–5 therapies.[8] GINA (2021) mentions potential strong predictors of a favorable asthma response include elevated blood eosinophils and frequent severe exacerbations in the past year; other predictors include adult-onset, nasal polyposis, low pulmonary function, or baseline maintenance OCS use.[8]

ERS/ATS (2020) recommends anti-IL5 therapies "as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma" (conditional recommendation, low quality evidence).[15] A recommendation regarding the use of anti-IL therapies is not provided for children or adolescents due to the limited number of patients within this age group receiving these therapies.[15] This guideline recommends a blood eosinophil threshold of ≥ 150 cells/µL to direct the initiation of anti-IL5 treatment in adults with severe asthma with previous exacerbations (Conditional recommendation, low evidence quality).[15]

EAACI (2020) recommends add-on benralizumab (aged ≥ 12 years), mepolizumab (aged ≥ 12 years), and reslizumab (aged ≥ 18 years) for severe eosinophilic asthma inadequately controlled on "optimal controller treatment".[2] The patient population definitions and blood eosinophil thresholds differ depending on the anti-IL5 therapy:

- The patient population for *benralizumab* is "defined as patients with uncontrolled asthma on high-dose ICS-LABA and who have blood eosinophil levels of > 300 cells/µL or > 150 cells/µL (for OCS-dependent patients)".[1,2]
- The patient population for *mepolizumab* is defined as patients with eosinophilic inflammation characterized by a blood eosinophil concentration ≥ 300 cells/µL in the past year or ≥ 150 cells/µL at treatment initiation. Mepolizumab is expected to have a better response on exacerbations in patients with higher concentrations of blood eosinophils.[2]
- The patient population for *reslizumab* is "defined as having at least one blood eosinophil count of 400 cells/µL or higher during a 2–4 weeks screening period and inadequately controlled asthma, receiving at least a medium-dose of ICS with or without another controller drug including OCS."[1,2] Reslizumab is expected to have a better response on pulmonary function and asthma control in patients with higher concentrations of blood eosinophils.[2]

The 2017 CTS position paper recommends anti-IL5 biologics for adults (≥ 18 years of age) with severe eosinophilic asthma that is uncontrolled on a high-dose ICS and at least an additional controller.[7] Moreover, these agents may be used for severe eosinophilic corticosteroid-dependent asthma to reduce or withdraw OCS therapy.[7] At the time of publication, there was limited evidence available to determine

the safety and efficacy of anti-IL5 therapies in the pediatric population.[7] The most robust responders to anti-IL5 biologics have elevated blood eosinophil levels; thus, CTS recommends using blood eosinophil thresholds of > 150 cells/µL at treatment initiation or in the previous year ≥ 300 cells/µL for mepolizumab and benralizumab, and ≥ 400 cells/µL for reslizumab to identify the best candidates for these therapies.[7]

Anti-IL 4 Receptor Treatment for Asthma (dupilumab)

Dupilumab is approved for **moderate-to-severe asthma with an eosinophilic phenotype or oral corticosteroid dependent asthma** in patients ≥ 6 years of age is dupilumab.[29] In October 2021, the FDA expanded the approval age of dupilumab in patients with moderate-to-severe asthma to children 6–11 years of age based on a phase 3 RCT (LIBERTY ASTHMA VOYAGE)[49] demonstrating a reduction in severe asthma exacerbations, improved pulmonary function, and better asthma control within this patient population.[50]

Several guidelines include dupilumab as an option for moderate to severe asthma, though these guidelines were published prior to the label extension for dupilumab so they may not include consideration of the most recent supportive information:

- GINA (2021 guideline) recommends add-on anti-IL 4 receptor treatment for patients (≥ 12 years of age) with "severe type 2 asthma, or requiring treatment with maintenance OCS".[8]
- Irrespective of eosinophil concentrations, ERS/ATS (2020) recommends add-on dupilumab for adults with severe eosinophilic asthma or severe corticosteroid-dependent asthma (conditional recommendation, low quality evidence).[15]
- Add-on dupilumab is recommended by EAACI (2020) for patients aged ≥ 12 years with severe eosinophilic asthma or severe allergic (T2) asthma (off-label use) unresponsive to "optimal controller treatment".[2] The patient population was characterized as patients with "severe asthma uncontrolled by medium- or high-dose ICS plus up to 2 additional controllers, including OCS".[2] T2 inflammation was indicated by increased blood eosinophils (> 150 cells/µL) and/or increased FeNO > 20 ppb.[2]
- Several guidelines mention positive predictors to dupilumab include higher concentrations of blood eosinophils (eg, > 150 cells/µL), and elevated FeNO (eg, >25 ppb).[8]

