Tezepelumab for Severe Asthma

Draft Evidence Report

September 16, 2021

Prepared for

AUTHORS:

ICER Staff and Consultants	Modeling Team
David M. Rind, MD, MSc Chief Medical Officer ICER **Jon Campbell, PhD, MS** Senior Vice President for Health Economics ICER **Belén Herce-Hagiwara, BA** Research Assistant ICER **Serina Herron-Smith, BA** Senior Research Assistant, Evidence Synthesis ICER **Noemi Fluetsch, MPH** Research Assistant, Health Economics and Outcomes Research ICER **Steven D. Pearson, MD, MSc** President ICER	**R. Brett McQueen, PhD** Assistant Professor, University of Colorado Anschutz Medical Campus **Eric Gutierrez, MPH** Statistical Analyst, University of Colorado Anschutz Medical Campus *The University of Colorado was responsible for the development of the cost-effectiveness model, interpretation of results, and drafting of the economic sections of this report; the resulting ICER reports do not necessarily represent the views of the University of Colorado.*

DATE OF PUBLICATION: September 16, 2021

How to cite this document: Rind DM, McQueen RB, Herron-Smith S, Herce-Hagiwara B, Gutierrez E, Campbell J, Fluetsch N, Pearson SD. Tezepelumab for Severe Asthma; Draft Evidence Report. Institute for Clinical and Economic Review, September 16, 2021. https://icer.org/wp-content/uploads/2021/05/ICER_Severe-Asthma_Draft-Evidence-Report_091621.pdf

David Rind served as the lead author for the report and wrote the background, comparative clinical effectiveness, other benefits, and contextual considerations sections of the report. Serina Herron-Smith and Belén Herce-Hagiwara led the systematic review and contributed to the associated sections in the comparative clinical effectiveness chapter. Brett McQueen and Eric Gutierrez developed the cost-effectiveness model and authored the corresponding sections of the report. Noemi Fluetsch conducted the potential budget impact analysis. Jon Campbell provided methods guidance and model validation for the cost-effectiveness and budget impact modeling efforts. Steven Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Cat Koola, Ashton Moradi, and Monica Frederick for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/

The funding for this report comes from government grants and non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers, or life science companies. ICER receives approximately 29% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. Life science companies relevant to this review who participate in this program include: AstraZeneca, Genentech, Sanofi, and Regeneron. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

About Midwest CEPAC

The Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. Midwest CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The Midwest CEPAC is an independent committee of medical evidence experts from across the Midwest, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about Midwest CEPAC is available at https://icer.org/who-we-are/people/independent-appraisal-committees/midwest-comparative-effectiveness-public-advisory-council-m-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following experts provided input that helped guide the ICER team as we shaped our scope and report. It is possible that expert reviewers may not have had the opportunity to review all portions of this draft report. None of these individuals is responsible for the final contents of this report, nor should it be assumed that they support any part of it. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer.org/wp-content/uploads/2021/05/ICER_Severe-Asthma_Stakeholder_List_050621.pdf

Expert Reviewers

Kaharu Sumino, MD, MPH
Associate Professor of Medicine
Washington University School of Medicine
No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Michael E Wechsler, MD
Professor of Medicine, Director NJH Cohen Family Asthma Institute
National Jewish Health
Dr. Michael Wechsler has received consulting fees and honoraria from the following health care companies: AstraZeneca, Amgen, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron, and Sanofi.

Table of Contents

List of Acronyms and Abbreviations Used in this Report

AAER	**Annualized Asthma Exacerbation Rate**
ACQ	**Asthma Control Questionnaire**
AE	**Adverse Event**
AHRQ	**Agency for Healthcare Research and Quality**
AQLQ	**Asthma Quality of Life Questionnaire**
CDC	**Centers for Disease Control and Prevention**
CI	**Confidence Interval**
ED	**Emergency Department**
evLY	**Equal Value Life Year**
FEV_1	**Forced Expiratory volume in one second**
ICS	**Inhaled Corticosteroids**
LABA	**Long-Acting Beta Agonist**
MCID	**Minimal Clinically Important Differences**
OCS	**Oral Corticosteroids**
OR	**Odds Ratio**
SoC	**Standard of Care**
SLR	**Systematic Literature Review**
RCT	**Randomized Controlled Trial**
RR	**Rate Ratio**
TSLP	**Thymic Stromal Lymphopoietin**
QALY	**Quality Adjusted Life Year**

Executive Summary

The Centers for Disease Control and Prevention (CDC) estimates that 25 million Americans, including 5 million children, have asthma.[1] Asthma leads to approximately 1.6 million emergency room visits, 180,000 hospitalizations, and 3,500 deaths each year in the US.[1,2] The societal costs are estimated to be $82 billion, including $50 billion in direct medical costs, $29 billion from asthma-related mortality, and $3 billion from missed work and school.[2] In the US, asthma is more than twice as common among Black children as among White children (13.5% and 6.4%, respectively), and remains somewhat more common among Black adults.[1]

Patients with severe asthma represent fewer than 5-10% of all individuals with asthma.[3] Asthma has been divided into different phenotypes with some overlap. About half of individuals with mild-to-moderate asthma exhibit the type 2 phenotype, and the proportion is believed to be larger in severe asthma.[4] Allergic asthma and eosinophilic asthma are generally forms of type 2 asthma.[5] None of the five biologic therapies that ICER reviewed in 2018 appeared to be effective for patients who had neither allergic asthma nor eosinophilia.

Tezepelumab is a new monoclonal antibody that targets thymic stromal lymphopoietin (TSLP).[6] It is administered by subcutaneous injection every four weeks. In this report, we review the clinical effectiveness of tezepelumab for severe asthma and also compare it with agents indicated for certain subpopulations: 1) omalizumab for patients with allergic asthma; and 2) dupilumab for patients with eosinophilic asthma. We also compare the efficacy of tezepelumab and dupilumab in patients dependent on chronic oral corticosteroids.

Patients, patient groups, and clinicians have emphasized the need for treatments that allow patients to return to their usual activities of daily living. Symptom relief, asthma control, and quality of life matter much more to patients than a reduction in asthma exacerbations.

In two randomized trials in a broad population of patients with severe asthma, tezepelumab improved symptom scores compared with placebo, but these improvements (0.20 to 0.34) were smaller than the minimal clinically important differences (MCIDs) of 0.5 on these scales.[6,7] However, in both trials, tezepelumab substantially reduced annualized asthma exacerbation rate (AAER) compared with placebo (RR 0.29 to 0.44).[6,7]

For patients with eosinophilic asthma, improvements in symptom scores and reductions in AAER were similar to the results seen with dupilumab. For patients with allergic asthma, improvements in symptoms were similar to those seen in older trials of omalizumab while reductions in AAER were somewhat greater than with omalizumab. Patients with non-eosinophilic asthma treated with tezepelumab showed similar improvements in symptom scores to patients with eosinophilic asthma in one of the two randomized trials, and only minimal improvement in the other trial. In one of the

two randomized trials, patients with non-eosinophilic asthma had larger reductions in AAER than those with eosinophilic asthma, while in the other randomized trial, reductions in AAER were smaller in such patients, but still appeared to be clinically meaningful.

In a separate randomized trial of tezepelumab in patients with steroid-dependent asthma, patients treated with tezepelumab were not more likely to reduce their oral corticosteroid (OCS) dose at week 48 than patients treated with placebo (odds ratio [OR] 1.28, 95% CI 0.69 to 2.35).[8] In contrast, a randomized trial of dupilumab found a greater reduction in OCS dose compared with placebo (70% vs 42%; p<0.001), and more patients had a reduction of OCS dose of at least 50% (80% vs. 50%; p<0.001).[9]

In all trials, adverse events with tezepelumab did not appear to be significantly different from placebo.[6,7] This is also true of dupilumab,[10] and long-term studies of dupilumab provide additional evidence of safety. Adverse events with omalizumab are uncommon,[10] however omalizumab carries a "black box" warning for anaphylaxis.[11]

Important uncertainties include the lack of head-to-head trials of these agents, the lack of longer term data on safety of the new mechanism of action of tezepelumab, and the inability to evaluate subpopulation effects among racial groups given the notable paucity of Black patients in the trials of tezepelumab; Black patients were also underrepresented in at least some trials of dupilumab and omalizumab. Overall, given the strength of evidence in different patient groups, ICER's ratings for comparative clinical effectiveness are as shown below.

Table ES1. Evidence Ratings

Treatment	Comparator	Population	Evidence Rating
Tezepelumab	Standard of care	*All Patients With Severe Asthma*	**C++**
Tezepelumab	Dupilumab	*Eosinophilic Asthma*	**I**
Tezepelumab	Omalizumab	*Allergic Asthma*	**I**
Tezepelumab	Dupilumab	*Steroid-Dependent Asthma*	**C-**

We performed an economic analysis of tezepelumab in the broad population of patients with severe asthma. Treatment with tezepelumab results in gains of 1.09 QALYs and 1.12 evLYs. From a health system perspective and using a placeholder net price of approximately $28,000 per year, we estimate a cost of $430,000 per QALY gained and $422,000 per evLY gained, which would exceed usual cost-effectiveness thresholds. Cost-effectiveness is only modestly improved when productivity and other broader effects are included within a modified societal perspective.

In summary, tezepelumab reduces exacerbations in patients with severe asthma, including in some types of asthma for which other biologic therapies are not effective. Because severe asthma is more prevalent among Black Americans, health gains from a successful treatment that has consistent benefits across racial subgroups would provide proportionally greater benefit to that

racial group on a population basis. As discussed above, however, studies have not adequately enrolled Black Americans to demonstrate such a consistent effect. Additionally, as with other biologic therapies, improvements in daily symptoms and quality of life are relatively small. Pricing for tezepelumab is not yet known but at anticipated prices the treatment will not reach traditional thresholds considered cost-effective in the US market.

1. Background

This Draft Report incorporates information and language from prior ICER reviews of asthma in 2016 and 2018.

The Centers for Disease Control and Prevention (CDC) estimates that 25 million Americans, including 5 million children, have asthma.[1] Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging of the airways. The disease follows a waxing and waning course with exacerbations initiated by allergens, cold weather, exercise, pollution, and other triggers. This leads to approximately 10 million office visits, 1.6 million emergency room visits, 180,000 hospitalizations, and 3,500 deaths each year in the US.[1,2] The societal costs are estimated to be $82 billion including $50 billion in direct medical costs, $29 billion from asthma-related mortality, and $3 billion from missed work and school.[2] In the US, asthma is more than twice as common among Black children as among white children (13.5% and 6.4%, respectively), and remains somewhat more common among Black adults.[1]

Severe asthma comprises a small but important subset of all individuals with asthma. Those with severe asthma represent fewer than 5-10% of all individuals with asthma but account for a substantial proportion of all asthma costs.[3,12] In addition to being treated with inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[13]

Asthma has been divided into different phenotypes with some overlap. T helper 2 (Th2) cells secrete interleukin (IL)-4, IL-5, and IL-13, which increase the proliferation, survival and recruitment of eosinophils and increase IgE levels.[4,14] About half of individuals with mild-to-moderate asthma exhibit the type 2 phenotype with increases in Th2 cells, and the proportion with this phenotype is believed to be larger in severe asthma.[4] Allergic asthma, which is associated with allergic rhinitis, atopy, and elevated IgE levels, is characteristic of approximately half of all patients with asthma and is generally a form of type 2 asthma.[5] The ICER report in 2018 reviewed five monoclonal antibodies that primarily targeted pathways involved in the allergic or type 2 inflammatory phenotypes of asthma. At that time, none of the biologic therapies appeared to be effective for patients who had neither allergic asthma nor eosinophilia.

Tezepelumab is a new monoclonal antibody that targets thymic stromal lymphopoietin (TSLP); TSLP is believed to play important roles in type 2 immunity but, also in other inflammatory pathways (see Figure A1).[5,6] It is administered by subcutaneous injection every four weeks (see Table D2.1).[5,6] By targeting a new pathway, tezepelumab may provide a new option both for patients for whom prior monoclonal antibodies were indicated but did not work, and also for the large number of patients

for whom existing monoclonal antibodies are not indicated. The US Food and Drug Administration granted breakthrough therapy designation to tezepelumab for the treatment of patients with severe asthma without an eosinophilic phenotype,[15] and an FDA decision is expected near the end of 2021.

Additional background information and definitions are available in the Supplement.

2. Patient and Caregiver Perspectives

This Draft Report was developed with input from diverse stakeholders, including patient groups, patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

ICER, both for this report, and for prior reports, has heard from patients, patient groups, and clinicians about the need for treatments that allow patients to return to their usual activities of daily living. Symptom relief, asthma control, and quality of life matter much more to patients than a reduction in asthma exacerbations. The majority of patients with severe asthma report having symptoms more than once a day and being scared and burdened by their symptoms. They report that their asthma prevents them from living the life that they want to live. The patients report that it also impacts their loved ones: they report that their asthma is a burden to their family and that their caregivers are scared about the possible consequences of asthma. They also have learned to fear the side effects of corticosteroids and want to minimize the use of both systemic and inhaled corticosteroids as much as possible.

We also heard about the excess burdens that asthma places on patients marginalized by society, both because of racism and because of economic inequality. We heard specific concerns that underrepresentation of marginalized groups in clinical trials is a problem in general and for the ICER Report in particular, and that ICER should highlight this issue and its implications for results and conclusions in the Evidence Report.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Procedures for the systematic literature review (SLR) assessing the evidence of tezepelumab, dupilumab, and omalizumab in severe asthma are described in Supplement D1.

Scope of Review

We reviewed the clinical effectiveness of tezepelumab plus usual care compared with usual care alone in adults and adolescents with severe asthma. We also reviewed the comparative effectiveness of tezepelumab and omalizumab in the subgroup of these patients for whom omalizumab is indicated (allergic asthma) and tezepelumab and dupilumab in the subgroup of these patients for whom dupilumab is indicated (eosinophilic asthma and asthma requiring chronic systemic corticosteroids). In ICER's 2018 Review, [30] we found insufficient evidence to distinguish the net benefit of the four treatments for eosinophilic asthma (mepolizumab, reslizumab, benralizumab, and dupilumab), so for this review, rather than comparing tezepelumab to all four treatments, we chose to compare only to dupilumab, given its broader indication for steroid-dependent asthma.

We sought evidence on patient-important outcomes including daily quality of life/daily symptoms, requirements for oral corticosteroids (OCS), and exacerbations, and also on physiologic measures of pulmonary function. The full scope of the review is detailed in the Supplement.

Evidence Base

Tezepelumab

Our search identified a total of 10 references arising from three randomized controlled trials of tezepelumab. Additional details of the study designs can be found in the Supplement D2.

The key randomized trials of tezepelumab are the phase 2 PATHWAY trial,[6] the phase 3 NAVIGATOR trial,[7] and the phase 3 SOURCE trial.[8]

PATHWAY compared low (70 mg every four weeks), medium (210 mg every four weeks), and high (280 mg every two weeks) dose tezepelumab with placebo in 550 adults with uncontrolled asthma.[6] The primary endpoint was the annualized asthma exacerbation rate (AAER) at 52 weeks. We will focus on the medium dose of tezepelumab. Additional information on this trial is provided in the Supplement D2.

NAVIGATOR randomized 1061 adult and adolescent patients with severe, uncontrolled asthma to receive tezepelumab 210 mg every 4 weeks or placebo for 52 weeks.[7] The primary endpoint was AAER. Additional information on this trial is provided in the Supplement D2.

SOURCE randomized 150 adult patients with severe, oral corticosteroid (OCS)-dependent asthma to receive tezepelumab 210 mg every 4 weeks or placebo for 48 weeks.[8] The primary endpoint was the categorized percentage reduction in daily OCS dose at week 48 without loss of asthma control. Additional information on this trial is provided in the Supplement D2.

Dupilumab

When used to treat eosinophilic asthma, dupilumab is approved at doses of 200 mg every two weeks and 300 mg every two weeks.

An unnamed phase 2b trial of dupilumab included both those dosing regimens (as well as two other dosing regimens) with 150 patients assigned to receive 200 mg every two weeks, 157 patients assigned to receive 300 mg every two weeks, and 158 patients assigned to receive placebo.[16] Patients had uncontrolled, persistent asthma.

LIBERTY ASTHMA QUEST (QUEST) randomized 1902 adults and adolescents with moderate-to-severe uncontrolled asthma to receive one of those two dosing regimens or one of two matched placebo regimens (with different volumes of placebo to match the different dupilumab dosing arms), with twice as many patients receiving dupilumab as placebo.[17] Additional information on this trial is provided in the Supplement D2.

In an analysis that combined the dosing regimens from QUEST and examined the subgroup of patients with eosinophiles ≥150 cells/µL, there were 889 such patients treated with dupilumab and 469 treated with placebo.[18]

LIBERTY ASTHMA VENTURE (VENTURE) randomized 210 adults and adolescents with OCS-dependent asthma to dupilumab 300 mg every two weeks or placebo for 24 weeks.[9] Steroid dosing was adjusted prior to randomization and then held steady for four weeks before being adjusted downward according to protocol through week 20. The primary endpoint was the percentage reduction in glucocorticoid dose at week 24. Additional information on this trial is provided in the Supplement D2.

Omalizumab

Omalizumab was first approved by the FDA in 2003,[19] and so much of the evidence base was generated when standards of care for the management of asthma were different from those today. ICER's 2018 evidence report included seven placebo-controlled trials of omalizumab in patients with

allergic asthma;[20-26] the results from those trials in that report are presented below. Additional information on these trials is provided in the Supplement D2.

3.2. Results

Clinical Benefits

The definition of an asthma exacerbation varied somewhat across trials (see Supplement A1), but generally counted worsening of asthma that led to: hospitalization; or an emergency department visit for where systemic glucocorticoids were administered; or treatment with systemic glucocorticoids for three or more days.

Tezepelumab

Additional results are available in the Supplement D2. In this main report, we focus on treatment with tezepelumab 210 mg every four weeks and present results from PATHWAY (adults with uncontrolled asthma), NAVIGATOR (adults and adolescents with severe, uncontrolled asthma), and SOURCE (adults with severe, OCS-dependent asthma).

Results from all three trials inform the key outcomes presented in the main report of daily symptoms and quality of life and exacerbation rate. Subgroup results from PATHWAY and NAVIGATOR examine these outcomes in patients with eosinophilic asthma (to match the approved population for dupilumab) and allergic asthma (to match the approved population for omalizumab). Last, we present results from SOURCE on tezepelumab for OCS-dependent asthma (also an approved indication for dupilumab), as this trial has the best evidence for the outcome of reduction of OCS requirements.

Daily Symptoms and Quality of Life

The six-item Asthma Control Questionnaire (ACQ-6) averages responses to six questions on a zero-to-six scale with lower numbers indicating better disease control; the minimal clinically important difference (MCID) is considered to be 0.5.[27] The Asthma Quality of Life Questionnaire averages responses to 32 questions on a one-to-seven scale with higher numbers indicating better asthma-related quality of life; the MCID is considered to be 0.5.[28]

In PATHWAY at 52 weeks, the decrease in ACQ-6 from baseline with tezepelumab was greater than with placebo but smaller than the MCID (-1.20 vs. -0.91; diff 0.29, 95% CI 0.01 to 0.56).[6] The increase in AQLQ was not statistically significantly different from placebo (1.17 vs. 0.97; diff 0.20, CI -0.09 to 0.48).

In NAVIGATOR at 52 weeks, the decrease in ACQ-6 from baseline with tezepelumab was greater than with placebo but smaller than the MCID (-1.55 vs. -1.22; diff 0.33, CI 0.20 to 0.46).[7] The

increase in AQLQ was greater with tezepelumab than with placebo but smaller than the MCID (1.49 vs. 1.15; diff 0.34, CI 0.20 to 0.47).

In SOURCE at 48 weeks, the decrease in ACQ-6 with tezepelumab was not statistically significantly different from placebo (-0.87 vs. -0.51; diff 0.37, CI -0.02 to 0.71).[8]

Annualized Asthma Exacerbation Rate (AAER)

In PATHWAY, the AAER was lower with tezepelumab compared with placebo (0.20 vs. 0.72; rate ratio [RR] 0.29, 95% CI 0.16 to 0.51).[6] Reductions in the AAER were also seen in NAVIGATOR (0.93 vs. 2.10; RR 0.44, CI 0.37 to 0.53). [7] In SOURCE, in patients with OCS-dependent asthma, there was no statistically significant reduction in AAER (RR 0.69, CI 0.44 to 1.09).[8]

Subgroups

To examine effects in eosinophilic asthma, we present in Table 3.1 the above outcomes with tezepelumab in patients with baseline eosinophil counts <150 cells/µL and ≥150 cells/µL to match a typical definition used. Of note, the primary outcome of reduction in AAER was numerically greater in patients without than with eosinophilia in PATHWAY while the reverse pattern was seen in NAVIGATOR.[29]

To examine results in allergic asthma, we present in Table 3.2 the data on tezepelumab in patients with a positive or negative serum IgE result specific to any perennial aeroallergen. A positive IgE result typically defines allergic asthma.