APPENDIX E – INCLUSION AND EXCLUSION CRITERIA IN PIVOTAL TEZEPELUMAB CLINICAL TRIALS

Table 12. Inclusion and Exclusion Criteria from Pivotal Clinical Trials for Tezepelumab

Phase 2 or 3 Trial Study identification number, Trial name, RCT design	**Inclusion Criteria**[a]	**Exclusion Criteria**[a]
SOURCE[35,36] (NCT03406078) *(currently, results are unpublished in medical journals)* A study to evaluate the efficacy and safety of tezepelumab in reducing OCS use in adults with OCS dependent asthma Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial	• **Age 18–80 years** • ≥ 40 kg • History of asthma requiring medium- or high-dose ICS (per GINA guideline) for ≥ 1 year prior to first visit. • Those taking a medium-dose ICS were required to have the dose escalated to a high-dose for ≥ 3 months prior to screening. • **A LABA and high-dose ICS** (> 500 µg fluticasone propionate dry powder formulation equivalents total daily dosage) prescribed by a physician for ≥ 3 months prior to first visit • **Allowance of other maintenance controller agents** per standard-of-care (eg, LAMA, LTRA, theophylline) if recorded for ≥ 3 months prior to first visit • Received OCS therapy for ≥ 6 months before screening and on a stable dose of 7.5 to 30 mg (prednisone or prednisolone equivalent) daily or daily equivalent for ≥ 1 month prior to first visit • Morning prebronchodilator FEV_1 < 80% predicted normal (at 1st or 2nd visit) • History of FEV_1 bronchodilator reversibility of ≥ 12% and ≥ 200 mL recorded within 1 year prior to the first visit, or at either the first or second visit • **≥ 1 documented asthma exacerbation** ≤ 1 year prior to the first visit • Prior to randomization, received the lowest effective OCS dose to control symptoms ≥ 2 weeks	• Any lung disease, other than asthma that would contribute to increased peripheral eosinophil levels • Any disease that may impact the safety of the patient or study results, based on investigator judgment • Any infection that needed antibiotic or antiviral therapy in the 2 weeks prior to the first visit or during enrollment • Untreated or refractory parasitic infection in the prior 6 months before the first visit • Previous cancer, HIV, or hepatitis B or C • Active smokers or previous smokers with a history of ≥ 10 pack-years • Use of immunosuppressive medication other than OCS in the 12 weeks prior to randomization • Use of any biologic medication, including experimental within 4 months (or 5 half-lives) prior to the first visit, or any experimental non-biologic medication within 30 days (or 5 half-lives) prior to the first visit • Previous anaphylactic reaction to any biologic agent • Pregnant, breastfeeding, or lactating
NAVIGATOR[13,34] (NCT03347279)	• **Age 12–80 years** • ≥ 40 kg	• Any lung disease other than asthma

Table 12. Inclusion and Exclusion Criteria from Pivotal Clinical Trials for Tezepelumab

Phase 2 or 3 Trial Study identification number, Trial name, RCT design	**Inclusion Criteria**[a]	**Exclusion Criteria**[a]
Tezepelumab in adults and adolescents with severe, uncontrolled asthma Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	• Confirmed diagnosis of asthma for ≥ 1 year by a healthcare provider prior to screening • History of asthma requiring medium- or high-dose ICS (per GINA guideline) for ≥ 1 year prior to first visit • Receiving a **medium- or high-dose ICS controller agent** (> 500 µg fluticasone propionate dry powder formulation equivalents total daily dosage) for ≥ 1 year prior to screening • **≥ 1 additional maintenance controller agent** per standard-of-care (eg, LABA, LTRA, theophylline), with or without oral glucocorticoid therapy for ≥ 3 months prior to informed consent • During the run-in phase, the morning prebronchodilator FEV_1 must be < 80% predicted normal (<90% for those aged 12–17 years) • During the run-in phase or prior to screening, the postbronchodilator FEV_1 reversibility of ≥12% and ≥ 200 mL must have been recorded **OR** a history of FEV_1 reversibility of ≥12% and ≥200 mL within the 1 year before the first visit • **≥ 2 documented asthma exacerbations** that resulted in hospitalization, or required the use of systemic corticosteroids for ≥ 3 consecutive days with or without an ED visit within 1 year prior to the date of informed consent • ACQ-6 score of ≥ 1.5 at screening and at randomization (questionnaire used to evaluate symptom control on a scale of 0–6)	• Any infection that needed antibiotic or antiviral therapy in the 2 weeks prior to the first visit or during the run-in phase • Untreated or refractory parasitic infection in the prior 6 months before the first visit • Previous cancer, HIV, or hepatitis B or C • Active smokers, including those using vaping devices (eg, electronic cigarettes) or patients with a history of ≥ 10 pack-years • Use of immunosuppressive medication (eg, methotrexate, cyclosporine) in the 12 weeks prior to randomization, except the use of OCS for asthma treatment • Use of any biologic medication, including experimental within 4 months (or 5 half-lives) prior to the first visit, or any experimental non-biologic medication within 30 days (or 5 half-lives) prior to the first visit • Immunoglobulin or blood products within 30 days before the first visit • Live attenuated vaccines within 30 days before randomization and during the study duration, including the follow-up period • Previous anaphylactic reaction to any biologic agent • Pregnant, breastfeeding, or lactating
PATHWAY[10] (NCT02054130) Tezepelumab in adults with uncontrolled asthma	• **Age 18–75 years** • ≥ 40 kg • Confirmed diagnosis of asthma for ≥ 1 year by a healthcare provider before the first visit • Receiving a stable dose (≥ 15 days before the first visit) of **medium-dose ICS** (250–500 µg fluticasone propionate dry	• Any lung disease other than asthma, but excluded those with occupational asthma • Any concomitant respiratory disease that may impact the safety of the patient or study results, based on investigator judgment • Acute respiratory infections (upper or lower) that needed antibiotic or antiviral therapy during the 15 days

Table 12. Inclusion and Exclusion Criteria from Pivotal Clinical Trials for Tezepelumab

Phase 2 or 3 Trial Study identification number, Trial name, RCT design	**Inclusion Criteria**[a]	**Exclusion Criteria**[a]
Phase 2, multicenter, randomized, double-blind, placebo-controlled trial	powder formulation or 220–440 µg fluticasone MDI equivalents total daily dosage) **OR high-dose ICS** (> 500 µg fluticasone propionate dry powder formulation or > 440 µg fluticasone MDI equivalents total daily dosage) **+ LABA** for ≥ 6 months before the first visit • **Allowance of other maintenance controller agents** per standard-of-care (eg, LAMA, LTRA, theophylline, maintenance OCS) are required to be stable ≥15 days before the first visit • Two separate documentations of a morning prebronchodilator FEV_1 of ≥ 40% but ≤ 80% of normal predicted value at either the first or second visit, and the third visit • **≥ 2 documented asthma exacerbations OR ≥ 1 severe exacerbation that required hospitalization within 1 year before the first visit.** An exacerbation was defined as an event requiring the use of systemic corticosteroids for ≥ 3 consecutive days with or without an ED visit or hospitalization • During screening, a postbronchodilator FEV_1 reversibility of ≥12% and ≥ 200 mL must have been recorded **OR** a history of FEV_1 reversibility of ≥12% and ≥200 mL during the past year • Two separate documentations of an ACQ-6 score of ≥ 1.5 during the screening period (questionnaire used to evaluate symptom control on a scale of 0–6)	before the first visit, during the screening/ run-in phase, or at the fourth visit • Presence of a "clinically significant infection" or any infection that needed antibiotic or antiviral therapy at the fourth visit • Untreated or refractory parasitic infection in the prior 24 weeks before the first visit • Previous cancer, HIV, or hepatitis B or C • Active smokers or those with a history of ≥ 10 pack-years • Use of immunosuppressive medication (eg, methotrexate, cyclosporine) during the 3 months before the first visit, except the use of OCS for asthma treatment • Use of any biologic medication, including experimental within 4 months (or 5 half-lives) before the first visit • Use of any experimental non-biologic medication within 30 days (or 5 half-lives) before the first visit • Immunoglobulin or blood products within 30 days before the first visit • Live attenuated vaccines during the 15 days preceding the first visit • Previous anaphylactic reaction to any biologic agent • Pregnant, breastfeeding, or lactating