Table 3.1. Key Outcomes at Week 52 by Blood Eosinophil Count

Blood Eosinophil Count (cells/µL)	Trial	Reduction in AAER vs. Placebo (RR)	Difference in ACQ-6 vs. Placebo	Difference in AQLQ vs. Placebo
≥150	PATHWAY	0.34	-0.35	0.29
	NAVIGATOR	0.39	-0.41	0.41
<150	PATHWAY	0.17	-0.30	0.44
	NAVIGATOR	0.61	-0.09	0.11

Data provided by Amgen.[29] AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, RR: rate ratio

Table 3.2. Key Outcomes at Week 52 by Serum IgE Specific to any Perennial Aeroallergen

Serum IgE	Trial	Reduction in AAER vs. Placebo (RR)	Difference in ACQ-6 vs. Placebo	Difference in AQLQ vs. Placebo
Positive	PATHWAY	0.20	-0.10	0.07
	NAVIGATOR	0.42	-0.29	0.34
Negative	PATHWAY	0.34	-0.59	0.66
	NAVIGATOR	0.49	-0.42	0.36

Data provided by Amgen.[29] AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, RR: rate ratio

Reduction in OCS Requirements

In SOURCE, patients treated with tezepelumab were not more likely to reduce their OCS dose at week 48 than patients treated with placebo (odds ratio [OR] 1.28, 95% CI 0.69 to 2.35).[8]

Dupilumab

Additional results are available in the Supplement D2. Dupilumab is indicated for adults and adolescents with moderate-to-severe asthma and either an eosinophilic phenotype or OCS dependence.[30] Although an exact definition of eosinophilic asthma does not appear in the label, a cutoff of ≥150 cells/µL is typically used. Outcomes of daily symptoms and quality of life and AAER in the subgroup of patients with eosinophilic asthma are available from the QUEST trial but not the unnamed phase 2b trial. Baseline eosinophil status cannot be assessed accurately in patients on chronic OCS (as in the VENTURE trial). The VENTURE trial provides the best evidence on dupilumab's effects on reducing OCS requirements.

Daily Symptoms and Quality of Life

Across the phase 2b trial and QUEST, as described in ICER's 2018 report and looking at patients across all eosinophil levels, the mean improvements in ACQ and AQLQ were greater with dupilumab 200 mg than with placebo (diff 0.39, 95% CI 0.25 to 0.53 and 0.29, CI 0.15 to 0.44, respectively), but smaller than the MCID.[10] Similar results were seen with the 300 mg dose (diff 0.22, CI 0.08 to 0.36 and 0.26, CI 0.12 to 0.40, respectively).

In the analysis looking at patients with **eosinophilic asthma** from QUEST, reduction in ACQ-5 from baseline was greater with dupilumab than with placebo (-1.47 vs -1.13, diff 0.34, p<0.001), but smaller than the MCID.[18]

In patients with OCS-dependent asthma in VENTURE, the decrease in ACQ-5 score from baseline was greater with dupilumab than with placebo (diff 0.47, CI 0.18 to 0.76) but smaller than the MCID.[9]

Annualized Asthma Exacerbation Rate (AAER)

Across the phase 2b trial and QUEST, dupilumab 200 mg and 300 mg reduced the rate of exacerbations compared with placebo (RR 0.44, 95% CI 0.34 to 0.58 and 0.40, CI 0.31 to 0.53, respectively).[31]

In the analysis looking at patients with **eosinophilic asthma** from QUEST, patients treated with dupilumab had fewer exacerbations than those treated with placebo (0.44 vs 1.05, RR 0.42, p<0.001).[18]

VENTURE assessed the rate of severe exacerbation events (those leading to hospitalization, an ED visit, or treatment for three or more days with systemic glucocorticoids at two or more times the current dose of OCS in patients with OCS-dependent asthma.[9] Patients treated with dupilumab had fewer such exacerbations than those treated with placebo (0.65 vs. 1.60; RR 0.41, CI 0.26 to 0.63)

Reduction in OCS Requirements

In VENTURE, the reduction in OCS dose was greater with dupilumab than with placebo (70% vs 42%; p<0.001).[9] More patients treated with dupilumab also had a reduction from baseline OCS dose of at least 50% (80% vs. 50%; p<0.001) and had a reduction in OCS dose to less than 5 mg/day (69% vs. 33%).

Omalizumab

Additional results are available in the Supplement D2. Omalizumab is indicated for patients with allergic asthma, defined as having a positive skin test or in vitro testing demonstrating reactivity to a perennial aeroallergen.[11] We present results from patients meeting this indication.

Daily Symptoms and Quality of Life

Across trials, the mean increase in AQLQ with omalizumab was greater than with placebo but smaller than the MCID (diff 0.26, 95% CI 0.05 to 0.57).[10] ACQ results were not available.

Annualized Asthma Exacerbation Rate (AAER)

Across trials, the rate of asthma exacerbations was lower with omalizumab than with placebo (RR 0.52, 95% CI 0.37 to 0.73).[10]

Harms

Additional results are available in the Supplement D2. In PATHWAY, adverse events, serious adverse events, and events leading to discontinuation of the trial agent were similar between tezepelumab and placebo.[6] In NAVIGATOR, adverse events, serious adverse events, and events leading to discontinuation were more common with placebo than with tezepelumab.[7]

As described in ICER's 2018 report, serious adverse events were similar between dupilumab and placebo. Adverse events leading to discontinuation were lower with the 200 mg dose than placebo but higher with the 300 mg dose than placebo. This was felt to possibly be a chance finding. Open-label extension studies in asthma,[32] as well as in atopic dermatitis,[33] provide evidence suggesting the safety of long-term treatment with dupilumab.

As described in ICER's 2018 report, serious adverse events were less common with omalizumab than placebo and adverse events leading to drug discontinuation were similar between omalizumab and placebo. Omalizumab carries a "black box" warning for anaphylaxis.[11]

Subgroup Analyses and Heterogeneity

Subgroup effects by race are discussed below. NAVIGATOR included 82 adolescents and the point estimate of reduction in AAER appeared to be smaller than that seen in the group as a whole and was not statistically significant (RR 0.70, 95% CI 0.34 to 1.46).[7]

Uncertainty and Controversies

The lack of head-to-head trials reduces our certainty in comparisons between tezepelumab and the other active therapies in the subgroups for which those therapies have been approved. Populations were not identical across the trials and standards of care have changed, raising the possibility that effects seen in a trial might have been different if used with different background therapy. Additionally, definitions of exacerbations have changed over time, and as medical care has changed it is possible that the likelihood of any particular exacerbation response, whether additions of OCS, referral to an ED, or hospitalization has changed as well. We are more concerned with this issue when comparing trials of omalizumab, most of which were performed many years ago, with more recent trials of tezepelumab For both of these concerns, we are uncertain of the magnitude or directionality of any such effects.

Patients treated in randomized trials of biologics typically have very high response rates even in the placebo arms of these trials. One paper noted proportions of patients treated with placebo achieving clinically meaningful improvements across biologics based on ACQ or AQLQ of 61% to 78% and 70% to 77%, respectively.[34] The authors raised the possibility that the very high placebo response was due to improved adherence to standard-of-care treatments while patients were being closely followed and monitored in randomized trials. This both suggests the possibility for substantially improving asthma outcomes in many patients through better administration of standard therapies alone, and raises the question of the generalizability of the results from randomized trials of biologics to patients being treated in routine practice.

Although we have evidence showing benefits of tezepelumab in patients without eosinophilic asthma and without allergic asthma, we do not have data on the subgroup with neither eosinophilic asthma nor allergic asthma. We asked the manufacturer for data for this subgroup but these data were not provided. As such, we have less certainty about the efficacy of tezepelumab in this subgroup.

The trials of tezepelumab (SOURCE) and dupilumab (VENTURE) in OCS-dependent asthma had somewhat different protocols.[9,35] SOURCE was longer than VENTURE (48-weeks vs. 24 weeks) and

did not consider an exacerbation during the dose reduction phase as an endpoint. It is unclear how these differences might have affected the trial results both in terms of magnitude and direction. Additionally, individual arm response rates are not available for SOURCE and so it is not possible to know the comparative response rates in the placebo arms of the two trials.

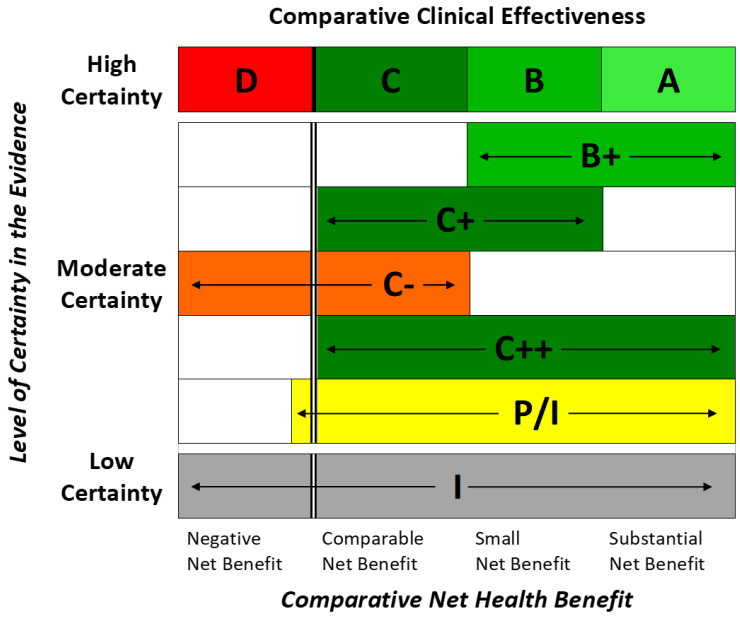
Tezepelumab has a new mechanism of action. In clinical trials to date, serious adverse events have been uncommon, but new biologic treatments are commonly found to have new safety concerns even after FDA approval.[36]

As discussed above, asthma is more common in Black Americans than in most other racial groups in the US. However, in PATHWAY 92.5% of patients were white, and in NAVIGATOR most patients were white or Asian with only 5.8% who were Black.[6,7] Data were not presented from either trial showing outcomes by racial subgroup, and given the small number of Black participants such data would likely be hard to interpret. As such, there are some questions about how the results generalize across important racial subgroups.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided in the Supplement.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

In the overall population of adults and adolescents with severe, uncontrolled asthma, tezepelumab added to standard-of-care therapy without biologics (as estimated by the placebo arm of the clinical trials) substantially reduces AAER. This is the case even in patients without eosinophilic asthma. However, in both eosinophilic and non-eosinophilic asthma patients the average effects of tezepelumab on daily symptoms and quality of life are small and generally smaller than the minimal clinically important difference (MCID) on scales measuring such outcomes. Improvements in AAER without large improvements in daily symptoms have been seen with other biologic therapies as well.

Tezepelumab has a new mechanism of action, targeting TSLP.[6] We do not find important safety signals in the clinical trials, but as noted above, new biologic therapies are frequently found to have safety concerns even after drug approval.[36] This uncertainty is balanced by the severity of disease in the patients for whom tezepelumab is intended such that we think net harm is unlikely. Additionally, in the absence of longer-term trials, it is uncertain whether benefits may increase or decrease over time.

On balance, we rate the net health benefit of tezepelumab added to standard-of-care therapy without biologics, compared with standard-of-care therapy alone in adults and adolescents with **severe, uncontrolled asthma** as "Comparable or Better" (C++). We have somewhat greater uncertainties about the effects in younger patients given the small number of adolescents studied.

In the subgroup of patients with eosinophilic asthma, reductions in AAER and (small) improvements in daily symptoms and quality of life seem similar to those seen with dupilumab. Dupilumab has substantially more evidence on long-term safety. In the absence of head-to-head trials we rate the evidence for tezepelumab compared with dupilumab in patients with **eosinophilic asthma** as "Insufficient" (I).

In the subgroup of patients with allergic asthma, reductions in AAER appear to be somewhat larger with tezepelumab than omalizumab while (small) improvements in daily symptoms and quality of life appear similar to those seen with omalizumab. However, there are important uncertainties introduced by the different time periods in which these therapies were assessed which affect both background therapies and outcome measurement. Omalizumab has substantially more evidence on long-term safety than tezepelumab, but omalizumab also is known to carry a risk for anaphylaxis. In the absence of more recent data on omalizumab and/or head-to-head trials, we rate the evidence for tezepelumab compared with omalizumab in patients with **allergic asthma** as "insufficient" (I).

In patients with steroid-dependent asthma, treatment with tezepelumab did not reduce the required dose of OCS. In contrast, in such patients, treatment with dupilumab led to substantial reduction in OCS dose. As noted above, dupilumab has substantially more evidence than tezepelumab on long-term safety. In the absence of head-to-head trials comparing the drugs in this population, and given the somewhat limited data available from the tezepelumab trial, for patients with **steroid-dependent asthma** we rate treatment with tezepelumab as "Comparable or Inferior" (C-) to treatment with dupilumab.

4. Long-Term Cost-Effectiveness

4.1. Methods Overview

The decision analytic model structure was informed by the primary aim, previous modeling evidence, the evidence review, and stakeholder input. The model structure was based on a previously developed model from prior ICER reports assessing the cost effectiveness of interventions in severe asthma.[31,37,38] The base case comparison was tezepelumab plus standard of care versus standard of care alone in patients with severe asthma. Scenarios evaluated subpopulations of those eligible for biologic therapy in patients with eosinophilic asthma and separately, allergic asthma by comparing tezepelumab and other representative biologics plus standard of care versus standard of care alone.

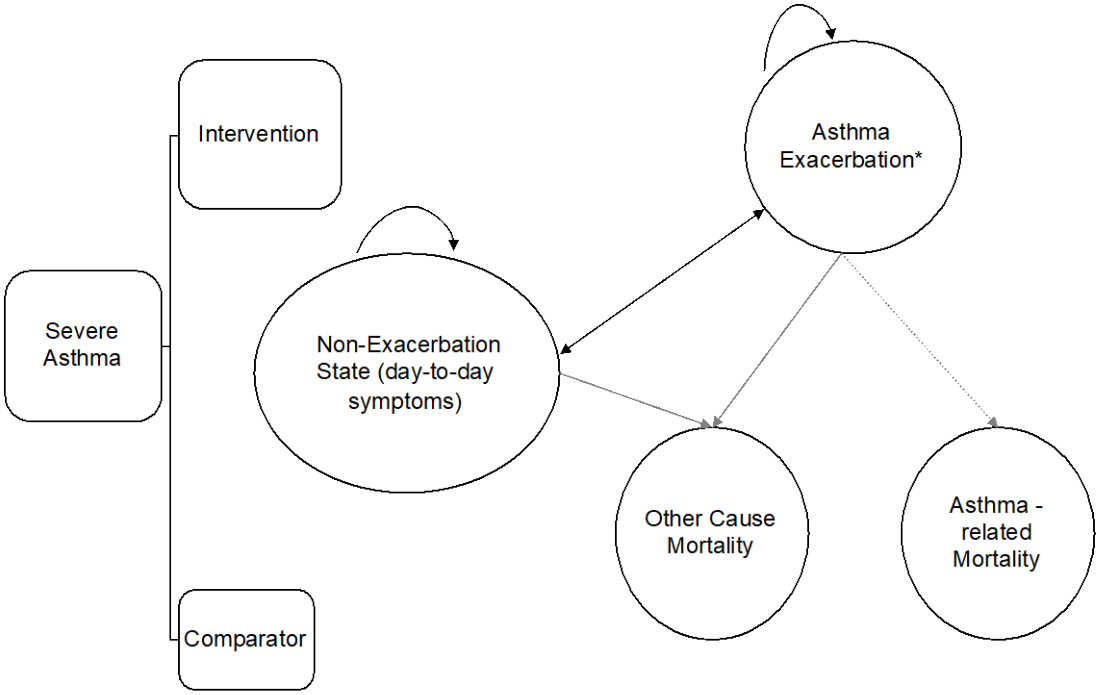
The Markov model includes three primary health states: 1) an asthma non-exacerbation state (i.e., day-to-day asthma symptoms), 2) an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst, asthma-related emergency department [ED] visit, or asthma-related hospitalization), and 3) death (including asthma-related mortality and other cause mortality) (Figure 4.1). The model structure is similar to other published asthma cost-effectiveness analysis (CEA) models, including ICER's 2018 report on biologic agents for the treatment of moderate-to-severe uncontrolled asthma with evidence of type 2 inflammation.[31,37,38]

A lifetime time horizon was assumed in the base case, consistent with the ICER Value Framework and other asthma cost-effectiveness models.[39,40] The discount rate for all future costs and outcomes was 3% per year. We used a cycle length of two weeks to reflect the average length of time for an asthma exacerbation and to be consistent with prior published cost-effectiveness analyses and asthma guidelines that suggest exacerbation events should only be considered new after at least a 7-day period.[41,42]

Key clinical inputs for the model, informed by the evidence review, include exacerbation rates (including oral steroid bursts, ED visits, and hospitalizations), chronic oral steroid use and potential reductions, asthma-related mortality, health-related quality of life utility, biologic treatment response, and adverse events.

Model outcomes for each intervention include total drug and non-drug health care costs, life years (LY) gained, quality-adjusted life years (QALYs) gained, equal value of life years (evLY) gained, and treatment response.

Figure 4.1. Model Structure



*Exacerbation could be defined into different subcategories:

1. Mild exacerbation: Asthma related event that requires an oral steroid burst (but not emergency department or hospitalization)
2. Moderate exacerbation: Asthma related event that requires admittance to the emergency department (but not a hospitalization)
3. Severe exacerbation: Asthma related event that requires a hospitalization

Target Population

The population of focus for the economic evaluation includes adults and adolescents with severe asthma.

Table 4.1. Baseline Population Characteristics

	Average Across Tezepelumab Trial Arms
Mean (SD) Age	52 (12)
Percent Female	66%
Mean (SD) Weight	78 (18)
Proportion of Patients with Chronic Oral Corticosteroid Use (SoC)	9.6%
Source	NAVIGATOR and PATHWAY[6,7]

SD: Standard deviation

Interventions

The intervention of interest is tezepelumab (Amgen and AstraZeneca) added to SoC (e.g., inhaled corticosteroid therapy and at least one additional controller medication).

Comparators

The comparator of interest is SoC alone, typically defined as daily inhaled corticosteroids plus at least one additional controller therapy. The SoC comparator mirrors the control arm of the randomized controlled trials that evaluated the clinical efficacy of tezepelumab. Other active comparators added to SoC are also be compared to SoC alone in scenario analyses including:

- Dupilumab (Dupixent®, Sanofi and Regeneron) in patients with eosinophilic asthma
- Omalizumab (Xolair®, Genentech) in patients with allergic asthma

Consistent with ICER's long-term value voting, pairwise comparisons between the interventions of interest were performed only if the clinical evidence review finds sufficient evidence on relevant outcomes suggesting clinical separation.

4.2. Key Model Assumptions and Inputs

Our model includes several assumptions described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Base-case utility for the non-exacerbation health state is allowed to be different for biologic plus SoC versus SoC alone due to potential improvements in day-to-day symptoms.	Without direct elicitation of utilities in trials comparing biologic plus SoC versus SoC alone, we rely on evidence of patient reported outcome instruments with known utility mappings. The relationship between EQ-5D utility and the Asthma Quality of Life Questionnaire was used for this analysis.[43]
Additional risks of death given oral steroid burst will not impact mortality over and above the severe asthma-related mortality rate for all living health states in the model.	Increased mortality rates are included for severe exacerbations consistent with United Kingdom evidence and calibrated to the United States population with severe asthma. No added mortality is included for oral steroid burst exacerbations given the risk of death found from the United Kingdom evidence was similar to the annual US risk of severe asthma-related mortality conditioned on age.[44,45]
Reduction in daily chronic oral glucocorticoid dose to a level of less than 5 mg is not harmful in terms of adverse events or disutility.	5 mg is a typical literature cutoff with chronic doses at or above 5 mg being considered harmful.[46]
Disutilities for hospitalizations, ED visits, and oral steroid bursts are assumed to be for two weeks.	Disutility is comparable to the NICE omalizumab, mepolizumab, and benralizumab assessment groups' reference-case [44,45]
Base-case model characteristics follow tezepelumab for severe asthma trial population characteristics; however, where possible real-world evidence inputs were included	The model characteristics such as baseline annualized exacerbation rates were reflective of pooled placebo arms of the NAVIGATOR and PATHWAY trials assessing the efficacy of tezepelumab; the percentage of exacerbation severity were derived from recent real-world evidence from the CHRONICLE study[47]

ED: emergency department, SoC: standard of care

Model inputs were estimated from the clinical review, published literature, and information from stakeholders. Key model inputs are shown in Table 4.3. These model inputs include ratios for reductions in exacerbations from tezepelumab add-on therapy, annualized exacerbation rates and proportions of exacerbations resulting in different severity levels, non-exacerbation mean health state utilities, annual price of therapies, and unit costs related to management of exacerbations.

Key Inputs

Table 4.3. Key Model Inputs

Parameter	Inputs		Source
Annualized Exacerbation Rate, end of study (95% CI)	1.82 (95% CI: 1.58, 2.08)		Averaged across placebo arm of NAVIGATOR and PATHWAY trials[6,7]
Proportion of Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	76.8%		Soong et al. 2020 Figure 1[47]
Proportion of Exacerbations Resulting in ED visit (without hospitalization)	9.1%		Soong et al. 2020 Figure 1[47]
Proportion of Exacerbations Resulting in Hospitalization	14.1%		Soong et al. 2020 Figure 1[47]
Severe Asthma Exacerbation Risk of Death	0.0068		Centers for Disease Control and Prevention [48]
Parameter	**Tezepelumab plus SoC**	**SoC Alone**	**Source**
Tezepelumab Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	0.41 (0.33, 0.53)	Reference group	Pooled PATHWAY and NAVIGATOR trials[6,7]
Tezepelumab Rate Ratio for Exacerbations Resulting in ED Visit (without hospitalization)	0.20 (0.10, 0.41)	Reference group	Pooled PATHWAY and NAVIGATOR trials[6,7]
Tezepelumab Rate Ratio for Exacerbations Resulting in Hospitalization	0.20 (0.10, 0.41)	Reference group	Pooled PATHWAY and NAVIGATOR trials[6,7]
Non-Exacerbation Mean Health State Utility for Tezepelumab plus SoC vs. SoC Alone (95% CI for tezepelumab mean difference vs. placebo)*	0.788 (0.774, 0.81)	0.745	Pooled PATHWAY and NAVIGATOR trials[6,7]
Annual Price for Therapy (Tezepelumab plus SoC vs. SoC Alone)	$27,859 + annual SoC costs	$6,494 ($5,297, $7,827)	Placeholder based on Dupilumab net price; Whittington et al. 2018[49]

*Placebo-corrected difference in AQLQ used to derive health state utility values by treatment arm

Clinical Inputs

Rate ratios for exacerbations resulting in steroid bursts, ED visits, and hospitalizations were pooled across the PATHWAY and NAVIGATOR trials and applied to contemporary evidence on the proportion of baseline exacerbation event subtypes from the CHRONICLE study.[47] The cycle-specific probability of asthma exacerbations is then calculated using the baseline annualized exacerbation rate and the respective exacerbation rate ratio estimates shown in Table 4.3. The evidence suggests no differences in serious adverse events exceeding 5% of the population that influence costs or disutilities with tezepelumab plus SoC versus SoC alone. The impact of chronic oral steroid use and associated long-run costs and disutility are included. We defined chronic oral steroid use as regular use of oral steroids resulting in a dose equivalent to at least 5 mg per day of prednisone, a

dose which is considered harmful and associated with increased adverse event costs and disutility.[46] We relied on tezepelumab evidence from NAVIGATOR estimating approximately 10% of patients on chronic oral steroid use. We then applied emerging evidence from SOURCE suggesting the odds of reducing oral steroid use was 1.28. We converted this odds ratio to a proportion reduction from SoC, suggesting patients on tezepelumab would reduce that proportion to approximately 8%.

Asthma-related mortality and other cause mortality were modeled for all living health states (non-exacerbation and exacerbation).[44,50,51] There is a known increased risk of death linked with asthma-related hospitalizations as described by Watson and colleagues, who analyzed a United Kingdom database including 250,043 asthma-related hospital admissions to determine the mortality rate following hospitalizations.[50] In a recent update described in the NICE benralizumab report, the average probability of death from a severe exacerbation was updated to 0.0078 per hospital admission for people aged 45 to 64 years of age. Specifically, clinical experts noted that some deaths originally recorded as asthma-related in the National Review of Asthma Deaths (NRAD) were later found to be unrelated to asthma, adjusting the probability downward. We relied on this input as a starting point, however, calibrated the model to reflect the expected number of deaths per year in the United States. In a recent report from the CDC, the reported number of deaths from asthma was approximately 3,500 in 2019.[48] From Section 7, Potential Budget Impact, we estimated approximately 2.2 million patients in the United States with severe asthma. Consistent with NICE analyses, we assumed that all asthma-related deaths occur from severe exacerbations. We further assumed that all asthma-related deaths occurred only within patients with severe asthma; this is a favorable assumption for a drug used to treat severe asthma. If each patient with severe asthma had one severe exacerbation in one year, then the probability of death per severe exacerbation would be approximately 0.0016. Setting the likelihood of a severe asthma exacerbation to the SoC arm input, we adjusted the probability of death given a severe exacerbation to ensure we are not undercounting deaths. These calibration exercises resulted in a severe asthma risk of death per event of 0.0068 as shown in Table 4.3, and estimated 3,526 excess asthma deaths of the 2.2 million patients with severe asthma in the first year of the model. Rate ratios from the use of tezepelumab (among the other biologic therapies) reduced transition to a severe exacerbation and thus reduced mortality indirectly.

Without commonly used utilities reported in the tezepelumab trials, we relied on evidence of patient reported outcome instruments with known utility mappings. The non-exacerbation health state utility value is specific to the evidence for tezepelumab plus SoC versus SoC alone. Evidence from tezepelumab trials (NAVIGATOR, PATHWAY, and Amgen data on file) include the responses from the Asthma Quality of Life Questionnaire (AQLQ) to derive utility values using the conversion from the AQLQ to the EQ-5D.[43] The least squares mean change and 95% confidence intervals from the AQLQ for tezepelumab plus SoC versus SoC alone provide the inputs for the aggregate mapping algorithm (EQ-5D = 0.14 + 0.12*AQLQ score). Disutilities for the exacerbation health states and for chronic OCS use were assumed to be the same across treatment strategies (i.e., the same for

biologic plus SoC vs. SoC alone).[52] Supplemental Tables E2.1 and E2.2 reports the utility mapping instrument results and disutility estimates.

Treatment response was defined by a change from baseline in ACQ-6 score of ≥ 0.5 at week 50 from the PATHWAY trial.[34] The analysis by Corren et al. assessed the impact of tezepelumab on patient-reported outcomes using both the ACQ-6 and the AQLQ(S)+12. We used the difference in the proportion of responders between tezepelumab plus SoC versus SoC alone as an outcome variable and the denominator in a cost per response calculation.

Economic Inputs

All costs used in the model were updated to first quarter of 2021 US dollars using methods following the ICER reference case. The treatment regimen and unit cost for each treatment is reported in Supplemental Tables E2.3 and E2.4. Given that tezepelumab has not received market approval, we assumed a placeholder price for the base-case results similar to dupilumab's current net price estimated in SSR Health. Treatment-related costs (SoC and asthma biologics) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states). Unit costs for health care utilization were the same across different treatments and populations. Unit costs are available in Supplemental Table E2.5. The annual cost of SoC in an incremental analysis compared to SoC alone will approximate an incremental difference of $0. We assumed the same annualized cost of SoC from the prior 2018 ICER review and consistent with Whittington et al. 2018, but inflated to current US dollars.

Scenario Analyses

We conducted the following scenario analyses:

1. Allergic asthma scenario analysis comparing tezepelumab plus SoC versus SoC alone and omalizumab plus SoC versus SoC alone in an allergic asthma population.

2. Eosinophilic asthma scenario analysis comparing tezepelumab plus SoC versus SoC alone and dupilumab plus SoC versus SoC alone in an eosinophilic population.

3. Modified societal perspective that includes components of productivity loss.

Inputs and results are presented in the Supplement E5.

4.3. Results

Base-Case Results

The base case comparison was tezepelumab plus standard of care versus standard of care alone in patients with severe asthma. The total discounted costs, life years (LYs), quality-adjusted life years (QALYs), equal value of life years (evLYs) gained, and the proportion who achieved response over the lifetime time horizon are detailed in Table 4.4. Using a placeholder price, Tezepelumab plus SoC had a total discounted cost of $697,000 with discounted QALYs, LYs, and evLYs of 15.00, 19.11, and 15.02, respectively. SoC alone had a total discounted cost of $228,000 with discounted QALYs, LYs, and evLYs of 13.91, 18.80, and 13.91, respectively.

Table 4.4. Results for the Base Case for Tezepelumab plus SoC Compared to SoC Alone

Treatment	Intervention Cost	Other Non-intervention Costs	Total Cost	QALY's	LYs	evLYs	% Responder†
Tezepelumab plus SoC*	$657,000	$40,000	$697,000	15.00	19.11	15.02	82%
SoC Alone	$122,000	$106,000	$228,000	13.91	18.80	13.91	70%

*Price is a placeholder based on net pricing of dupilumab

† response defined as change from baseline in Asthma Control Questionnaire-6 score of ≥ 0.5

Table 4.5 presents the discounted lifetime incremental results from the base-case analysis, which include incremental cost-effectiveness ratios for incremental cost per QALY gained, cost per LY gained, cost per evLY gained and cost per additional responder. Total discounted costs for tezepelumab plus SoC were approximately $450,000 greater than SoC alone; gains in QALYs, LYs, and evLYs were 1.09, 0.32, and 1.11 in relation to SoC alone. This resulted in incremental cost-effectiveness ratios of approximately $430,000 per QALY gained, $1,480,000 per LY gained, and $422,000 per evLY gained.

Table 4.5. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained	Cost per Responder†
Tezepelumab plus SoC*	SoC alone	$430,000	$1,480,000	$422,000	$4.7 million

*Price is a placeholder based on net pricing of dupilumab

† response defined as change from baseline in Asthma Control Questionnaire-6 score of ≥ 0.5

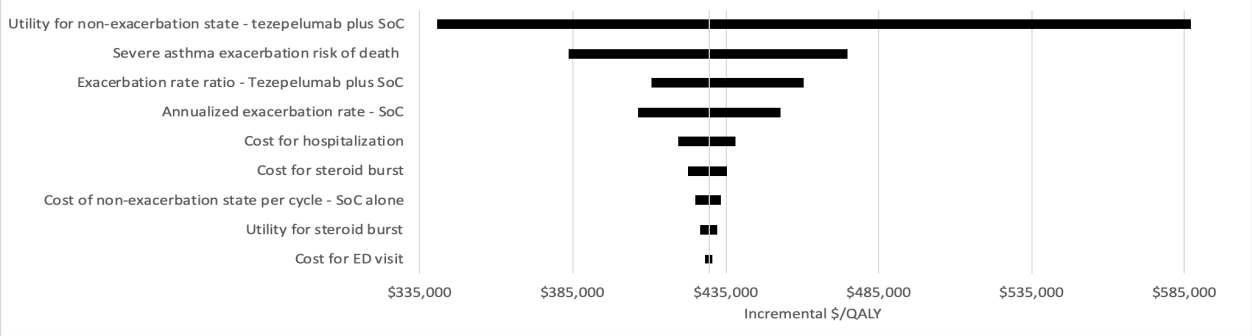
Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors or plausible

parameter ranges). Figure 4.2 presents the tornado diagram resulting from the one-way sensitivity analysis for tezepelumab plus SoC versus Soc alone. Key drivers of cost-effectiveness estimates include the utility for non-exacerbation state for tezepelumab plus Soc and SoC alone, severe asthma exacerbation risk of death, annualized exacerbation rate for SoC alone, and exacerbation rate ratio for tezepelumab plus SoC.

Probabilistic sensitivity analyses were also be performed by jointly varying multiple model parameters over at least 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Tables 4.6 and 4.7 present the probability of reaching certain cost-effectiveness thresholds for tezepelumab plus SoC versus SoC alone. A total of 0% and 0% of iterations for tezepelumab plus SoC versus SoC alone were beneath a threshold of $150,000 per QALY and $150,000 per evLY, respectively. Additional information on sensitivity analyses are available in E4.

Figure 4.2. Tornado Diagram



*Tezepelumab price is a placeholder based on net pricing of dupilumab

Table 4.6. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: Tezepelumab plus SoC vs. SoC alone

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Tezepelumab plus SoC*	0%	0%	0%	0%

*Price is a placeholder based on net pricing of dupilumab

Table 4.7. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Tezepelumab plus SoC vs. SoC alone

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Tezepelumab plus SoC*	0%	0%	0%	0%

*Price is a placeholder based on net pricing of dupilumab

Scenario Analyses

Full results of all scenario analyses are presented in Supplement Section E5.

Threshold Analyses

Tables 4.8 and 4.9 present the annual price needed for each therapy to reach commonly cited cost-effectiveness thresholds

Table 4.8. QALY-Based Threshold Analysis Results

	WAC per Year	Net Price per Year	Annual Price to Achieve $50,000 per QALY	Annual Price to Achieve $100,000 per QALY	Annual Price to Achieve $150,000 per QALY	Annual Price to Achieve $200,000 per QALY
Tezepelumab		$27,859.88*	$6,200	$9,000	$12,000	$15,000

*Price is a placeholder based on net pricing of dupilumab

Table 4.9. evLY-Based Threshold Analysis Results

	WAC per Year	Net Price per Year	Annual Price to Achieve $50,000 per evLY	Annual Price to Achieve $100,000 per evLY	Annual Price to Achieve $150,000 per evLY	Annual Price to Achieve $200,000 per evLY
Tezepelumab		$27,859.88*	$6,300	$9,200	$12,100	$15,000

*Price is a placeholder based on net pricing of dupilumab

Model Validation

We used several approaches to validate the model. First, we provided preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we will also share the model with the relevant manufacturers for external verification around the time of publishing this draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area.

Uncertainty and Controversies

The model analysis was limited by several factors. The price of tezepelumab is currently a placeholder price based on the net price of dupilumab per year. Long-run clinical evidence on biologic treatment responders as well as discontinuation was not available and, with respect to that limitation, we assumed constant treatment benefits and long-run (lifetime) treatment duration. Given severe asthma is not thought to be progressive or a worsening disease for most individuals

eligible for biologic therapy, changes to model assumptions on treatment discontinuation or the addition of evaluating treatment response and stopping rules would likely have limited impact on the lifetime incremental findings.

Mortality was assigned an indirect impact in the model through reduced asthma-related hospitalizations. Differences in mortality were not observed in the clinical evidence review. While there may be mortality reductions from the reduction in severe exacerbations, this has not been proven and there is controversy around appropriate estimates for modeling analyses. NICE's recent assessment of dupilumab included an indirect impact on mortality for OCS bursts; however that evidence was previously generated from an inpatient data sample in the UK with no reference to asthma care outside of the hospital setting. Further, in NICE's assessment of benralizumab, the upper estimate of mortality for those aged greater than 45 was revised downward to 0.0078, suggesting fewer asthma-related deaths than previously estimated. Additionally, both NICE reports acknowledged the considerable uncertainty around mortality estimates and conducted scenario analyses setting added exacerbation-related mortality to 0. Given there is no direct evidence linking asthma biologics, including tezepelumab, to reductions in asthma mortality we calibrated our asthma mortality estimation in the SoC arm of the model to be consistent with recent national statistics on asthma mortality in the United States.[48] We then applied the rate ratio reduction for severe exacerbations from pooled tezepelumab trials to estimate the incremental impact of indirectly reducing mortality. We acknowledge the possibility of a non-zero probability of death outside of hospital setting. However, given our model analysis was calibrated to the number of asthma-related deaths per year in the United States, any change to deaths outside of the hospital setting would have to coincide with re-calibration of the model outputs. In other words, our model analysis accounted for all annual estimated US asthma deaths despite only modeling a subset of overall asthma, and any change to the location of those deaths will likely influence the resources used (e.g., hospital costs) rather than the incremental difference in survival between treatment arms. Further research should identify specific probabilities of death from asthma exacerbations within and outside of the hospital setting to inform future modeling exercises.

Health utility for the day-to-day non-exacerbation health state was identified as a key influential input of biologic benefit with significant uncertainty. However, without reporting standard measures of utility scores from the trials, we relied on the AQLQ mapping algorithm to the EQ-5D. The resulting non-exacerbation state health utility values were slightly lower than our previous estimates. For the scenario analyses, multiple AQLQ estimates were submitted from manufacturers and estimated from various evidence sources. Given we compared each biologic in scenario analyses to SoC alone, we allowed for variation in the non-exacerbation state health utility values across biologics but kept SoC values fixed. We acknowledge that utility estimates are numerically different for different biologics, however, they are not statistically different. Further, differences in utility values between each biologic and SoC alone are all within a range of 0.03 – 0.06. Future

research should focus on direct elicitation of validated health-related quality of life utility inputs in addition to mapping algorithms between the AQLQ and validated utility instruments

The modified societal perspective may not be comprehensive. We included costs from lost productivity and time away from school from a recent 7 year US nationally representative population participating in the Medical Expenditure Panel Survey. The sample size of severe asthma was small, however, the relative reduction in lost productivity between severe and moderate asthma was similar to the relative impact of dupilumab versus SoC alone on missed work due to severe exacerbation events.[53] However, there are still gaps in the modified societal perspective analysis and those missing components can be found in the impact inventory table in the supplement.

We updated the distribution of exacerbation categories using the most recent and best available real-world evidence on treatment for exacerbations from the CHRONICLE study. These estimates were another key driver of the model that are indirectly represented in the one-way sensitivity analysis and tornado diagram. This change produced greater cost offsets and greater improvements in QALYs. Future evidence should validate these findings to be consistent in other severe asthma populations.

4.4 Summary and Comment

The base-case findings suggest that tezepelumab plus SoC provide clinical benefit in terms of gains in QALYs, LYs, and evLYs over SoC alone but do so with increased costs to the health system and society. For scenario analyses within the allergic and eosinophilic asthma populations, we find similar results to the base case. Model findings across all comparisons were sensitive to health-related quality of life improvements, severe asthma exacerbation risk of death, annualized exacerbation rates, and rate reductions in exacerbations from tezepelumab.

5. Contextual Considerations and Potential Other Benefits

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Contextual considerations relate to the relative priority that should be given to **any** effective treatment for severe asthma, while potential other benefits or disadvantages are judgments specifically about tezepelumab. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Contextual Considerations

Contextual Consideration	Relevant Information
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	Death from asthma is uncommon, with about 3500 deaths ascribed to asthma in the US in 2019.[54] Asthma can progress over time.
Magnitude of the lifetime impact on individual patients of the condition being treated	Severe asthma can start at any age, and patients with severe asthma have daily symptoms that interfere with nearly all activities and that markedly reduce quality of life.
Other (as relevant)	

Table 5.2. Potential Other Benefits or Disadvantages

Potential Other Benefit or Disadvantage	Relevant Information
Patients' ability to achieve major life goals related to education, work, or family life	Ability to achieve life goals for some patients is likely to be affected by frequency of asthma exacerbations, and so tezepelumab is likely to help some patients with these goals. However, daily symptoms are probably a more important factor interfering with achieving goals and the effect of tezepelumab on such symptoms is relatively small.
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	Reduction of exacerbations in adolescents and adults is likely to reduce missed days of work for caregivers, however it is uncertain whether this effect would be large enough to importantly impact major life goals.
Patients' ability to manage and sustain treatment given the complexity of regimen	NA
Health inequities	Asthma disproportionately affects Black Americans and those living in urban centers. Although overall air quality has improved in the US over the past six decades and smoking rates have declined, socioeconomic disparities in pulmonary health have persisted or widened.[55] ICER calculated that the Health Improvement Distribution Ratio, looking at the relative proportion of any health gains from treatment of asthma that go to Black Americans is 1.21. (See Supplement)

6. Health Benefit Price Benchmarks

ICER does not provide health benefit price benchmarks as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the health benefit price benchmarks that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the potential total budgetary impact of tezepelumab for patients 12 years of age or older with severe uncontrolled asthma. We used an annualized placeholder price of $27,860 per treated patient per year and the three threshold prices (at $50,000, $100,000, and $150,000 per QALY) for tezepelumab in our estimates of budget impact. For this analysis, we assumed that all patients eligible for treatment with tezepelumab were currently uncontrolled and therefore received treatment with standard of care. All costs were undiscounted and estimated over a five-year time horizon.

This budget impact analysis included the estimated number of individuals 12 years of age and older with severe, uncontrolled asthma in the US who would be eligible for treatment with tezepelumab. Using this approach, we derived an estimate of 1.3 million patients in the US eligible for treatment with tezepelumab, based on 2019 data.

Our estimate begins with prevalent cases of asthma in the US of 23.4 million for those 12 and older.[56] From there, we assumed that about 9.5% of patients could be classified as having severe asthma (10% of adults and 5% of adolescents) arriving at approximately 2.2 million patients.[57-59] Of patients who are diagnosed with severe asthma, we assumed that 60.4% had severe asthma that remains uncontrolled to arrive at 1.3 million patients eligible for treatment with tezepelumab.[60,61] We assumed that 20% of these 1.3 million patients would initiate treatment in each of the five years, or approximately 270,000 patients per year.

The aim of the potential budgetary impact analysis is to document the percentage of patients who could be treated at selected prices without crossing a potential budget impact threshold that is aligned with overall growth in the US economy. The five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $734 million per year for new drugs. ICER's methods for estimating potential budget impact are described in detail in the Supplement Section F.

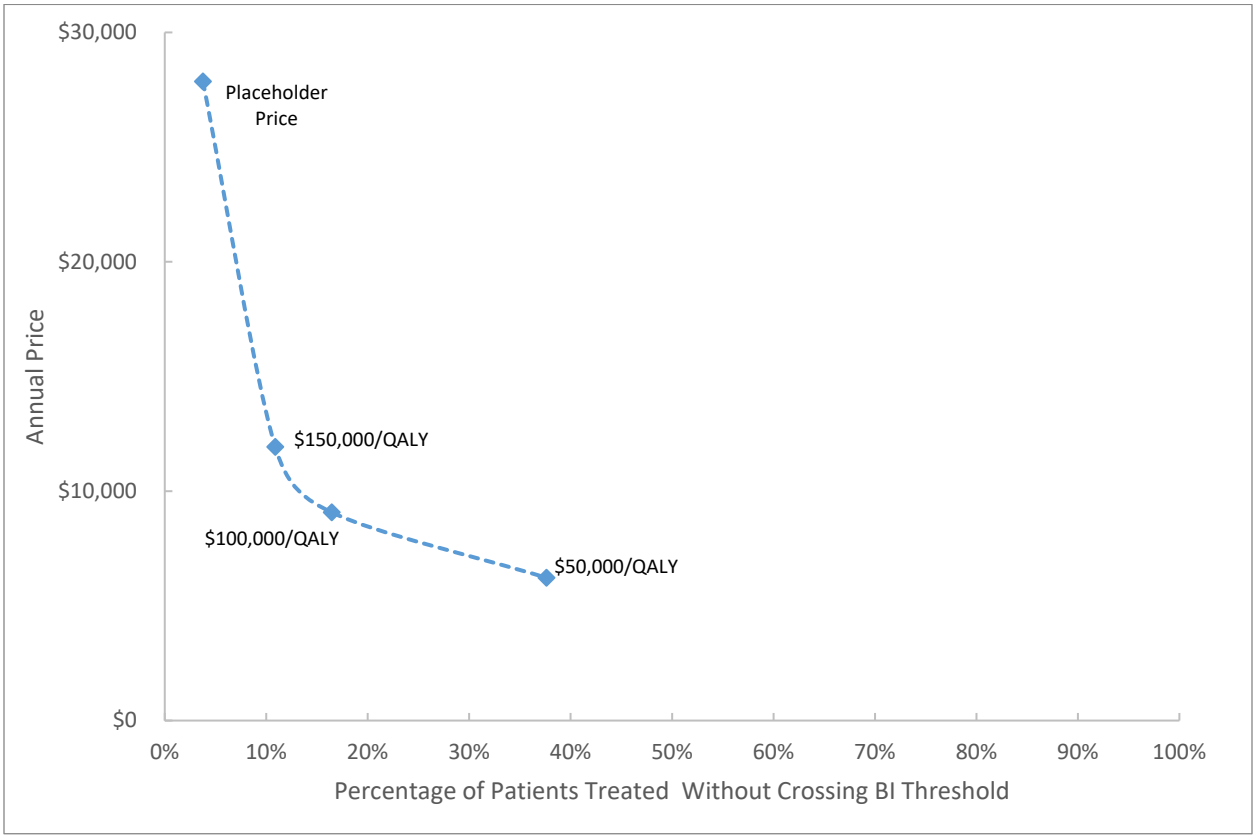
7.2. Results

The average annual per patient total and net cost findings across the annualized placeholder price and the prices that achieve three different cost-effectiveness thresholds for tezepelumab are presented the Supplement Section F.