Abbreviations: ACQ-6, Asthma Control Questionnaire, six-question version; ED, emergency department; FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$ agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; RCT, randomized controlled trial; SABA, short-acting beta$_2$ agonist

[a] *See study publication and supplementary information, if available for a complete list of inclusion and exclusion criteria*

APPENDIX F – EXISTING PRIOR AUTHORIZATION REQUEST FORM

Antiasthmatic Monoclonal Antibodies
(CinQair, Dupixent, Fasenra, Nucala, Tezspire, Xolair)

Member and Medication Information (required)	
Member ID:	Member Name:
DOB:	Weight:
Medication Name/ Strength:	Dose:
Directions for use:	

Provider Information (required)		
Name:	NPI:	Specialty:
Contact Person:	Office Phone:	Office Fax:

FAX FORM AND RELEVANT DOCUMENTATION INCLUDING:
LABORATORY RESULTS,
CHART NOTES and/or UPDATED LETTER OF MEDICAL NECESSITY
TO 855-828-4992

Criteria for Approval (all criteria must be met and documented in submitted chart notes):

- ❑ Medication is prescribed by or in consultation with a physician who specializes in the disease treatment.
- ❑ Documentation of FDA approved diagnosis: _____Chart Note Page #: _____
  - Allergen testing, if applicable. Chart Note Page #: __
  - Other confirmation testing, if applicable. Chart Note Page #: __
- ❑ Use must follow FDA-approved labeling *(including monitoring for boxed warnings and contraindications).*
  - Applicable monitoring for boxed warnings. Chart Note Page #: _____
- ❑ Documentation of appropriate first line treatments or interventions, if current treatment standards recommend other treatment modalities or interventions prior to use of the requested drug. Chart Note Page #: _____

Non-Preferred Product: *(Criteria above must also be met)*

- ❑ Minimum 3-month trial and failure of at least one preferred product in this therapeutic class, or prescriber must demonstrate medical necessity for non-preferred product.
  Medication(s): _____Chart Note Page #: _____ Dates of therapy: _____Details of Failure: _____

Off Label or Compendia Use of FDA-Approved Drugs Additional Criterion:
Requests for any off-label indications must be supported by at least one (1) major multi-site study or three (3) smaller studies published in JAMA, NEJM, Lancet or other peer review specialty medical journals within the most recent five (5) years. Supporting documentation must be included. Compendia use must be recommended by generally-accepted compendia such as American Hospital Formulary Service Drug Information (AHFS), United States Pharmacopeia-Drug Information (USP-DI), and the DRUGDEX Information System.
Diagnosis: _____Duration of treatment: _____

Re-authorization Criteria: *Please submit pre-treatment and current information*
Updated letter with medical justification or updated chart notes demonstrating positive clinical response.

Initial Authorization: Up to six (6) months
Re-authorization: Up to one (1) year

Notes:

- Use appropriate HCPCS code for billing
  Coverage and Reimbursement code look up:
  https://health.utah.gov/stplan/lookup/CoverageLookup.php HCPCS NDC Crosswalk:
  https://health.utah.gov/stplan/lookup/FeeScheduleDownload.php
- Patient must have regular appointments to receive or follow up on the medication in the prescriber's office. The patient must remain in the office for an adequate amount of time to allow for observation and treatment of anaphylaxis, if necessary. If/when any change of dose is requested, the prescriber must indicate, in writing, the reasoning for the dose increase.

PROVIDER CERTIFICATION

I hereby certify this treatment is indicated, necessary and meets the guidelines for use.

_____ _____

Prescriber's Signature Date

Last Updated 2/1/2022