Figure 7.1 illustrates the potential budget impact of treatment of the eligible population with tezepelumab, based on the annualized placeholder price, as well as the prices that achieve three

different cost-effectiveness thresholds of $150,000, $100,000, and $50,000 per QALY compared to treatment with standard of care alone. Approximately 3.8% of the roughly 270,000 patients could be treated each year without crossing the ICER budget impact threshold of $734 million per year over five years at the annualized placeholder price of $27,860. At the three threshold prices (approximately $11,927, $9,077, and $6,226 per year of treatment, respectively) 10.9%, 16.5% and 37.6% could be treated with tezepelumab without reaching the potential budget impact threshold.

Figure 7.1. Budgetary Impact of Tezepelumab in Patients with Severe Uncontrolled Asthma



References

1. Centers for Disease Control and Prevention. Most Recent National Asthma Data. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Published 2019. Accessed April 18, 2021.
2. Centers for Disease Control and Prevention. ASTHMA FACTS - CDC's National Asthma Control Program Grantees. https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf. Published 2013. Accessed 05/15, 2018.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2021.
4. Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol.* 2015;15(1):57-65.
5. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. *The New England journal of medicine.* 2017;377(10):965-976.
6. Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma. *The New England journal of medicine.* 2017;377(10):936-946.
7. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *The New England journal of medicine.* 2021;384(19):1800-1809.
8. Wechsler M, Gow AM, Brightling CE, et al. Oral Corticosteroid-Sparing Effect of Tezepelumab in Adults with Severe Asthma. *American Thoracic Society.* 2021;203.
9. Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *The New England journal of medicine.* 2018;378(26):2475-2485.
10. Tice JA, Walsh JM, Synnott P, Kumar V. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. 2018.
11. Food and Drug Administration (FDA). Xolair Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Published 2007. Accessed 05/15, 2018.
12. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA Steps 4 or 5 treatment. *Curr Med Res Opin.* 2018;34(12):2075-2088.
13. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of allergy and clinical immunology.* 2007;120(5 Suppl):S94-138.
14. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181(4):315-323.
15. Amgen. Tezepelumab granted breakthrough therapy designation by US FDA for the treatment of patients with severe asthma without an eosinophilic phenotype. https://investors.amgen.com/news-releases/news-release-details/tezepelumab-granted-breakthrough-therapy-designation-us-fda. Published 2018. Accessed April 18, 2021.
16. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet (London, England).* 2016;388(10039):31-44.
17. Castro M, Corren J, Pavord ID, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *The New England journal of medicine.* 2018;378(26):2486-2496.

18. Corren J, Katelaris CH, Castro M, et al. Effect of exacerbation history on clinical response to dupilumab in moderate-severe uncontrolled asthma. *The European respiratory journal.* 2021.
19. (FDA) FaDA. Xolair Label. 2003.
20. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. *Allergy.* 2004;59(7):709-717.
21. Humbert M, Beasley R, Ayres J, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy.* 2005;60(3):309-316.
22. Busse WW, Morgan WJ, Gergen PJ, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *The New England journal of medicine.* 2011;364(11):1005-1015.
23. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Annals of internal medicine.* 2011;154(9):573-582.
24. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma.* 2012;49(2):144-152.
25. Busse W, Spector S, Rosen K, Wang Y, Alpan O. High eosinophil count: a potential biomarker for assessing successful omalizumab treatment effects. *The Journal of allergy and clinical immunology.* 2013;132(2):485-486.
26. Li J, Kang J, Wang C, et al. Omalizumab Improves Quality of Life and Asthma Control in Chinese Patients With Moderate to Severe Asthma: A Randomized Phase III Study. *Allergy, asthma & immunology research.* 2016;8(4):319-328.
27. Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: composite scores of asthma control. *The Journal of allergy and clinical immunology.* 2012;129(3 Suppl):S24-33.
28. Wilson SR, Rand CS, Cabana MD, et al. Asthma outcomes: quality of life. *The Journal of allergy and clinical immunology.* 2012;129(3 Suppl):S88-123.
29. Amgen. Data on File. In:2021.
30. Food and Drug Administration (FDA). Dupixent Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Published 2018. Accessed 11/01/2018, 2018.
31. ICER. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. *Institute for Clinical and Economic Review.* 2018.
32. Michael E. Wechsler, Linda B. Ford, Jorge F. Maspero, et al. Dupilumab Long Term Safety and Efficacy in Patients With Asthma: LIBERTY ASTHMA TRAVERSE. *European Respiratory Society International Congress 2020.* 2020.
33. Beck LA, Thaçi D, Deleuran M, et al. Dupilumab Provides Favorable Safety and Sustained Efficacy for up to 3 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *Am J Clin Dermatol.* 2020;21(4):567-577.
34. Corren J, Garcia Gil E, Griffiths JM, et al. Tezepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma in PATHWAY. *Ann Allergy Asthma Immunol.* 2021;126(2):187-193.
35. Wechsler ME, Colice G, Griffiths JM, et al. SOURCE: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of tezepelumab

in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. *Respir Res.* 2020;21(1):264.
36. Downing NS, Shah ND, Aminawung JA, et al. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. *Jama.* 2017;317(18):1854-1863.
37. ICER. Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and ValueBased Price Benchmarks. *Institute for Clinical and Economic Review.* 2016.
38. McQueen RB, Sheehan DN, Whittington MD, van Boven JFM, Campbell JD. Cost-Effectiveness of Biological Asthma Treatments: A Systematic Review and Recommendations for Future Economic Evaluations. *PharmacoEconomics.* 2018.
39. Institute for Clinical and Economic Review. Modifications to the ICER value assessment framework for treatments for ultra-rare diseases. http://icer-review.org/wp-content/uploads/2020/01/ICER_URD_Framework_Adapt_013120.pdf. Published 2020. Accessed.
40. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2018;21(3):258-265.
41. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy.* 2010;65(9):1141-1148.
42. Reddel H, Taylor D, Bateman E, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American Journal of Respiratory and Critical Care Medicine.* 2009;180(1):59-99.
43. Tsuchiya A, Brazier J, McColl E. Deriving preference-based single indices from non-preference based condition-specific instruments: Converting AQLQ into EQ5D indices. *White Rose Research Online.* 2002.
44. de Vries F, Setakis E Fau - Zhang B, Zhang B Fau - van Staa TP, van Staa TP. Long-acting {beta}2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *The European respiratory journal.* 2010;36(3):494-502.
45. National Institute for Health and Care Excellence. Benralizumab for treating severe eosinophilic asthma TA565. In: NICE, ed. London2019.
46. Lefebvre P, Duh MS, Lafeuille MH, et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Current medical research and opinion.* 2017;33(1):57-65.
47. Soong W, Ambrose C, Trevor J, et al. P203 REAL-WORLD ASTHMA EXACERBATION AND HOSPITALIZATION RATES BY TREATMENT AMONG SPECIALIST-TREATED UNITED STATES SEVERE ASTHMA PATIENTS. *Annals of Allergy, Asthma & Immunology.* 2020;125(5):S27.
48. National Center for Health Statistics. National Vital Statistics System: Mortality (1999-2018). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://wonder.cdc.gov/ucd-icd10.html. Accessed.
49. Whittington MD, McQueen RB, Ollendorf DA, et al. Assessing the value of mepolizumab for severe eosinophilic asthma: a cost-effectiveness analysis. *Ann Allergy Asthma Immunol.* 2017;118(2):220-225.
50. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respiratory medicine.* 2007;101(8):1659-1664.

51. Levy M, Andrews R, Buckinghma R, et al. Why asthma still kills: The national review of asthma deaths (NRAD). In: Physicians RCo, ed. London: Royal College of Physicians; 2014.
52. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary care respiratory journal: journal of the General Practice Airways Group.* 2007;16(1):22-27.
53. Song HJ, Blake KV, Wilson DL, Winterstein AG, Park H. Medical Costs and Productivity Loss Due to Mild, Moderate, and Severe Asthma in the United States. *J Asthma Allergy.* 2020;13:545-555.
54. Centers for Disease Control and Prevention. Asthma FastStats. https://www.cdc.gov/nchs/fastats/asthma.htm. Published 2021. Accessed August 11, 2021.
55. Gaffney AW, Himmelstein DU, Christiani DC, Woolhandler S. Socioeconomic Inequality in Respiratory Health in the US From 1959 to 2018. *JAMA Intern Med.* 2021;181(7):968-976.
56. Centers for Disease Control and Prevention. Most Recent National Asthma Data. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Published 2019. Accessed.
57. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *The Journal of allergy and clinical immunology.* 2015;135(4):896-902.
58. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *European Respiratory Journal.* 2014;43(2):343.
59. Ahmed H, Turner S. Severe asthma in children-a review of definitions, epidemiology, and treatment options in 2019. *Pediatr Pulmonol.* 2019;54(6):778-787.
60. Centers for Disease Control and Prevention. Uncontrolled Asthma among Adults, 2016. https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-adults.htm. Published 2019. Accessed.
61. Centers for Disease Control and Prevention. Uncontrolled Asthma Among children, 2012-2014. https://www.cdc.gov/asthma/asthma_stats/uncontrolled-asthma-children.htm. Published 2019. Accessed.
62. GINA. Global Strategy For Asthma Management and Prevention: Updated 2021. 2021.
63. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *The European respiratory journal.* 2020;55(1).
64. Tejwani V, Chang HY, Tran AP, et al. A multi-stakeholder Delphi consensus core outcome set for clinical trials in moderate-to-severe asthma (coreASTHMA). *Ann Allergy Asthma Immunol.* 2021.
65. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
66. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current. Published 2020. Accessed.
67. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine.* 2009;6(7):e1000097.
68. Michael E. Wechsler, Linda B. Ford, Jorge F. Maspero, et al. Dupilumab Long Term Safety and Efficacy in Patients With Asthma: LIBERTY ASTHMA TRAVERSE. *European Respiratory Society (ERS) International Congress.* 2020.
69. Hanania NA, Rosén K, Griffin NM, et al. Response to Omalizumab Observed Over Wide Range of Blood Eosinophil Levels. *Journal of Allergy and Clinical Immunology.* 2018;141(2).
70. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. Published 2008. Accessed.

71. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. https://icer-review.org/methodology/icers-methods/icer-evidence-ratingmatrix/. . Published 2020. Updated January 31, 2020. Accessed.
72. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
73. Bourdin A, Menzies-Gow A, Chupp G, et al. Reductions in Asthma Exacerbation-Related Hospitalizations and EmergencyDepartment Visits in Patients with Severe, Uncontrolled Asthma Treated withTezepelumab: Results from the Phase 3 NAVIGATOR Study. *American Thoracic Society.* 2021;203.
74. Menzies-Gow A, Brightling CE, Ambrose CS, et al. Effect of Tezepelumab in Oral Corticosteroid-Dependent Patients with Severe Asthma: Results From the Phase 3 NAVIGATOR Study. *American Thoracic Society.* 2021;203.
75. Castro M, Rabe KF, Corren J, et al. Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. *ERJ Open Res.* 2020;6(1).
76. Corren J, Castro M, O'Riordan T, et al. Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):516-526.
77. Corren J, Chen S, Callan L, Gil EG. The effect of tezepelumab on hospitalizations and emergency department visits in patients with severe asthma. *Ann Allergy Asthma Immunol.* 2020;125(2):211-214.
78. Corren J, Colice G, Salapa K, Bowen K, Llanos-Ackert JP. Tezepelumab Efficacy in Patients with Allergic and Non-Allergic Asthma: A Post Hoc Analysis of the PATHWAY Phase 2b Study. *Journal of Allergy and Clinical Immunology.* 2021;147(2):AB157.
79. Corren J, Garcia Gil E, Parnes JR, Pham T, Griffiths JM. Tezepelumab treatment effect on annualized rate of exacerbations by baseline biomarkers in uncontrolled severe asthma patients: Phase 2b PATHWAY study. *American Journal of Respiratory and Critical Care Medicine.* 2019;199(9).
80. Corren J, Menzies-Gow A, Ambrose CS, et al. The effect of tezepelumab in patients with allergic and non-allergic asthma: results from the NAVIGATOR phase 3 study. *European Academy of Allergy and Clinical Immunology.* 2021.
81. Menzies-Gow A, Corren J, Bourdin A, et al. Efficacy and Safety of Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma: Results from the Phase 3 NAVIGATOR Study. *Journal of Allergy and Clinical Immunology.* 2021;147(2).
82. M. Castro, J. Corren, I.D. Pavord, et al. A Randomized, Controlled Phase 3 Study, LIBERTY ASTHMA QUEST, Evaluating the Efficacy and Safety of Dupilumab in Uncontrolled Moderate-to-Severe Asthma. *American Thoracic Society.* 2018.
83. Corren J, Castro M, Chanez P, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Ann Allergy Asthma Immunol.* 2019;122(1):41-49 e42.
84. ID Pavord, AH Khan, B Neupane, et al. S135 Dupilumab efficacy vs standard of care in patients with uncontrolled, persistent asthma – a meta analysis. *Thorax.* 2021;76.
85. K.F. Rabe, P.K. Nair, G.G. Brusselle, et al. Dupilumab in Patients with Corticosteroid-Dependent Severe Asthma: Efficacy and Safety Results from the Randomized, Double-Blind, Placebo-Controlled Phase 3 LIBERTY ASTHMA VENTURE Study. *American Thoracic Society.* 2018.
86. M. Castro, K. Rabe, M. Kraft, et al. A7086 - Dupilumab Improved Lung Function in Patients with Uncontrolled, Moderate-to-Severe Asthma. *American Thoracic Society.* 2019.

87. Lawrence D. Sher, Michael E. Wechsler, Klaus F. Rabe, et al. Assessment of Long-Term Maintenance of OCS Reduction and Efficacy in the Dupilumab LIBERTY ASTHMA TRAVERSE Extension Study. *American Thoracic Society.* 2021;203.
88. Maspero JF, FitzGerald JM, Pavord ID, et al. Dupilumab efficacy in adolescents with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA QUEST. *Allergy.* 2021;76(8):2621-2624.
89. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama.* 2016;316(10):1093-1103.
90. Sullivan PW, Li Q, Bilir SP, et al. Cost-effectiveness of omalizumab for the treatment of moderate-to-severe uncontrolled allergic asthma in the United States. *Current Medical Research and Opinion.* 2020;36(1):23-32.
91. Sutter Health Palo Alto Medical Foundation. Oral Corticosteroids. Accessed 06/15/2018, 2018.
92. Luskin AT, Chipps BE, Rasouliyan L, Miller DP, Haselkorn T, Dorenbaum A. Impact of asthma exacerbations and asthma triggers on asthma-related quality of life in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol Pract.* 2014;2(5):544-552.e541-542.
93. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Techonlogy Assessment.* 2013;17(52).
94. Genentech. Data on File (received: Agust 24, 2021).
95. Suruki RY, Daugherty JB, Boudiaf N, Albers FC. The frequency of asthma exacerbations and healthcare utilization in patients with asthma from the UK and USA. *BMC Pulmonary Medicine.* 2017;17(1):74.
96. Physician Fee Schedule Final Rule. 2020. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched.
97. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2019;22(8):931-941.
98. Trevor J, Lugogo N, Carr W, et al. Exacerbations in US Severe Asthma: Incidence, Characteristics, Predictors, and Effects of Biologic Treatments. *Annals of Allergy, Asthma & Immunology.*
99. 2017 National Population Projections Datasets. 2018. Accessed September 15, 2018.
100. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf. Published 2020. Accessed.

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Annualized Asthma Exacerbation Rate (AAER): The effect on AAER was the primary outcome of many trials. AAER was the rate of exacerbations, calculated on an annual basis.

Asthma Control Questionnaire (ACQ): The ACQ is a seven-item questionnaire that includes five questions on symptoms (ACQ-5), an additional question on rescue inhaler use (ACQ-6) and FEV_1 (ACQ-7). Scores range from zero to six with higher scores indicating worse control and a change of 0.5 points being minimal clinical important difference.

Asthma Quality of Life Questionnaire (AQLQ) : the AQLQ is a 32-item questionnaire covering four domains (symptoms, activity limitation, emotional function, and environmental stimuli). It is scored from one to seven with higher numbers representing better quality of life. The minimally important difference is 0.5 points.

FEV_1: The FEV_1 is the maximal volume of air that a person is able to blow out in one second. It is a measure of airflow obstruction in the lungs with lower values representing greater obstruction.

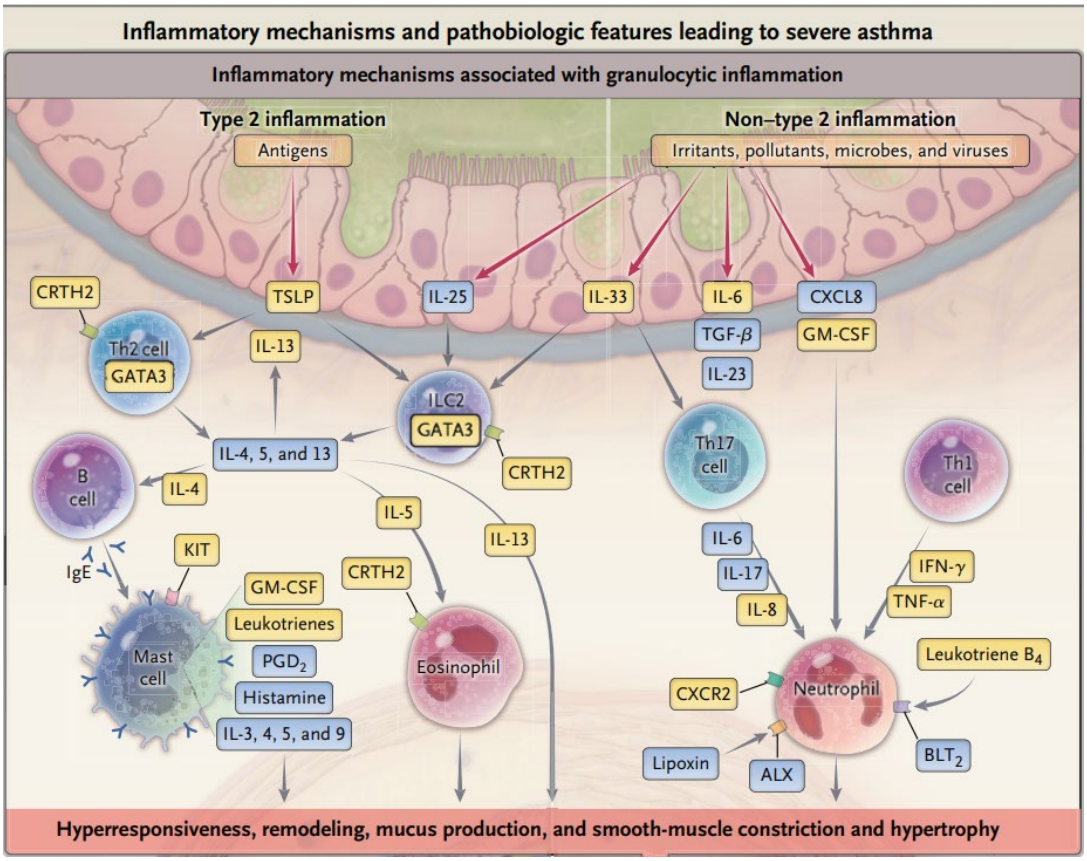
Severe Asthma: Asthma that requires either OCS for >50% of the year or the combination of high dose ICS and a LABA or other controller medication (leukotriene inhibitor/theophylline) to maintain control.

Asthma Exacerbation: An asthma exacerbation is generally defined as a worsening of asthma symptoms leading to treatment with systemic glucocorticoids for three or more days, an emergency department visit for where systemic glucocorticoids were administered, or hospitalization, but definitions varied somewhat across trials:

- PATHWAY (Asthma exacerbation): Worsening of asthma symptoms that led to systemic glucocorticoid use or a doubling of a stable maintenance regimen of oral glucocorticoids for three or more days, an emergency department visit that led to systemic glucocorticoid treatment, or hospitalization
- NAVIGATOR (Asthma exacerbation): Worsening of asthma symptoms that led to systemic glucocorticoid use for three or more consecutive days, an emergency department visit that resulted in the use of systemic glucocorticoids for three or more consecutive days, or hospitalization
- LIBERTY ASTHMA QUEST (Severe asthma exacerbation): Deterioration of asthma leading to systemic glucocorticoid use for three or more days, an emergency department visit leading to treatment with systemic glucocorticoids, or hospitalization

- LIBERTY ASTHMA VENTURE (Severe asthma exacerbation): Events leading to treatment with systemic glucocorticoids at ≥2 times the current dose of oral glucocorticoid for three or more days, an emergency department visit, or hospitalization
- EXTRA (Clinically significant asthma exacerbation): Worsening of asthma symptoms requiring treatment with systemic corticosteroids
- INNOVATE (Protocol-defined asthma exacerbation): Worsening asthma symptoms requiring systemic corticosteroid use for three or more days. For patients receiving long-term oral corticosteroids, an exacerbation was a 20 mg or more increase in the average daily dose of oral prednisone or a comparable dose of another systemic corticosteroid.

Figure A1. Pathways Involved in Asthma with Type 2 Inflammation and Non-Type 2 Inflammation



Modified with permission from Israel et al. 2017, Copyright Massachusetts Medical Society.

Legend. Inflammatory, Immunologic, and Pathobiological Features Leading to Severe Asthma. Type 2 inflammation is most commonly initiated by the adaptive immune system on recognition of allergens through the actions of thymic stromal lymphopoietin (TSLP), which stimulates type 2 helper T (Th2) cells and innate lymphoid cells of group 2 (ILC2) to differentiate and produce the type 2 cytokines interleukin (IL) 4, IL-5, and IL-13. This differentiation depends on activation of the GATA3 transcription factor. These cytokines result in the production of IgE (through the action of IL-4) and subsequent activation of mast cells (which depend on stem cell factor and its receptor, KIT, for normal development and survival) and activation and recruitment of eosinophils through IL-5. IL-13 acts on smooth muscle to induce hyperresponsiveness and remodeling; it also stimulates the epithelium to

increase cytokine production and stimulates mucus production. Mast cells produce multiple mediators and cytokines that cause airway smooth-muscle contraction, eosinophil infiltration, remodeling, and amplification of the inflammatory cascade through additional cytokine production (IL-3, IL-4, IL-5, and IL-9). Mast cells also synthesize prostaglandin D2 (PGD2), which stimulates upstream cells and eosinophils through its actions at the receptor known as CRTH2. The type 2 pathway can also be activated by factors such as infectious agents and irritants that stimulate the innate immune system through production of such cytokines as IL-33 (through its receptor ST2) and IL-25 (through its receptor IL-17RB), which in turn stimulate ILC2 and Th2 cells. The cytokines released in response to these agents can also activate non–type 2 pathways. Type 17 helper T (Th17) cells and their products can play a major role in attracting and stimulating neutrophils. The epithelium also produces cytokines that stimulate Th17 cells; in addition, it produces cytokines that directly stimulate neutrophils. These innate immune stimuli also activate type 1 helper (Th1) cells, which are more classically involved in host defenses against pathogens and can also stimulate neutrophils. In addition, some patients may have reduced ability to synthesize pro-resolving compounds such as lipoxins, which have a role in down-regulating neutrophilic inflammation and antagonizing effects of leukotrienes. Some patients with severe asthma may not have cellular evidence of activation of these pathways and are considered to have "paucigranulocytic" asthma. To produce clinical presentations of severe asthma, these phenotypic inflammatory patterns can induce or combine with any or several of the following: airway hyperresponsiveness, smooth-muscle hypertrophy, structural airway remodeling, or mucus secretion. Substances in yellow have been or are currently being targeted for treatment of severe asthma. ALX lipoxin A4 receptor, BLT2 leukotriene B4 receptor 2, CXCL8 CXC motif chemokine ligand 8, CXCR3 CXC chemokine receptor 3, GM-CSF granulocyte– macrophage colony-stimulating factor, TFG-β transforming growth factor β, and TNF-α tumor necrosis factor α.

Table A1. Dosing Route and Administration for All Drugs

Drug	Dosing	Mechanism	Indication
Tezepelumab *Amgen/AstraZeneca*	70-280 mg SC Q4W	TSLP	Patients with severe asthma with or without an eosinophilic phenotype, receiving ICS/LABA with or without OCS and additional controllers
Dupilumab (Dupixent®) *Sanofi/Regeneron*	200-300 mg SC Q2W	Anti-IL-4Rα	Age ≥12 years with moderate to severe asthma with an eosinophilic phenotype or with OCS-dependent asthma
Omalizumab (Xolair®) *Genentech*	75-375 mg SC Q2W or Q4W*	Anti-IgE	Age ≥6 years with moderate to severe persistent asthma testing positive for perennial aeroallergen whose symptoms are inadequately controlled with ICS

A2. Potential Cost-Saving Measures in Severe Asthma

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/wp-content/uploads/2021/03/ICER_2020_2023_VAF_013120-4-2.pdf). These services are ones that would not be directly affected by tezepelumab (e.g., reduction in exacerbations, ED visits, and hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of asthma beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used

for patients with asthma that could be reduced, eliminated, or made more efficient. No suggestions were received.

B. Patient Perspectives: Supplemental Information

B1. Methods

During ICER's scoping, open input, and public comment periods, we received public comment submissions from 8 stakeholders (two patient advocacy groups, three manufacturers, one clinical society, and two individuals) and participated in conversations with 12 key informants (three patient advocacy groups, four clinical experts, and four manufacturers, one individual). Some stakeholders played more than one role in our outreach. We also reviewed patient input received during prior ICER reviews of asthma in 2016 and 2018. The feedback received from written input and scoping conversations helped us to discuss the impact on patients described in Chapter 2 of the draft evidence report.

C. Clinical Guidelines

Clinical practice guidelines for the treatment of severe asthma have been issued by several US and non-US-based organizations. These guidelines are summarized below.

Global Initiative for Asthma (GINA)[62]

Launched in 1993 in collaboration with the National Heart, Lung and Blood Institute (NHLB), National Institutes of Health (NIH) and the World Health Organization (WHO), the GINA science committee conducts a systematic review each year to provide yearly updates on asthma management and prevention.

Asthma severity is assessed based on the level of treatment required to control symptoms and exacerbations and can change over the course of a few months or years. GINA defines severe asthma as asthma that remains 'uncontrolled' despite optimized treatment with high dose ICS-LABA or that requires high dose ICS-LABA to prevent it from becoming "uncontrolled". GINA has several definitions to differentiate between uncontrolled, difficult-to-treat, and severe asthma.

- *Uncontrolled asthma*: Poor symptom control and/or frequent exacerbations
- *Difficult-to-treat asthma*: uncontrolled despite prescribing medium or high dose ICS with a second controller (usually LABA) or with a maintenance OCS, or that requires a high dose to maintain good symptom control and reduce risk of exacerbations.
- *Severe asthma*: a subset of difficult-to-treat asthma that is uncontrolled despite adherence with maximal optimized high dose ICA_LABA treatment and management of contributory factors, or that worsens when high dose treatment is decreased

The GINA guidelines detail a diagnosis and management pathway specifically for difficult-to-treat and severe asthma:

1. Adults and adolescents are diagnosed with difficult-to-treat asthma
2. Look for factors contributing to symptoms, exacerbations, and poor quality of life such as poor inhaler technique, suboptimal adherence, or comorbidities.
3. Optimize management including asthma education, modifying treatment, add-on non-biologic therapy, non-pharmalogical interventions
4. If the asthma is still uncontrolled after 3 to 6 months, the patient is diagnosed with severe asthma

5. Assess the severe asthma phenotype. A patient may have type 2 airway inflammation (blood eos ≥150 cells/µl or FeNO ≥20 ppb or asthma clinically allergen-driven or need for maintenance OCS

    a. If a patient has type 2 inflammation, may consider adherence tests, increase ICS dose for 3-6 months or add-on type two biologic therapy with anti-IgE, anti-IL5/Anti-IL5R or Anti-IL4R

    b. If a patient is not type 2, may continue to try to optimize management, avoid exposures (tobacco smoke, allergens) or consider add-on treatment with LAMA or azithromycin

6. Patient and their care team should continue to review their response and optimize management as needed

American Thoracic Society (ATS) and European Respiratory Society (ERS)[58,63]

The American Thoracic Society (ATS) and European Respiratory Society (ERS) provide recommendations for the management of severe asthma in adults and children in a 2020 update to their 2014 guidelines.

The ATS-ERS Task Force defines severe asthma for patients ages six and up as asthma requiring high dose inhaled corticosteroids plus a second controller to prevent it from becoming "uncontrolled" or asthma that remains "uncontrolled" despite receiving this therapy. Uncontrolled asthma is defined as meeting at least one of four criteria:

1) Poor asthma control: Asthma Control Questionnaire (ACQ) Score ≥1.5
2) Frequent severe asthma exacerbations requiring two or more systemic corticosteroid bursts in the previous year
3) Serious exacerbations resulting in at least one hospitalization, ICU stay or mechanic ventilation in the previous year
4) Limited airflow: FEV_1 >80% predicted normal

The Task Force recommends defining and diagnosing severe asthma using the following three steps:

Step 1: Confirm a diagnosis of asthma and rule out "difficult-to-treat asthma". Severe asthma should only include patients with refractory asthma or those with comorbidities like severe sinus disease or obesity that are not yet fully treated. Patients with "difficult-to-treat asthma" should have their diagnosis confirmed and managed by a specialist for at least three months.

Step 2: Distinguish severe asthma from moderate or mild asthma. Severe asthma patients require treatment with high dose inhaled corticosteroids and an additional controller like long acting β2-agonist (LABA), leukotriene modifier or theophylline and/or systemic corticosteroids. Those who

stopped this treatment due to lack of response after an adequate trial are also included in the definition of severe asthma. This definition does not include those with untreated severe asthma, however.

Step 3: Distinguish controlled from uncontrolled severe asthma. Patients meeting any of the four criteria for "uncontrolled asthma" listed above while on high-dose therapy can be identified as having severe asthma. Patients who do not meet the criteria for uncontrolled asthma but worsen on tapered corticosteroids also meet the definition of severe asthma.

For the treatment of severe asthma, the Task Force made the following recommendations with regard to biologic therapies:

- Suggest using anti-IL5/IL5R therapies in adult patients with severe uncontrolled eosinophilic asthma, with a suggested eosinophil cut point of ≥150 cells/µl.
- Suggest using anti-IL4/13 therapy in adult patients with severe eosinophilic asthma (eosinophil cut point not stated) or severe corticosteroid-dependent asthma.
- Suggest considering eosinophil cut point of ≥260 cells/µl and FeNO ≥19.5 ppb to identify adults and adolescents with the greatest likelihood of response to anti-IgE therapy.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The population of focus for the review were adults and adolescents with severe asthma.

Apart from the subpopulations described below (related to indications for the comparator therapies), we also examined efficacy in subgroups defined by:

- Allergic vs. non-allergic asthma phenotypes
- Eosinophil level
- Race and ethnicity
- Socioeconomic status
- Age

Interventions

The full list of interventions is as follows:

Tezepelumab (Amgen and AstraZeneca)

Comparators

We compared tezepelumab to:

- Dupilumab (Dupixent®, Sanofi and Regeneron) in patients for whom dupilumab is indicated
- Omalizumab (Xolair®, Genentech) in patients for whom omalizumab is indicated
- Usual care (estimated by placebo arms of clinical trials) in all patients with severe asthma

Outcomes

A multistakeholder project launched in 2019 concluded that a core set of outcomes that should be measured in trials of therapies for severe asthma includes severe asthma exacerbation, change in asthma control, asthma-specific or severe asthma-specific quality of life, asthma-specific hospital stay or admission, and asthma-specific emergency department visits.[64]

Although this core outcomes set was published after trials of the therapeutic agents subject to this review were conducted, the set helped inform outcomes that were sought as part of this review.

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Daily quality of life
    - Daily symptoms (including nocturnal symptoms and impact on daily activities)
    - Asthma control
    - Asthma-related hospitalizations and emergency department visits
    - Use/reduction in use of OCS
    - Corticosteroid side effects
    - Asthma exacerbations and severe exacerbations
    - Missed time from school or work
    - Mortality
    - Adverse events including
        - Serious adverse events
        - Treatment-emergent adverse events
        - Adverse events leading to treatment discontinuation
- Other Outcomes
    - Pulmonary function testing including forced expiratory volume in 1 second (FEV_1)
    - Adherence
    - Blood eosinophil levels

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least 24 weeks duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the United States.

Table D1. PRISMA 2009 Checklist

		Checklist Items
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on tezepelumab, dupilumab, and omalizumab for severe asthma followed established best research methods.[65,66] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[67] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer.org/policy-on-inclusion-of-grey-literature-in-evidence-reviews/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data.

Table D1.2. Tezepelumab Search Strategies: EMBASE

1	'asthma'/exp
2	('tezepelumab' OR 'AMG 157' OR 'AMG157' OR 'AMG-157' OR 'MEDI 9929' OR 'MEDI9929' OR 'MEDI-9929' OR 'MEDI19929' OR 'MEDI 19929' OR 'MEDI-19929'):ti,ab
3	#1 AND #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp OR 'animal model'/exp) NOT 'human'/exp
5	#3 NOT #4
6	#5 AND [English]/lim
7	#6 AND ('chapter'/it or 'comment'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'review'/it OR 'opinion'/it)
8	#6 NOT #7

Search ran on June 14, 2021

Table D1.3. Tezepelumab Search Strategy: Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to Present

1	"asthma".ti,ab.
2	("tezepelumab" or "AMG 157" or "AMG157" or "AMG-157" or "MEDI 9929" or "MEDI9929" or "MEDI-9929" or "MEDI19929" or "MEDI 19929" or "MEDI-19929").ti,ab.
3	1 and 2
4	(animals not (humans and animals)).sh.
5	3 not 4
6	limit 5 to English language
7	6 and ("chapter" or "comment" or "editorial" or "letter" or "note" or "short survey" or "review" or "opinion").pt
8	6 not 7

Search ran on June 14, 2021

Table D1.4. Dupilumab and Omalizumab Search Strategy: EMBASE

1	'asthma'/exp
2	('dupixent' OR 'dupilumab' OR 'REGN 668' OR 'REGN668' OR 'REGN-668' OR 'SAR 231893' OR 'SAR231893' OR 'SAR-231893'):ti,ab
3	('xolair' OR 'omalizumab' OR 'rhuMAb-E25' OR 'RG3648' OR 'RG 3648' OR 'RG-3648' OR 'IGE 025' OR 'IGE025' OR 'IGE-025'):ti,ab
4	#1 AND (#2 OR #3)
5	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp OR 'animal model'/exp) NOT 'human'/exp
6	#4 NOT #5
7	#6 AND [English]/lim
8	#7 AND ('chapter'/it or 'comment'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'review'/it OR 'opinion'/it)
9	#7 NOT #8
10	#9 AND [randomized controlled trial]/lim
11	#10 AND [2018-2021]/py

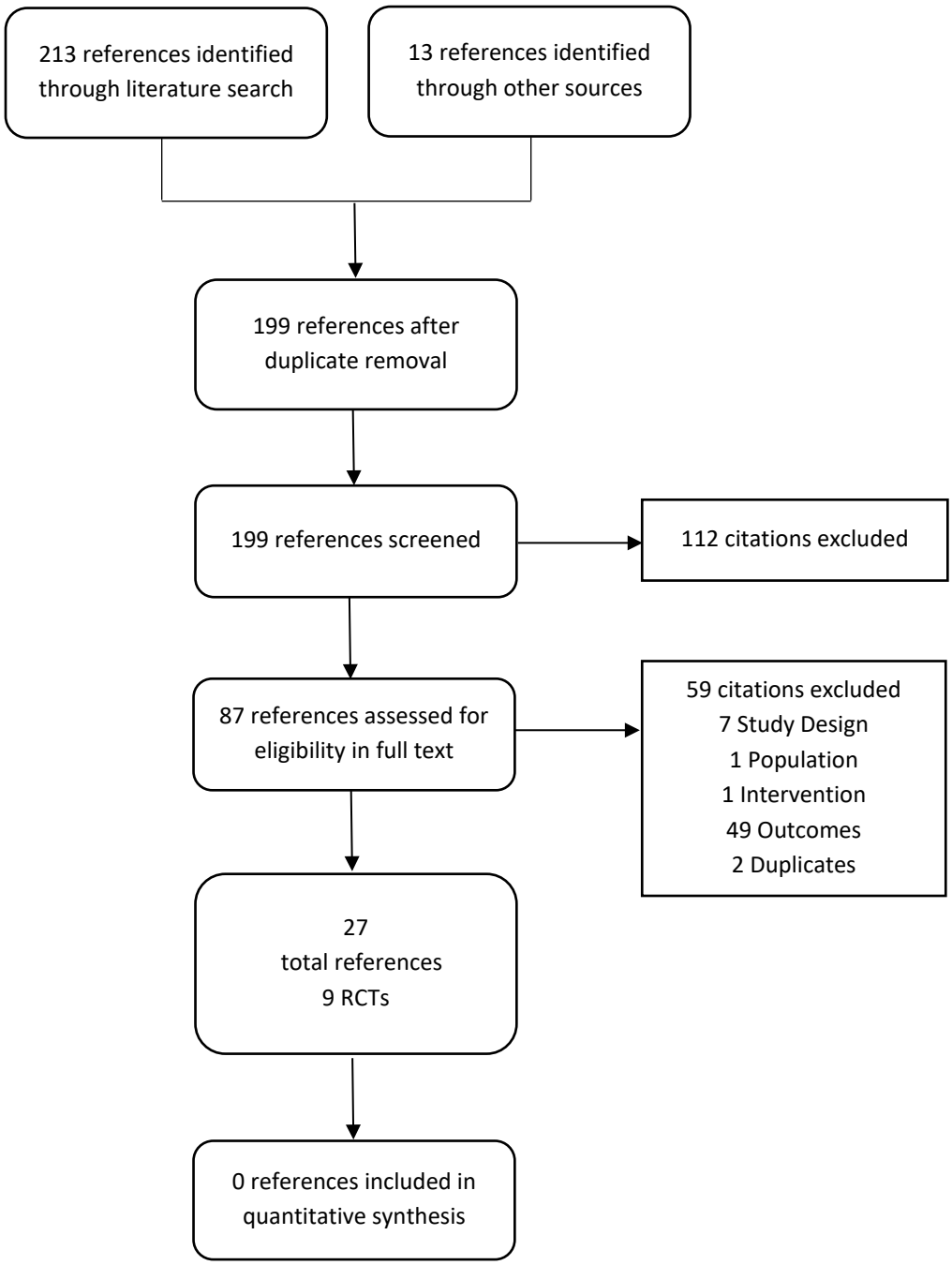
Search ran on June 14, 2021

Table D1.5. Dupilumab and Omalizumab Search Strategy: Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily, Ovid MEDLINE and Versions® 1946 to Present

1	"asthma".ti,ab.
2	("dupixent" OR "dupilumab" OR "REGN 668" OR "REGN668" OR "REGN-668" OR "SAR 231893" OR "SAR231893" OR "SAR-231893").ti,ab.
3	("xolair" OR "omalizumab" OR "rhuMAb-E25" OR "RG3648" OR "RG 3648" OR "RG-3648" OR "IGE 025" OR "IGE025" OR "IGE-025").ti,ab.
4	1 and (2 or 3)
5	(animals not (humans and animals)).sh.
6	4 not 5
7	limit 6 to English language
8	7 and ("chapter" or "comment" or "editorial" or "letter" or "note" or "short survey" or "review" or "opinion").pt
9	7 not 8
10	limit 9 to randomized controlled trial
11	limit 10 to yr="2018-Current"

Search ran on June 14, 2021

Figure D1. PRISMA flow Chart Showing Results of Literature Search for Severe Asthma



Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. We performed an assessment of publication bias for tezepelumab, dupilumab, and omalizumab using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. For this review we did not find any evidence of publication bias for tezepelumab and dupilumab. However we identified three long term extension trials for omalizumab (NCT00109187, NCT00482508, and NCT00482248) that have not yet been published.

Study Selection

We performed screening at both the abstract and full-text level. Two investigators screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. Two investigators reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to dupilumab and omalizumab. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Our literature search identified 213 potentially relevant references (see Figure D1). After de-duplicating and screening titles and abstracts, 74 references were included for full-text screening. Final included studies were clinical trials in adults and or adolescents with severe asthma reporting on outcomes outlined in the PICOTS. 14 references relating to three RCTs of tezepelumab, four of dupilumab, and two of omalizumab met final inclusion criteria for abstraction. 13 additional references were included and abstracted from outside of our literature search, including submissions from manufacturers.

Tezepelumab

A total of 11 references relating to three RCTs[6,7,29] comparing tezepelumab to placebo met our inclusion criteria.

Dupilumab

A total of 13 references relating to three RCTs[9,17,68] and one phase 2b[16] comparing dupilumab to placebo met our inclusion criteria.

Omalizumab

A total of three references relating to two RCTs[21,23] and a pooled analysis[69] comparing omalizumab to placebo met our inclusion criteria.

Quality of Individual Studies

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[70] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

Also note, we did not rate SOURCE in tezepelumab and TRAVERSE and VOYAGE in dupilumab as they were only available in grey literature with limited reporting of details prohibiting evaluation of the studies' quality. See Table D3.1 for the quality ratings.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[71,72]

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Section D4) and synthesized qualitatively in the body of the review.

D2. Additional Clinical Evidence

Table D2.1. Biologic Therapies for Severe Asthma

Drug	Dosing	Mechanism	Indication
Tezepelumab *Amgen/AstraZeneca*	70-280 mg SC Q4W	TSLP	Patients with severe asthma without an eosinophilic phenotype, receiving ICS/LABA with or without OCS and additional controllers
Dupilumab (Dupixent®) *Sanofi/Regeneron*	200-300 mg SC Q2W	Anti-IL-4Rα	Age ≥12 years with moderate to severe asthma with an eosinophilic phenotype or with OCS-dependent asthma
Omalizumab (Xolair®) *Genentech*	75-375 mg SC Q2W or Q4W*	Anti-IgE	Age ≥6 years with moderate to severe persistent asthma testing positive for perennial aeroallergen whose symptoms are inadequately controlled with ICS

ICS: inhaled corticosteroids, IgE: immunoglobulin E, IL: interleukin, LABA: long-acting beta agonists, mg: milligram, OCS: oral corticosteroids, Q2W: every other week, Q4W: every four weeks, SC: subcutaneous
* dosing and frequency determined by serum total IgE level and body weight

Table D2.2. Overview of Key Studies

Drug	Trials	N	Outcomes
Tezepelumab	PATHWAY	550	AAER at 52 weeks, change form baseline in pre-BD FEV1, ACQ-6, AQLQ
	NAVIGATOR	1061	AAER at 52 weeks, change form baseline in pre-BD FEV1, ACQ-6, AQLQ
	SOURCE	150	Reduction in OCS use without losing asthma control at 48 weeks, AAER
Dupilumab	Phase 2b	776	Change from baseline in pre-BD FEV1 at 12 and 24 weeks, AAER, time to severe exacerbation during treatment, ACQ-5, AQLQ
	QUEST	1902	AAER at 52 weeks, change from baseline in pre-BD FEV1, severe exacerbations leading to hospitalization, loss of asthma control
	VENTURE	210	Reduction in OCS use without losing asthma control at 24 weeks
Omalizumab	EXTRA	850	AAER at 48 weeks, AQLQ, rescue medication use
	INNOVATE	484	Clinically significant asthma exacerbations at 24 weeks, quality of life, hospitalization/emergency department visits, rescue medication use

AAER: annualized asthma exacerbation rate, ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, FEV1: forced expiratory volume in one second, OCS: oral corticosteroids, Pre-BD: prebronchodilator

Trials of Tezepelumab

We identified three phase 3 RCTs of tezepelumab in severe asthma.[6,7,29] The trials are described in detail below and additional details can be found in Evidence Table D4.3. NAVIGATOR and PATHWAY have been published and the data for these trials are informed by the clinical trial report, conference posters and data on file from Amgen. SOURCE is not yet published and the information provided is informed by data provided by Amgen and a conference abstract.

PATHWAY

The PATHWAY trial was a multicenter, double-blind, placebo-controlled phase 2 RCT evaluating the efficacy and safety of three doses of tezepelumab compared to placebo. Patients were randomized 1:1:1:1 to tezepelumab 70 mg (N =138), 210 mg (N = 137), or 280 mg (N = 137) or to placebo (N = 138) once every 4 weeks for 52 weeks. The 550 included patients were 18 to 75 years of age with asthma that was uncontrolled despite taking medium to high dose inhaled corticosteroids with LABA. Patients had a history of at least two asthma exacerbations requiring systemic glucocorticoid treatment or at least one severe exacerbation leading to hospitalization in the year prior to trial entry. Patients had prebronchodilator forced expiratory volume in 1 second (pre-BD FEV_1) values between 40% and 80% of the predicted normal value and a six-item Asthma Control Questionnaire score of at least 1.5. At baseline, treated patients were mean 51.6 years old, 65.6% female, and predominantly white (91.6%) with a mean asthma control score (ACQ-6, range 0-6) of 2.68 and a mean quality of life score (AQLQ, range 1-7) of 4.14.[6] Additional baseline characteristics can be found in Evidence Table D4.3.

The primary endpoint was the annualized rate of asthma exacerbations (AAER) per patient-year at week 52. Key secondary endpoints included change from baseline in pre and postbronchodilator FEV1, ACQ-6 score, AQLQ score, asthma symptom score, and the annualized rate of severe asthma exacerbations at week 52. The primary endpoint as well as changes in prebronchodilator FEV1, ACQ-6, and AQLQ were assessed in subgroups according to blood eosinophil count and allergic status.

NAVIGATOR

The NAVIGATOR trial was a 52-week, phase 3, multicenter, double-blind RCT that compared the efficacy and safety of tezepelumab (210 mg) to placebo subcutaneously every 4 weeks in 1061 patients. Included patients were 12 to 80 years of age with physician diagnosed asthma and had to have receive medium or high-dose inhaled glucocorticoids for at least 12 months before screening and an additional controller medication. Enrolled patients also had a morning pre-BD FEV_1 less than 80% of normal value (<90% for adolescents) during run-in and a postbronchodilator FEV_1 of at least 12% before or during the run-in period. Patients also had to have at least two asthma exacerbations defined as worsening of asthma symptoms that led to hospitalization, an emergency department visit that resulted in the use of systemic glucocorticoids in the 12 months before informed consent. Patients who had received biologic treatment (marketed or experimental) could be included in the last dose had been administered more than four months prior or more than five half-lives before screening. Patients were randomized 1:1 to either tezepelumab (N= 529) or placebo (N= 532) with a mean age of 49.6, of which 36.5% were male, 62.2% were white, and the mean pre-BD FEV_1 at baseline was 62.7.[7] Additional baseline characteristics can be found in Evidence Table D3.3.

The primary endpoint was the AAER over 52 weeks in the overall patients. This endpoint was also assessed in patients with a baseline eosinophil count of less than 300 cells per microliter. Secondary endpoints include change from baseline in pre-BD FEV_1, ACQ-6, and AQLQ.

SOURCE

The SOURCE trial is an ongoing phase 3, multicenter, parallel group RCT that is evaluating the effect of tezepelumab (210 mg) to placebo subcutaneously every 4 weeks on oral corticosteroid (OCS) dose reduction in adults with OCS-dependent asthma. Eligible patients much be receiving OCS as an asthma treatment prior to screening (6 months), taking a stable dose (7.5-30 mg) of prednisone daily prior to screening (1 month) as well as a medium to high dose ICS for prior to screening (12 months). Patients receiving medium dose ICS must have had their dose increased to a high dose for at least 3 months prior to screening. Eligible patients also had to be taking a LABA with or without an additional controller medication three months before screening and patients on additional maintenance asthma controller medications were permitted to enter the study if use had been documented for at least three months or a biologic if the wash out period of 4 months or 5 half-lives was completed. Patients also had to at least one asthma exacerbation in the 12 months before screening. Patients were enrolled 1:1 to tezepelumab (N= 74) or placebo (N= 76) with a mean age of 53.4 years, 62.7% female patients, 20.19% Black or African-American, with a mean pre-BD FEV1 of 1.575 liters. [8] Additional baseline characteristics can be found in Evidence Table D3.3.

The primary endpoint is percentage reduction from baseline in OCS dose at week 48 (defined as 90-100%, 75- <90%, 50- <75%, 0- <50%, or no change or increase). Secondary endpoints include AAER, proportion of patients with 100% reduction on OCS dose and change from baseline in pre-BD FEV_1.

Table D2.3. Key Trials of Tezepelumab

Trial	Arms	Key Baseline Characteristics
PATHWAY	Tezepelumab 70 mg (N = 138) Tezepelumab 210 mg (N = 137) Tezepelumab 280 mg (N = 137) Placebo (N = 138)	**Age, mean years:** 51.6 **Female, %:** 65.6 **Black, %:** 3.5 **Pre-BD FEV_1 (L), mean:** 1.85 **Pre-BD FEV_1 (% predicted), mean:** 59.4 **AQLQ, mean:** 4.14 **ACQ-6, mean:** 2.68
NAVIGATOR	Tezepelumab 210 mg (N = 528) Placebo (N = 531)	**Age, mean years:** 49.5 **Female, %:** 63.5 **Black, %:** 5.8 **Pre-BD FEV_1 (L), mean:** 1.8 **Pre-BD FEV_1 (% predicted), mean:** 62.8 **AQLQ, mean:** 3.9 **ACQ-6, mean:** 2.8
SOURCE	Tezepelumab 210 mg (N = 74) Placebo (N = 76)	**Age, mean years**: 53.4 **Female, %:** 62.7 **Black, %:** 20.2 **Pre-BD FEV_1 (L), mean:** 1.57 **Pre-BD FEV_1 (% predicted), mean:** NR **AQLQ, mean:** 2.47 **ACQ-6, mean:** 2.47

Key Trials of Dupilumab

We identified three RCTs of dupilumab in severe asthma.[9,16,17] The trials are described in detail below and additional details can be found in Evidence Table D2.4. QUEST and VENTURE have been published and the data for these trials are informed by the clinical trial report and conference posters. TRAVERSE is not yet published and data for this trial is informed by conference abstracts.

Phase 2b

The Phase 2b trial was a 24-week double-blind, placebo-controlled dose-ranging RCT evaluating the efficacy and safety of dupilumab in adults with uncontrolled persistent asthma. Included patients were over the age of 18 years with a diagnosis of asthma for at least a year while receiving medium to high dose inhaled corticosteroids plus LABA for at least one month prior to screening. Patients were also required to have at least one systemic corticosteroid burst therapy, hospitalization, or emergency visit requiring systemic steroid treatment in the year prior. The 776 enrolled patients were randomized 1:1:1:1:1 to dupilumab 200 mg every 4 weeks (N = 154), 300 mg every 4 weeks (N = 157), 200 mg every 2 weeks (N = 150), 300 mg every 2 weeks (N = 157), or placebo (N = 150). Across the two dupilumab arms dosing once every 2 weeks (the FDA recommended dosing schedule) and the placebo arm, patients were mean 49.2 years of age, 65.2% female, predominantly white (77.8%).[16] Additional baseline characteristics can be found in Evidence Table D2.4.

The primary endpoint was change from baseline in FEV_1 (liters) in patients with at least 300 eosinophils per microliter at week 12. Secondary endpoints were change in FEV_1 at 24 weeks, AAER, asthma symptom score, ACQ-5, and AQLQ.

LIBERTY ASTHMA QUEST

The LIBERTY ASTHMA QUEST trial was a 52-week phase 3 RCT that compared the efficacy of dupilumab to placebo in patients with moderate-to-severe asthma. Patients enrolled were 12 years of age or older with diagnosed persistent asthma for 12 months or more (according to GINA guidelines) and on current treatment with medium-to-high dose inhaled glucocorticoid with up to two additional controllers. Patients enrolled also had a pre-BD FEV_1 of <80% of the normal volume (<90% for adolescents), an ACQ-5 score of 1.5 or higher, and worsening asthma in that last year that lead to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for three days or more. Patients were randomized 2:2:1:1 to 200mg dupilumab (N= 631) or matched placebo 1.14 ml (N= 317) or 300mg dupilumab (N= 633) or matched placebo 2.00 ml (N= 321) with an average mean age 47.9 years, 62.9% female, average pre-BD FEV_1 at baseline of 1.78 liters, and average ACQ-5 score of 2.76.[9] Additional baseline characteristics can be found in Evidence Table D3.4.

The primary endpoints were annualized rate of severe exacerbation events during the 52-weeks and the absolute change from baseline in pre-BD FEV_1 at week 12. Secondary endpoints include percent change in pre-BD FEV_1 at 52 weeks, and severe asthma exacerbation resulting in hospitalization or emergency department visit.

LIBERTY ASTHMA VENTURE

LIBERTY ASTHMA VENTURE is a 24-week double-blind, placebo-controlled, phase 3 RCT assessing the efficacy and safety of dupilumab in patients with oral glucocorticoid-dependent severe asthma. The 210 included patients were older than 12 years of age with physician-diagnosed asthma receiving treatment with systemic glucocorticoids for at least 6 months prior to trial entry and high dose inhaled glucocorticoids with up to two controllers for at least 3 months. Patients were randomized 1:1 to 300 mg of dupilumab (N =) or matched placebo (N =) every two weeks. Overall, enrolled patients were mean 51.3 years of age, 60.5% female, and had an average ACQ-5 score of 2.50.[17] Additional baseline characteristics can be found in Evidence Table D2.4.

The primary endpoint was the change in the oral glucocorticoid dose without losing asthma control from baseline to week 24. Key secondary endpoints are a reduction of at least 50% in oral glucocorticoid dose and the proportion of patients with the maximum possible reduction in oral glucocorticoid dose. Other secondary endpoints were the annualized rate of severe exacerbations and change from baseline in pre-BD FEV_1 and the ACQ-5 score at week 24.

LIBERTY ASTHMA TRAVERSE

LIBERTY ASTHMA TRAVERSE is an ongoing, single-arm, 96-week, open-label extension study evaluating the long-term efficacy, tolerability, and safety of dupilumab added on to standard of care in adults and/or adolescents. TRAVERSE enrolled 1,902 patients who had participated in the previous dupilumab asthma studies (DRI, EXPEDITION, QUEST, or VENTURE). Baseline characteristics are not currently available, however key outcomes of interest include treatment-emergent adverse events, AAER, change from baseline in pre-BD FEV1, ACQ-5, and AQLQ. Subgroups of interest in this study includes patients with blood EOS of ≥300, ≥150, and FeNO ≥25ppb.

Table D2.4. Key Trials of Dupilumab

Trial	Arms	Key Baseline Characteristics
Phase 2b*	Dupilumab 200 mg Q2W (N = 150) Dupilumab 300 mg Q2W (N = 157) Placebo (N = 158)	**Age, mean years:** 49.2 **Female, %:** 65.2 **Black, %:** 4.9 **Pre-BD FEV_1 (L), mean:** 1.8 **Pre-BD FEV_1 (% predicted), mean:** 60.8 **ACQ-5, mean**: 2.74 **AQLQ, mean**: 4.02
LIBERTY ASTHA QUEST	Dupilumab 200 mg (N= 631) Placebo 1.14 ml (N= 317) Dupilumab 300 mg (N= 633) Placebo 2.00 ml (N= 321)	**Age, mean years:** 47.9 **Female, %:** 62.9 **Black, %:** NR **Pre-BD FEV_1 (L), mean:** 1.78 **Pre-BD FEV_1 (% predicted), mean:** 58.4 **ACQ-5, mean**: 2.76 **AQLQ, mean:** NR
LIBERTY ASTHMA VENTURE	Dupilumab 300 mg (N = 103) Placebo (N = 107)	**Age, mean years:** 51.3 **Female, %:** 60.5 **Black, %:** NR **Pre-BD FEV_1 (L), mean:** 1.58 **Pre-BD FEV_1 (% predicted), mean:** 52.2 **ACQ-5, mean:** 2.5 **AQLQ, mean**: NR
LIBERTY ASTHMA TRAVERSE		NA

NA: not available, Q2W: once every two weeks

* Baseline characteristics exclude the dupilumab Q4W 200 mg and 300 mg arms

Key Trials of Omalizumab

We identified two phase 3 RCTs of omalizumab in severe allergic asthma.[21,23] The trials are described in detail below and additional details can be found in Evidence Table D3.5. EXTRA and INNOVATE have been published and the data for these trials are informed by the clinical trial report and a conference abstract.

EXTRA

EXTRA was a 48-week, prospective, multicenter, double-blind, placebo-controlled phase 3 RCT assessing the efficacy and safety of omalizumab in patients with inadequately controlled, severe allergic asthma. Patients were randomized to either omalizumab with dosing based on body weight and total serum IgE level, minimum 0.0008 mg/kg per IgE (IU/mL) Q2W or 0.0016 mg/kg per IgE (IU/mL) Q4W (N = 427) or placebo (N = 421) for 48 weeks. Included patients were between 12 and 75 years of age with at least one year of severe allergic asthma and uncontrolled despite use of high dose ICS and LABAs. Patients also had at least one asthma exacerbation during the 12 months prior to the trial. At baseline, patients were mean 44.5 years of age, 65.8% female, majority white (74.4%) with an AQLQ score of 4.0.[23] Additional baseline characteristics can be found in Evidence Table D3.5.

The primary endpoint was the rate of asthma exacerbations during the 48 week treatment period. Secondary endpoints were change in asthma symptom severity score, mean puffs per day of rescue medication, and overall asthma-related quality of life (AQLQ).

INNOVATE

The INNOVATE trial was a 28-week, multicenter, randomized, double-blind phase 3 RCT comparing the efficacy, safety, and tolerability in omalizumab versus placebo in patients with persistent severe allergic asthma. Eligible patients were 12 to 75 years old with a positive skin prick test to ≥1 perennial aeroallergen they might be exposed to during the study, severe persistent asthma requiring regular treatment with beclomethasone dipropionate (BDP) or LABA, an FEV of ≥40 to <80% of predicted normal value, and at least two severe asthma exacerbations requiring systemic corticosteroids, or one severe exacerbation requiring hospitalization or emergency room treatment, in the past 12 months. Additional asthma medications such as theophylline's or oral b agonists were allowed if taken regularly starting at least 4 weeks prior. Patients were randomized 1:1 to omalizumab (N= 209) or placebo (N= 210) with a mean age of 43.3, 66.6% female, 6.7% Black, and mean AQLQ score of 3.9.[21] Additional baseline characteristics can be found in Evidence Table D3.5.

The primary endpoint was severe exacerbation rate, however due to baseline differences in exacerbation history, a post hoc adjustment was made and included in the analysis. Additional secondary endpoints were emergency visits for asthma, AQLQ, and change from baseline in pre-BD FEV_1.

Table D2.5. Key Trials of Omalizumab

Trial	Arms	Key Baseline Characteristics
EXTRA	Omalizumab (N = 427) Placebo (N = 421)	**Age, mean years:** 44.5 **Female, %:** 65.8 **Black, %:** 20.8 **Pre-BD FEV_1 (L), mean:** NR **Pre-BD FEV_1 (% predicted), mean:** 64.9 **ACQ-5, mean:** NR **AQLQ, mean:** 4.0
INNOVATE	Omalizumab (N = 209) Placebo (N = 210)	**Age, mean years:** 43.3 **Female, %:** 66.6 **Black, %:** 6.7 **Pre-BD FEV_1 (L), mean:** NR **Pre-BD FEV_1 (% predicted), mean:** 61.3 **ACQ-5, mean**: NR **AQLQ, mean:** 3.9

ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, FEV_1: forced expiratory volume in one second, L: liters, N: total number, NR: not reported, pre-BD: prebronchodilator

Clinical Outcomes of Tezepelumab

Daily Symptoms and Quality of Life In Additional Tezepelumab Doses

In PATHWAY at 52 weeks, the reductions in ACQ-6 from baseline in the low dose (70 mg every four weeks) and high dose (280 mg every four weeks) arms were similar to those seen in the intermediate dose of tezepelumab (low: -1.17; diff 0.26, 95% CI -0.01 to 0.52) and (high: -1.22, diff 0.31, CI 0.04 to 0.58); both smaller than the MCID. The improvement in AQLQ in the low dose arms was not statistically significantly different from placebo (1.12 vs 0.97; diff 0.14, CI -0.13, 0.42) but the improvement in the high dose arm was (1.32 vs. 0.97, diff 0.34, CI 0.0, 0.63; P=0.017).[6]

Annualized Asthma Exacerbation Rate (AAER) in Additional Tezepelumab Doses

In PATHWAY at week 52, the AAER was statistically significantly lower with tezepelumab as compared to placebo in both the low (0.27 vs. 0.72; rate ratio [RR] 0.38, 95% CI 0.25 to 0.58) and high dose arms (0.23 vs. 0.72; rate ratio [RR] 0.34, 95% CI 0.21. to 0.53).[6]

Pulmonary Function Tests

The key secondary outcome is change from baseline in prebronchodilator FEV_1 (pre-BD FEV_1). The minimum clinically important difference (MCID) for FEV_1 is considered to be 0.1 liters (100-200 mL).[7]

In PATHWAY, the least-squares mean change from baseline in pre-BD FEV_1 at week 52 statistically improved in the 210 mg tezepelumab arm compared to placebo (0.08L vs. -0.06L; diff 0.13, 95% CI 0.03 to 0.23; P=0.009). A dose response in pre-BD FEV_1 was seen across the three tezepelumab

doses, with all improvements being statistically significant. Patients with eosinophilic asthma (baseline EOS ≥300 cells/µL) on 210 mg of tezepelumab also experienced higher pre-BD FEV_1 than those on placebo (0.11 vs -0.10; diff 0.21; CI 0.06 to 0.35). For those with baseline ESO ≥150, EOS <150 and <300 cells/µL, however, the difference between any tezepelumab dose and placebo was smaller than the MCID.[6,29] See Table D2.6 for more details.

In NAVIGATOR at 52 weeks, the mean change from baseline in pre-BD FEV_1 was statistically greater for patients on tezepelumab compared to placebo (0.23L vs. 0.09L; Diff 0.13; CI: 0.08 to 0.18; P<0.001). Patients on tezepelumab also had a clinically greater change in the baseline EOS ≥150 (0.28 vs. 0.11 diff 0.17; CI: 0.11 to 0.23) and ≥300 (0.37 vs. 0.14; diff 0.23; CI: 0.15 to 0.31) subgroups compared to placebo. Patients on tezepelumab with baseline EOS <150 and <300 also had greater change versus placebo, but the difference was smaller than the MCID (diff 0.03 and 0.07).[7] See Table D2.6 for more details.

The NAVIGATOR trial investigators did not report on post-BD FEV_1.

Data are not yet available on pulmonary function tests in SOURCE.

Table D2.6. Pulmonary Function Test Results in Tezepelumab

Group	Trial	Pre-BD FEV1 (L), LS Mean (SE)		Post-BD FEV1 (L), LS Mean (SE)	
		PBO	TEZ 210mg	PBO	TEZ 210mg
Overall	PATHWAY	-0.06 (NR)	0.08 (NR)	-0.06 (NR)	0.10 (NR)
	NAVIGATOR	0.23 (0.02)	0.09 (0.02)	NR	NR
EOS ≥150	PATHWAY	-0.10 (NR)	0.07 (NR)	NR	NR
	NAVIGATOR	0.11 (0.02)	0.28 (0.02)	NR	NR
EOS <150	PATHWAY	-0.01 (NR)	-0.02 (NR)	NR	NR
	NAVIGATOR	0.07 (0.04)	0.10 (0.04)	NR	NR
EOS ≥300	PATHWAY	-0.10 (NR)	0.11 (NR)	NR	NR
	NAVIGATOR	0.14 (0.03)	0.37 (0.03)	NR	NR
EOS <300	PATHWAY	-0.04 (NR)	0.01 (NR)	NR	NR
	NAVIGATOR	0.06 (0.02)	0.13 (0.02)	NR	NR

BD: bronchodilator, EOS: blood eosinophil count, FEV1: forced expiratory volume in one second, L: liters, LS: least-squares mean, NR: not reported, PBO: placebo, SE: standard error, TEZ: tezepelumab

Hospitalization and Emergency Department (ED) Visits

In PATHWAY, patients on 210 mg of tezepelumab experienced fewer AAER leading to hospitalizations or ED visits than placebo (0.7 vs 3.6; diff 0.15 CI: 0.04, 0.58).[6]

In NAVIGATOR, AAER requiring hospitalization or ED visits for patients on tezepelumab was lower compared to placebo (0.06 vs. 0.28; RR: 0.21; CI: 0.12 to 0.37).[7] Tezepelumab also prolonged time to first exacerbation requiring hospitalization or ED visits (RR: 65%; HR: 0.35) and reduced asthma-related hospitalization (3.2% vs. 7.0%) compared to placebo.[73]

OCS-Dependent Patients

Of the 100 patients receiving maintenance oral corticosteroids (mOCS) during NAVIGATOR (tezepelumab, n= 49, placebo, n= 51), tezepelumab-treated patients had lower AAER compared to placebo (2.12 vs. 2.94; RR: 28%; CI: -26 to 59). Tezepelumab-treated patients also had clinically greater improvement compared to placebo in pre-BD FEV_1 (0.29 vs. 0.02; diff 0.27; CI: 0.1 to 0.44) and numerically greater improvements in ACQ-6 (-0.85 vs. -1.50; diff 0.65; CI: 0.22 to 1.08) and AQLQ (0.81 vs 1.32; diff 0.50; CI: 0.4 to 0.97).[74]

Clinical Outcomes of Dupilumab

Pulmonary Function Tests

In the Phase 2b trial at week 24, a statistically significant improvement in Pre-BD FEV_1 was seen versus placebo in both the 200 mg dose (16.6L vs. 7.0; diff 9.6, CI 4.5, 14.7; P=0.0003) and the 300 mg dose dupilumab arms (17.3 vs. 7.0; diff 10.3, CI 5.3, 15.4; P<0.0001).[16]

At week 12 in LIBERTY ASTHMA QUEST, dupilumab had a statistically greater improvement in in Pre-BD FEV_1 versus matched placebo in both the low dose (0.32 vs. 0.18; diff 0.14; P<0.001) and high dose (0.34 vs. 0.21; diff 0.13; P<0.001) arms.[17] In patients with EOS ≥300 at baseline, high dose dupilumab had the greatest improvement in Pre-BD FEV_1 versus matched placebo (0.47 vs. 0.22; diff 0.24; CI: 0.16 to 0.32; P<0.001) compared to low dose versus matched placebo (0.43 vs. 0.21; diff 0.21; CI: 0.13 to 0.29). This trend in improvement continued for low dose in the EOS ≥150 to <300 (0.28 vs. 0.17; diff 0.11) and <150 groups (0.19 vs. 0.13; diff 0.06), however high dose dupilumab had no difference in improvement compared to matched placebo in the ≥150 to <300 group (0.25 vs. 0.25).[17] The improvements in pre-BD FEV_1 sustained through week 52 for both doses. Patients on high dose dupilumab had a mean improvement of 0.35 (diff 0.13; CI: 0.08 to 0.19) and low dose had an improvement of 0.36 (diff. 0.20; CI: 0.14 to 0.25).[75]

See Table D2.7 below for additional timepoints and subgroup data on QUEST pulmonary function tests.

Table D2.7. Pulmonary Function Tests in LIBERTY ASTHMA QUEST

Group	Change in Pre-BD FEV1, LS Mean				Change in Post-BD FEV1, LS Mean			
	Low dose		High Dose		Low Dose		High Dose	
	PBO	DUP	PBO	DUP	PBO	DUP	PBO	DUP
Week 12								
Overall	0.18	0.32	0.21	0.34	0.01	0.15	0.04	0.14
EOS ≥150	0.19	0.26	0.23	0.37	0.01	0.19	0.04	0.17
EOS ≥300	0.21	0.43	0.22	0.47	0.04	0.29	0.07	0.27
Week 52								
Overall	0.16	0.36	0.22	0.35	-0.04	0.15	0.01	0.14
EOS ≥150	0.15	0.40	0.23	0.39	-0.04	0.20	0.01	0.16
EOS ≥300	0.17	0.47	0.23	0.48	-0.01	0.29	0.03	0.25

Data from LIBERTY ASTHMA QUEST and Castro 2020 ERJ.[17,75] BD: bronchodilator, DUP: dupilumab, EOS: blood eosinophil count, FEV1: forced expiratory volume in one second, LS: least-squares, PBO: placebo

In LIBERTY ASTHMA VENTURE, dupilumab-treated patients had a statistically significant improvement in Pre-BD FEV_1 compared to placebo (0.01 vs. 0.22; diff 0.22; CI: 0.09 to 0.34; P<0.001).[9]

Hospitalization and Emergency Department (ED) Visits

In the Phase 2b study, no data on hospitalizations or emergency department visits were reported.

In LIBERTY ASTHMA QUEST, rates of asthma-hospitalizations were lower in the low dose dupilumab arm versus matched placebo (0.035 vs. 0.065). Data on the high dose arm and matched placebo is not available.[17]

In LIBERTY ASTHMA VENTURE, no data on hospitalizations or emergency department visits were reported.

Oral Corticosteroid-Dependent Patients

In LIBERTY ASTHMA VENTURE, a greater percentage of patients taking high dose dupilumab achieved a ≥90% reduction in oral glucocorticoid dose at 24 weeks (55.3% vs. 30.8%). High dose dupilumab also had a greater percentage of patients achieve ≥75% (68.9% vs. 39.3%), ≥50% (79.6% vs. 53.3%) and ≥0% (86.4% vs. 68.2%).[17]

Subgroups

In a post hoc analysis of the phase 3 QUEST study,[18] patients across the high type 2 biomarker subgroups (defined as patients with elevated biomarkers) had lower AAER (range: 0.16 to 0.65) compared to placebo (range: 0.86 to 2.35). Patients with F_{eNO} ≥25 and EOS ≥150 at baseline had a greater benefit in pre-BD FEV_1 than the overall population versus matched placebo in high dose (diff 0.33; CI: 0.24 to 0.43) and low dose (diff 0.26; CI: 0.17 to 0.35) arms.[75]

In a post hoc analysis of QUEST patients who met the criteria for allergic asthma (as defined by the eligibility criteria used by physicians for omalizumab), high dose and low dose dupilumab patients had a greater reduction in annualized severe exacerbation rate (high dose: 46% and low dose: 37%) compared to matched placebo at week 52. Reductions in AAER also occurred in both doses versus placebo in the EOS ≥150 (55% vs. 42%) and EOS ≥300 (62% and 57%) groups.[76] Patients in QUEST who did not meet the criteria for allergic asthma saw similar reductions across both doses versus placebo (overall: 60% and 45%; EOS ≤150: 71% and 63%; ≥300: 75% and 71%).[76] See the point estimates in Table D2.8 below.

In pre-BD FEV_1 at week 12, QUEST allergic asthma patients had significant improvement for both doses of dupilumab (diff 0.13 and 0.16, respectively) versus placebo. Similar results occurred in non-allergic patients on dupilumab (low dose: 014 vs. high dose: 0.09). ACQ-5 score had improvements for allergic patients on dupilumab (high dose: -0.26 vs. low dose: -0.28) at week 24. Non-allergic patients on low dose dupilumab had a significant improvement in ACQ-5 (0.44; CI: 0.22 to 0.65; P<0.001) versus matched placebo and high dose had a nominal improvement versus matched placebo (0.08; CI: 0.12 to 0.29).[76]

Table D2.8. Additional Data for Allergic and Non-Allergic Patients in LIBERTY ASTHMA QUEST

Group	Allergic Status	Annualized Severe Exacerbation Rate (estimate, 95%CI)			
		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg
Overall	Allergic	0.74 (0.57 to 095)	0.46 (0.38 to 0.57)	0.97 (0.77 to 1.24)	0.53 (0.43 to 0.65)
EOS ≥150		0.86 (0.64 to 1.15)	0.52 (0.39 to 0.64)	1.05 (0.80 to 1.40)	0.47 (0.37 to 0.61)
EOS ≥300		0.89 (0.64 to 1.25)	0.38 (0.28 to 0.54)	1.15 (0.84 to 1.59)	0.44 (0.32 to 0.60)
Overall	Non-Allergic	1.07 (0.82 to 1.42)	0.43 (0.35 to 0.55)	0.92 (0.70 to 1.20)	0.51 (0.40 to 0.65)
EOS ≥150		1.23 (0.90 to 1.70)	0.36 (0.26 to 0.48)	1.02 (0.75 to 1.40)	0.38 (0.28 to 0.50)
EOS ≥300		1.38 (0.95 to 1.99)	0.34 (0.23 to 0.50)	1.28 0.89 to 1.86)	0.37 (0.26 to 0.53)

95%CI: 95% confidence interval, DUP: dupilumab, EOS: blood eosinophil count, PBO: placebo, mg: milligram, ml: milliliter

Clinical Outcomes of Omalizumab

Pulmonary Function Tests

In EXTRA and INNOVATE, pre-BD FEV_1 in liters was not assessed.

Hospitalization

For omalizumab-treated patients in INNOVATE, rates of total emergency visits were lower than placebo (0.24 vs. 0.43; RR 0.56; CI: 0.32 to 0.97). Omalizumab also had lower rates for hospital admissions (0.06 vs. 0.12), emergency room visits (0.04 vs. 0.06) and unscheduled doctor visits (0.13 vs. 0.24).[21]

Supplemental Harms

For a complete list of all harms, please see Evidence Tables D3.13 to D3.17.

Table D2.9. Select Pooled Harms from Key Studies

Drug	Trial	AEs	SAEs	Treatment-related AEs	Discontinuation	Mortality
Tezepelumab	PATHWAY*	251 (60.9)	40 (9.7)	3 (0.7)†	56 (13.6)	1 (0.2)
	NAVIGATOR	836 (78.9)	125 (11.75)	NR	93 (8.8)	2 (0.4)
Dupilumab	Phase 2b	358 (77.6)	32 (7)	NR	30 (6.5)	0§
	QUEST	1550 (81.7)	157 (8.3)	NR	228 (12.0)	8 (0.4)
	VENTURE	133 (63)	15 (7.5)	NR	7 (3.5)	0 (0)
Omalizumab	EXTRA	668 (79.9)	84 (9.9)	NR	177 (20.8)	3 (0.7)
	INNOVATE	356 (73.8)	66 (13.7)	51 (10.5)	52 (10.7)	NR

AEs: adverse events, NR: not reported, SAEs: serious adverse events. All data are pooled estimates and presented as n (%).

* Includes 70 mg, 210 mg, and 280 mg doses of tezepelumab

† Serious treatment-related adverse event

‡ Overall discontinuation

§ Adverse event-related mortality

D3. Evidence Tables

Table D3.1. Study Quality

Trial	Comparable Groups	Non-differential Follow-up	Patient/ Investigator Blinding	Clear Definition of Intervention	Clear Definition of Outcomes	Selective Outcome Reporting	Measurements Valid	Intention-to-treat Analysis	Approach to Missing Data	USPSTF Rating
Tezepelumab										
PATHWAY	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MAR and MM	Good
NAVIGATOR	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	LOCF and MAR	Good
Dupilumab										
QUEST	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MMRM	Good
VENTURE	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good
Omalizumab										
EXTRA	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MM	Good
INNOVATE	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	MI	Good

LOCF: last observation carried forward, MAR: missing at random, MM: mixed-effects model, MMRM: mixed-effects model with repeated measures, MI: multiple imputation

Table D3.2. Study Design

Trial	Study Design	Treatment Arms	Included Population	Key Outcomes [Timepoint]
Tezepelumab				
PATHWAY NCT02054130	Phase 2b, RCT, DB, PC N = 550 Setting: Global (12 countries)	**Arm 1**: Placebo + SoC **Arm 2**: TEZ 70 mg + SoC **Arm 3**: TEZ 210 mg + SoC **Arm 4**: TEZ 280 mg+ SoC Treatment duration: 52 weeks	- Ages 18-75 years - Physician-diagnosed asthma - Controller regimen of medium/high dose ICS + LABA - History of ≥2 exacerbations or ≥1 severe exacerbation resulting in hospitalization within 12 months	**Primary**: AAER [52 weeks] **Secondary**: Change from baseline in pre-BD FEV_1, ACQ-6, AQLQ
NAVIGATOR NCT03347279	Phase 3 RCT, MC, DB, PC N = 1061 Setting: Global (18 countries)	**Arm 1**: Placebo + SoC **Arm 2**: TEZ 210 mg + SoC Treatment duration: 52 weeks	- Ages 12-80 years - Physician-diagnosed asthma for ≥12 months - Controller regimen of medium/high dose ICS for ≥12 months + 1 additional controller for ≥3 months - History of ≥2 exacerbations within 12 months	**Primary**: AAER [52 weeks] **Secondary**: Change from baseline in pre-BD FEV_1, ACQ-6, AQLQ
SOURCE NCT03406078	Phase 3 RCT, MC, DB, PC N = 150 Setting: Global (7 countries)	**Arm 1**: Placebo + SoC **Arm 2**: TEZ 210 mg + SoC Treatment duration: 48 weeks	- Ages 18-80 years - Physician-diagnosed asthma for ≥12 months - Controller regimen of medium/high dose ICS for ≥12 months; high dose ICS + LABA for ≥3 months; OCS for ≥6 months - History of ≥1 exacerbations within 12 months	**Primary**: Reduction in OCS use without losing asthma control [48 weeks] **Secondary**: AAER
Dupilumab (Dupixent®)				
Unnamed Phase 2b NCT01854047	Phase 2 RCT, DB, PC, Dose-Ranging Study N = 776 Setting: Global (16 countries)	**Arm 1**: Placebo Q2W **Arm 2**: DUP 200 mg Q2W **Arm 3**: DUP 300 mg Q2W **Arm 4**: DUP 200 mg Q4W **Arm 5**: DUP 300 mg Q4W Treatment duration: 24 weeks	- Ages 18 and above - Physician-diagnosed moderate to severe, uncontrolled asthma for ≥12 months based on GINA 2009 Guidelines - Regimen of medium/high dose ICS + LABA - Hospitalization, emergency or urgent care visit or systemic corticosteroid treatment for worsening asthma within prior year	**Primary**: Change from baseline in FEV_1 [12 and 24 weeks] **Secondary**: Annualized rate of severe exacerbations, time to severe exacerbation, loss of asthma control
LIBERTY ASTHMA QUEST NCT02414854	Phase 3 RCT, DB, PC N = 1902	**Arm 1**: Placebo (matched for DUP 200 mg) + SoC **Arm 2**: DUP 200 mg Q2W + SoC **Arm 3**: Placebo (matched for DUP 300 mg) + SoC	- Ages 12 and above - Physician-diagnosed asthma for ≥12 months - Controller regimen of medium/high dose ICS + 1 additional controller for ≥3 months	**Primary**: Annualized rate of severe exacerbations [52 weeks] **Secondary**: Change from baseline in pre-BD FEV_1, severe

	Setting: Global (22 countries)	**Arm 4**: DUP 300 mg Q2W + SoC Treatment duration: 52 weeks		exacerbations resulting in hospitalization, loss of asthma control
LIBERTY ASTHMA VENTURE NCT02528214	Phase 3 RCT, DB, PC N = 210 Setting: Global (17 countries)	**Arm 1**: Placebo + SoC **Arm 2**: DUP 300 mg Q2W + SoC Treatment duration: 24 weeks	- Ages 12 and above - Physician-diagnosed asthma for ≥12 months - Controller regimen of high dose ICS + 1 additional controller for ≥3 months	**Primary**: Reduction in OCS use without losing asthma control [24 weeks]
LIBERTY ASTHMA TRAVERSE NCT02134028	Phase 3 OL, Long-term Extension Study N = 2282 Setting: Global (27 countries)	**Arm 1:** Placebo/DUP **Arm 2**: DUP/DUP	- Patients who completed previous dupilumab asthma clinical studies	**Primary**: Treatment-emergent adverse evets [108 weeks]
Omalizumab (Xolair®)				
EXTRA NCT00314574	Phase 3b RCT, MC, DB, PC N = 850 Setting: United States, Canada	**Arm 1**: Placebo + SoC **Arm 2**: OMA (minimum 0.008 mg/kg/IgE Q2W or minimum 0.016 mg/kg/IgE Q4W) + SoC Treatment duration: 48 weeks	- Ages 12 to 75 - History of severe allergic and inadequately controlled asthma - Controller regimen of medium/high dose ICS + LABA, with/without other controllers - History of ≥1 exacerbations within 12 months - Positive skin test within 12 months	**Primary**: AAER [48 weeks] **Secondary**: Change in Total Asthma Symptom Score, rescue medication use, AQLQ, FeNO, treatment-emergent adverse events
INNOVATE NCT00046748	Phase 3 RCT, MC, DB, PC N = 484 Setting: N/A	**Arm 1**: Placebo + SoC **Arm 2**: OMA (minimum 0.0016 mg/kg/IgE) + SoC Treatment duration: 28 weeks	- Ages 12 to 75 - Diagnosis of severe allergic asthma - Controller regimen of high dose ICS + LABA - History of ≥2 exacerbations or ≥1 severe exacerbation within 12 months - Positive skin prick test	**Primary**: Clinically significant asthma exacerbations [24 weeks] **Secondary**: Quality of life, hospitalizations/emergency visits, rescue mediation use, safety/tolerability

AAER: annualized asthma exacerbation rate, ACQ: Asthma Control Questionnaire, AE: adverse event, AQLQ: Asthma Quality of Life Questionnaire, DB: double-blind, DUP: dupilumab, FEV_1: forced expiratory volume in 1 second, GINA: Global Initiative for Asthma, ICS: inhaled corticosteroids, IgE: immunoglobulin E, kg: kilogram, LABA: long-acting beta agonists, MC: multicenter, mg: milligram, N: total number, N/A: not applicable, OCS: oral corticosteroids, OL: open-label, OMA: omalizumab, PC: placebo-controlled, pre-BD: prebronchodilator, Q2W: once every two weeks, Q4W: once every four weeks, RCT: randomized controlled study, SAE: serious adverse event, SoC: standard of care, TEZ: tezepelumab

Table D3.3. Baseline Characteristics: Tezepelumab Trials[6-8,29,73,74,77-81]

Trial		PATHWAY				NAVIGATOR		SOURCE	
Asthma Population		Severe uncontrolled				Severe uncontrolled		OCS-dependent	
Arms		PBO	TEZ 70 mg	TEZ 210 mg	TEZ 280 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
N		138	138	137	137	531	528	76	74
Age, years (SD)		52.3 (11.7)	50.8 (12.4)	52.7 (12.7)	50.4 (12.3)	49.0 (15.9)	49.9 (16.3)	53.4 (11.9)	53.5 (12.1)
Female sex, n (%)		94 (68.1)	89 (64.5)	87 (63.5)	91 (66.4)	337 (63.5)	335 (63.4)	45 (59.2)	49 (66.2)
BMI, kg/m^2 (SD)		28.5 (5.6)	28.3 (5.1)	28.5 (4.9)	27.6 (5.0)	28.3 (6.9)	28.7 (7.1)	NR	NR
Race, n (%)	White	123 (89.1)	131 (94.9)	128 (93.4)	122 (89.1)	327 (61.6)	332 (62.9)	NR	NR
	Black	6 (4.3)	4 (2.9)	3 (2.2)	6 (4.4)	31 (5.8)	30 (5.7)	0 (0.0)	1 (1.4)
	Asian	6 (4.3)	3 (2.2)	5 (3.6)	5 (3.6)	149 (28.1)	147 (27.8)	NR	NR
	Indigenous	NR	NR	NR	NR	1 (0.2)	0 (0.0)	NR	NR
	Other	2 (1.4)	0 (0)	0 (0)	2 (1.5)	23 (4.3)	19 (3.6)	NR	NR
Exacerbations in prior year, n (%)	Mean (SD)	2.5 (1.2)	NR	2.4 (1.2)	NR	2.7 (1.4)	2.8 (1.4)	2.0 (1.0)	2.0 (1.9)
	1 or 2	110 (79.7)	109 (79.0)	105 (76.6)	117 (85.4)	325 (61.2)	310 (58.7)	NR	NR
	≥3	28 (20.3)	29 (21.0)	32 (23.4)	20 (14.6)	206 (38.8)	218 (41.3)	NR	NR
Pre-BD FEV_1	Liters (SD)	1.82 (0.59)	1.91 (0.67)	1.83 (0.58)	1.83 (0.57)	1.9 (0.7)	1.8 (0.7)	1.593 (0.637)	1.556 (0.504)
	% predicted normal (SD)	60.0 (13.5)	60.5 (13.7)	59.0 (12.5)	58.8 (11.8)	62.7 (18.0)	62.8 (18.0)	NR	NR
ICS dose level	Medium, n (%)	73 (52.9)	67 (48.6)	70 (51.1)	71 (51.8)	132 (24.9)	131 (24.8)	0 (0.0)	1 (1.4)
	High, n (%)	65 (47.1)	71 (51.4)	67 (48.9)	66 (48.2)	398 (75.0)	397 (75.2)	76 (100)	73 (98.6)
OCS use, n (%)		N/A	N/A	N/A	N/A	51 (9.6)	49 (9.3)	NR	NR
ACQ-6 Score*, mean (SD)		2.66 (0.69)	2.72 (0.79)	2.70 (0.80)	2.64 (0.74)	2.8 (0.8)	2.8 (0.8)	2.46 (1.03)	2.48 (1.07)
AQLQ Score†, mean (SD)		4.09 (0.87)	4.17 (0.93)	4.20 (0.91)	4.08 (0.91)	3.9 (1.0)	3.9 (1.0)	4.11 (1.02)	4.14 (1.18)
Asthma Symptom Score‡, mean (SD)		1.70 (0.59)	1.67 (0.62)	1.74 (0.57)	1.67 (0.60)	1.4 (0.7)	1.4 (0.7)	NR	NR
Blood eosinophil count, mean cells/µL (SD)		380 (328)	352 (288)	365 (351)	385 (433)	353 (488)	327 (293)	232 (154)	253 (203)
Total IgE, mean IU/mL (SD)		475 (1272)	323 (890)	484 (1402)	358 (595)	614.1 (1159.5)	515.7 (959.8)	300.89 (521.39)	298.71 (576.28)
FeNO, mean ppb (SD)		N = 137; 37.8 (39.7)	N = 137; 35.6 (47.8)	N = 135; 31.5 (29.8)	N = 133; 33.3 (34.4)	N = 527; 46.3 (44.7)	N = 522; 41.4 (36.3)	NR	NR
Th2 Status, n (%)	Low, n (%)	62 (45.3)	75 (54.7)	70 (51.9)	74 (54.4)	NR	NR	NR	NR
	High, n (%)	75 (54.7)	62 (45.3)	65 (48.1)	62 (45.6)				
Allergic Status	Allergic	64 (46.4)	NR	71 (51.8)	NR	341 (64.2)	339 (64.2)	34 (44.7)	25 (33.8)

Trial		PATHWAY				NAVIGATOR		SOURCE	
Asthma Population		Severe uncontrolled				Severe uncontrolled		OCS-dependent	
Arms		PBO	TEZ 70 mg	TEZ 210 mg	TEZ 280 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
	Non-Allergic	66 (47.8)		57 (41.6)		177 (33.3)	184 (34.8)	39 (51.3)	44 (59.5)
	Unknown	8 (5.8)		9 (6.6)		13 (2.4)	5 (0.9)	3 (3.9)	5 (6.8)
Nasal polyposis with chronic rhinosinusitis, n (%)		NR	NR	NR	NR	69 (13.0)	79 (15.0)	NR	NR
Baseline characteristics not reported: Asthma severity, mean disease duration, comorbid atopic dermatitis, or comorbid allergic rhinitis, OCS dose									

ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, BMI: body mass index, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, IgE: immunoglobulin E, IU: international units, kg/m^2: kilograms per meter squared, mg: milligram, mL: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, PBO: placebo, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, ppb: parts per billion, SD: standard deviation, TEZ: tezepelumab, µL: microliter

* Scores range from 0 to 6; lower scores indicate better disease control; a score of 1.5 indicates uncontrolled asthma

† Scores range from 1 to 7; higher scores indicate better asthma-related quality of life

‡ Scores range from 0 (no symptoms) to 4 (worst possible symptoms)

Table D3.4. Baseline Characteristics: Dupilumab Trials[16,17,82]

Trial		Phase 2b[§]			LIBERTY ASTHMA QUEST				LIBERTY ASTHMA VENTURE	
Asthma Population		Moderate-to-Severe			Moderate-to-Severe				OCS-dependent	
Arms		PBO	DUP 200 mg	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO	DUP 300 mg
N		158	150	157	317	631	321	633	107	103
Age, years (SD)		49.0 (12.7)	51.0 (13.4)	47.5 (12.4)	48.2 (15.6)	47.9 (15.3)	48.2 (14.7)	47.7 (15.6)	50.7 (12.8)	51.9 (12.5)
Female sex, n (%)		104 (65.8)	96 (64.0)	103 (65.6)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	65 (60.7)	62 (60.2)
BMI, kg/m^2 (SD)		60 (38.0)	65 (43.3)	63 (40.1)	29.76 (7.3)	29.05 (6.5)	29.21 (7.0)	29.07 (6.7)	29.8 (6.0)	28.9 (5.9)
Race, n (%)	White	119 (75.3)	114 (76.0)	129 (82.2)	NR	NR	NR	NR	100 (93.5)	97 (94.2)
	Black	9 (5.7)	9 (6.0)	5 (3.2)					NR	NR
	Asian	25 (15.8)	25 (16.7)	22 (14.0)					NR	NR
	Indigenous	NR	NR	NR					NR	NR
	Other	5 (3.2)	2 (1.3)	1 (0.6)					NR	NR
Exacerbations in prior year, mean (SD)		2.27 (2.25)	1.85 (1.43)	2.37 (2.29)	2.07 (1.58)	2.07 (2.66)	2.31 (2.07)	2.02 (1.86)	2.17 (2.24)	2.01 (2.08)
Disease duration, mean years (SD)		21.96 (16.46)	23.95 (15.73)	20.21 (13.43)	20.21 (13.43)	NR	NR	NR	19.2 (13.0)	20.8 (14.8)
Pre-BD FEV_1	Liters (SD)	1.82 (0.55)	1.79 (0.52)	1.85 (0.53)	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.63 (0.61)	1.53 (0.53)
	% predicted normal (SD)	60.96 (10.72)	61.23 (11.00)	60.76 (10.39)	58.43 (13.22)	58.38 (13.52)	58.35 (13.87)	58.51 (13.52)	52.69 (15.14)	51.64 (15.28)
High ICS dose level, n (%)		NR	NR	NR	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	NR	NR
OCS dose (mg/day), mean (SD)		NR	NR	NR	N/A	N/A	N/A	N/A	11.75 (6.31)	10.75 (5.90)
ACQ-5 Score*, mean (SD)		2.69 (0.80)	2.73 (0.82)	2.80 (0.83)	2.71 (0.73)	2.76 (0.80)	2.77 (0.77)	2.77 (0.76)	2.58 (1.09)	2.42 (1.24)
AQLQ Score†, mean (SD)		4.12 (1.10)	4.03 (1.15)	3.91 (1.13)	4.26 (1.02)	4.31 (1.08)	4.30 (1.03)	4.28 (1.05)	NR	NR
Asthma Symptom Score‡, mean (SD)		AM: 1.17 (0.79); PM: 1.32 (0.81)	AM: 1.24 (0.81); PM: 1.42 (0.79)	AM: 1.25 (0.78); PM: 1.47 (0.85)	NR	NR	NR	NR	NR	NR
Blood eosinophil count, mean cells/µL (SD)		342.3 (300.0)	361.1 (352.7)	322.9 (245.1)	370 (338)	349 (345)	391 (419)	351 (369)	325 (298)	370 (316)
Total IgE, mean IU/mL (SD)		NR	NR	NR	394 (625)	461 (818)	448 (797)	415 (701)	NR	NR
FeNO, mean ppb (SD)		NR	NR	NR	34.47 (28.54)	34.45 (34.91)	38.39 (38.00)	34.01 (29.74)	39.62 (34.12)	35.55 (28.34)
Atopic dermatitis, n (%)		16 (10.4)	10 (6.7)	16 (10.4)	35 (11.0)	61 (9.7)	38 (11.8)	62 (9.8)	10 (9.3)	11 (10.7)
Allergic rhinitis, n (%)		102 (66.2)	99 (66.4)	94 (61.0)	221 (69.7)	421 (66.7)	225 (70.1)	438 (69.2)	61 (57.0)	58 (56.3)

Trial	Phase 2b[§]			LIBERTY ASTHMA QUEST				LIBERTY ASTHMA VENTURE	
Asthma Population	**Moderate-to-Severe**			**Moderate-to-Severe**				**OCS-dependent**	
Arms	**PBO**	**DUP 200 mg**	**DUP 300 mg**	**PBO 1.14 ml**	**DUP 200 mg**	**PBO 2.0 ml**	**DUP 300 mg**	**PBO**	**DUP 300 mg**
Nasal polyposis, n (%)	18 (11.7)	25 (16.8)	30 (19.5)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	30 (28.0)	23 (22.3)
Chronic rhinosinusitis, n (%)	18 (11.7)	23 (15.4)	32 (20.8)					38 (35.5)	33 (32.0)
Baseline characteristics not reported: Asthma severity, 1 or 2 or ≥3 exacerbations in the prior year, Th2 status, allergic status, OCS use (n), medium ICS dose,									

ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, BMI: body mass index, DUP: dupilumab, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, IgE: immunoglobulin E, IU: international units, kg/m^2: kilograms per meter squared, mg: milligram, mL: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, PBO: placebo, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, ppb: parts per billion, SD: standard deviation, µL: microliter

* Higher scores indicate less control; a global score ranging from 0 to 6 is calculated. The MCID is 0.5.

† Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5.

‡ Lower scores indicate more mild symptoms; AM and PM scores are calculated ranging from 0 to 4.

§ Dupilumab arms presented here are Q2W: the FDA recommended dosing schedule. Q4W arms not presented.

Table D3.5. Baseline Characteristics: Dupilumab Blood Eosinophil Subgroups[16]

Trial		Phase 2b[§]		
Asthma Population		Moderate-to-Severe		
Arms		Overall	EOS ≥300	EOS <300
N		776	325	451
Age, years (SD)		48.6 (13.0)	48.0 (12.8)	49.1 (13.0)
Female sex, n (%)		490 (63)	197 (61)	293 (65)
BMI, kg/m^2 (SD)		29.45 (6.34)	28.97 (6.21)	29.79 (6.42)
Race, n (%)	White	607 (78)	247 (76)	360 (80)
	Black	42 (5)	14 (4)	28 (6)
	Asian	115 (15)	60 (18)	55 (12)
	Indigenous	2 (<1)	1 (<1)	1 (<1)
	Other	10 (1)	3 (1)	7 (2)
Exacerbations in prior year, mean (SD)		2.17 (2.14)	2.37 (2.34)	2.02 (1.98)
Disease duration, mean years (SD)		22.03 (15.42)	20.22 (14.46)	23.33 (15.96)
Pre-BD FEV_1	Liters (SD)	1.84 (0.54)	1.82 (0.56)	1.86 (0.53)
	% predicted normal (SD)	60.77 (10.72)	59.16 (11.08)	61.94 (10.31)
High ICS dose + LABA, n (%)		384 (51)	174 (55)	210 (48)
ACQ-5 Score*, mean (SD)		2.74 (0.81)	2.73 (0.85)	2.75 (0.79)
AQLQ Score†, mean (SD)		4.02 (1.09)	3.98 (1.16)	4.04 (1.04)
Asthma Symptom Score‡, mean (SD)		AM: 1.25 (0.80); PM: 1.44 (0.81)	AM: 1.26 (0.80); PM: 1.48 (0.82)	AM: 1.25 (0.79); PM: 1.40 (0.80)
Blood eosinophil count, mean cells/µL (SD)		347.46 (427.59)	590.09 (572.92)	172.02 (69.90)
Total IgE, mean IU/mL (SD)		435.05 (753.88)	558.93 (931.65)	345.58 (578.14)
FeNO, mean ppb (SD)		39.10 (35.09)	51.70 (42.40)	29.73 (24.66)
Atopic dermatitis, n (%)		79 (10)	37 (11)	42 (10)
Allergic rhinitis, n (%)		494 (65)	209 (65)	285 (65)
Nasal polyposis, n (%)		125 (16)	85 (26)	40 (9)
Baseline characteristics not reported: asthma severity, 1-2 or ≥3 exacerbations in prior year, medium ICS dose level, OCS use, Th2 status, allergic status, comorbid chronic rhinosinusitis				

ACQ-6: Asthma Control Questionnaire 6, AQLQ: Asthma Quality of Life Questionnaire, BMI: body mass index, DUP: dupilumab, EOS: blood eosinophil count, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, IgE: immunoglobulin E, IU: international units, kg/m^2: kilograms per meter squared, LABA: long-acting beta agonists, mg: milligram, mL: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, PBO: placebo, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, ppb: parts per billion, SD: standard deviation, µL: microliter

* Higher scores indicate less control; a global score ranging from 0 to 6 is calculated. The MCID is 0.5.

† Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5.

‡ Lower scores indicate more mild symptoms; AM and PM scores are calculated ranging from 0 to 4.

§ Includes the dupilumab Q4W arms

Table D3.6. Baseline Characteristics: Dupilumab Allergic Asthma Subgroups[76,82]

Trial	LIBERTY ASTHMA QUEST							
Allergic Subgroup	**Allergic**				**Non-Allergic**			
Arms	**1.14 PBO**	**200 mg**	**2.0 PBO**	**300 mg**	**1.14 PBO**	**200 mg**	**2.0 PBO**	**300 mg**
N	183	360	179	361	134	271	142	272
Age, years (SD)	44.0 (16.8)	45.5 (16.0)	44.1 (14.9)	43.9 (15.8)	54.0 (11.8)	51.0 (13.7)	53.2 (12.8)	52.7 (13.6)
Female sex, n (%)	101 (55.2)	196 (54.4)	114 (63.7)	216 (59.8)	97 (72.4)	191 (70.5)	104 (73.2)	178 (65.4)
BMI, kg/m^2 (SD)	29.3 (7.35)	28.47 (6.35)	28.78 (6.88)	28.91 (6.91)	30.39 (7.09)	29.82 (6.67)	29.76 (7.02)	29.27 (6.37)
Severe exacerbations in prior year, mean (SD)	1.89 (1.48)	1.98 (2.99)	2.22 (1.99)	1.79 (1.33)	2.32 (1.68)	2.18 (2.16)	2.43 (2.17)	2.33 (2.35)
Pre-BD FEV$_1$, liters (SD)	1.84 (0.64)	1.85 (0.64)	1.84 (0.61)	1.88 (0.58)	1.66 (0.55)	1.70 (0.58)	1.64 (0.49)	1.66 (0.61)
ACQ-5 Score*, mean (SD)	2.69 (0.69)	2.73 (0.82)	2.73 (0.76)	2.74 (0.78)	2.75 (0.77)	2.80 (0.77)	2.81 (0.79)	2.80 (0.74)
Blood eosinophil count, median cells/µL (IQR)	290 (150 - 490)	240 (120 - 470)	260 (160-440)	240 (140 - 430)	250 (130-470)	250 (120 - 460)	270 (120-470)	270 (130-510)
Total IgE, median IU/mL (IQR)	337 (147-629)	304 (137-835.5)	315 (142-763)	326 (152-762)	60 (24-147)	63 (24 -135)	67 (24-154)	64 (24-150)
FeNO, median ppb (IQR)	27 (15- 50)	25 (16-45)	30 (17.5-53)	24 (14-42)	24 (14-42)	22 (13-36)	22.5 (13.5-39.5)	24 (14-43)
Atopic dermatitis, n (%)	21 (11.5)	48 (13.3)	32 (17.9)	42 (11.6)	14 (10.4)	13 (4.8)	6 (4.2)	20 (7.4)
Allergic rhinitis, n (%)	142 (77.6)	265 (73.6)	140 (78.2)	284 (78.7)	79 (59)	156 (57.6)	85 (59.9)	154 (56.6)
Baseline characteristics not reported: Race, asthma severity, 1-2 or ≥3 exacerbations in prior year, disease duration, pre-BD FEV$_1$ (% predicted normal), ICS dose level, OCS use, AQLQ score, Asthma Symptom Score, Th2 status, comorbid nasal polyposis, or chronic rhinosinusitis								

ACQ-6: Asthma Control Questionnaire 6, AQLQ: Asthma Quality of Life Questionnaire, BMI: body mass index, DUP: dupilumab, EOS: blood eosinophil count, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, IgE: immunoglobulin E, IU: international units, IQR: interquartile range, kg/m^2: kilograms per meter squared, mg: milligram, mL: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, PBO: placebo, pre-BD FEV$_1$: prebronchodilator forced expiratory volume in 1 second, ppb: parts per billion, SD: standard deviation, µL: microliter

* Higher scores indicate less control; a global score ranging from 0 to 6 is calculated. The MCID is 0.5.

Table D3.7. Baseline Characteristics: Omalizumab Trials[21,23]

Trial		EXTRA		INNOVATE	
Asthma Population		Severe allergic		Severe persistent	
Arms		PBO	OMA	PBO	OMA
N		421	427	210	209
Age, years (SD)		45.3 (13.9)	43.7 (14.3)	43.3 (13.49)	43.4 (13.29)
Female sex, n (%)		295 (70.1)	262 (61.4)	138 (65.7)	141 (67.5)
BMI, kg/m^2 (SD)		31.5 (7.3)	32.0 (7.8)	NR	NR
Race, n (%)	White	318 (75.5)	313 (73.3)	164 (78.1)	163 (78.0)
	Black	86 (20.4)	90 (21.1)	14 (6.7)	14 (6.7)
	Asian	11 (2.6)	12 (2.8)	3 (1.4)	2 (1.0)
	Indigenous	1 (0.2)	3 (0.7)	NR	NR
	Other	5 (1.2)	9 (2.1)	29 (13.8)	30 (14.4)
Exacerbations in prior year*, n (%)	Mean (SD)	1.9 (1.5)	2.0 (2.2)	2.41 (1.09)	2.64 (1.56)
	1 or 2	NR	NR	132 (62.9)	121 (57.9)
	≥3	NR	NR	78 (37.1)	86 (41.1)
Disease duration, mean years (SD)		24.7 (15.8)	22.8 (15.4)	22.7 (14.72)	23.3 (15.23)
Pre-BD FEV$_1$, % predicted normal (SD)		64.4 (13.9)	65.4 (15.2)	61.6 (13.83)	61.0 (14.42)
ICS dose, mean mg/µL		NR	NR	2359	2301
OCS use, n (%)		73 (17.1)	71 (16.9)	42 (20.0)	49 (23.4)
AQLQ Score†, mean (SD)		3.9 (1.1)	4.0 (1.1)	3.9 (1.12)	3.9 (1.05)
Asthma Symptom Score‡, mean (SD)		3.9 (1.8)	3.9 (1.8)	3.3 (2.04)	3.2 (2.12)
Total IgE, mean IU/mL (SD)		175.1 (133.7)	178.7 (134.5)	189.6 (153.1)	197.6 (145.2)
FeNO, mean ppb (SD)		29.2 (29.7)	28.5 (26.9)	NR	NR
Baseline characteristics not reported: Asthma severity, baseline eosinophil count, pre-BD FEV$_1$ (liters), ACQ-5 or 6, ICS dose level (medium or high), OCS dose, Th2 status, comorbid atopic dermatitis, allergic rhinitis, nasal polyposis, or chronic rhinosinusitis					

ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, FeNO: fractional exhaled nitric oxide, ICS: inhaled corticosteroids, IgE: immunoglobulin E, IU: international units, kg/m^2: kilograms per meter squared, mg: milligram, mL: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, OMA: omalizumab, PBO: placebo, pre-BD FEV$_1$: prebronchodilator forced expiratory volume in 1 second, ppb: parts per billion, SD: standard deviation, µL: microliter

* For INNOVATE, exacerbations in the past 14 months

† Scores range from 1 to 7; higher scores indicate better asthma-related quality of life

‡ Scores range from 0 (no symptoms) to 4 (worst possible symptoms)

§ Based off of inclusion criteria

Table D3.8. Efficacy Outcomes: Tezepelumab[6-8,29,73,74,77-81]

Trial		PATHWAY				NAVIGATOR		SOURCE	
Follow-up		52 weeks				52 weeks		48 weeks	
Arms		PBO	TEZ 70 mg	TEZ 210 mg	TEZ 280 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
N		138	138	137	137	531	528	76	74
AAER	≥1 exacerbation, n (%)	43 (31.2)	30 (21.7)	21 (15.3)	25 (18.2)	319 (60.1)	231 (43.8)	NR	NR
	Events per patient year (95%CI)	0.72 (0.61, 0.86)*	0.27 (0.20, 0.36)*	0.20 (0.14, 0.28)*	0.23 (0.17, 0.32)*	2.10 (1.84, 2.39)	0.93 (0.80, 1.07)	2.00 (1.46, 2.74)	1.38 (0.98, 1.95)
	Relative reduction v. placebo, % (95%CI); p-value	REF	62 (42, 75)*; p<0.001	71 (54, 82)*; p<0.001	66 (47, 79)*; p<0.001	REF	56 (47, 63); p<0.001	REF	31 (-9, 56); p=0.11
Annualized Rate of Severe Exacerbations	≥1 severe event, n (%)	9 (6.5)	5 (3.6)	3 (2.2)	4 (2.9)	NR		NR	
	Events per patient year (95%CI)	0.14 (0.08, 0.22)	0.04 (0.01, 0.09)	0.02 (0.00, 0.07)	0.03 (0.01, 0.08)				
	Difference v. placebo, % (95%CI); p-value	REF	74 (3, 93); p=0.045	86 (29, 97); p=0.017	74 (-10, 94); p=0.067				
Pre-BD FEV_1 (% predicted)	N evaluated	131	130	121	116	NR		NR	
	Change from baseline, LS mean	-1.60	6.71	7.90	8.84				
	Difference v. placebo (95%CI); p-value	REF	8.30 (2.31, 14.30); p=0.007	9.50 (3.45, 15.56); p=0.002	10.44 (4.37, 16.51); p<0.001				
Pre-BD FEV_1 (Liters)	N evaluated	131	130	121	116	531	528	64	65
	Change from baseline, LS mean (SE)	−0.06	0.07	0.08	0.1	0.23 (0.02)	0.09 (0.02)	-0.04 (0.05)	0.21 (0.05)
	Difference v. placebo (95%CI); p-value	REF	0.12 (0.02, 0.22); p=0.015	0.13 (0.03, 0.23); p=0.009	0.15 (0.05, 0.25); p=0.002	REF	0.13 (0.08, 0.18); p<0.001	REF	0.26 (0.13, 0.39); NR
Post-BD FEV_1 (Liters)	N evaluated	130	130	121	115	NR		NR	
	Change from baseline, LS mean	–0.06	0.12	0.1	0.13				
ACQ-6 Score	N evaluated	53	52	44	49	531	528	68	66
	Change from baseline, LS mean	-0.91	-1.17	-1.2	-1.22	-1.22 (0.05)	-1.55 (0.05)	-0.51 (0.12)	-0.87 (0.13)

Trial		PATHWAY				NAVIGATOR		SOURCE	
Follow-up		52 weeks				52 weeks		48 weeks	
Arms		PBO	TEZ 70 mg	TEZ 210 mg	TEZ 280 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
	Difference v. placebo (95%CI); p-value	REF	-0.26 (-0.52, 0.01); p=0.059	-0.29 (-0.56, -0.01); p=0.039	-0.31 (-0.58, -0.04); p=0.024	REF	-0.33 (-0.46, -0.20); p<0.001	REF	0.37 (-0.02, 0.71); NR
AQLQ Score	N evaluated	47	51	41	48	529	527	NR	
	Change from baseline, LS mean	0.97	1.12	1.17	1.32	1.15 (0.05)	1.49 (0.05)		
	Difference v. placebo (95%CI); p-value	REF	0.14 (-0.13, 0.42); p=0.309	0.20 (-0.09, 0.48); p=0.185	0.34 (0.06, 0.63); p=0.017	REF	0.34 (0.20, 0.47); p<0.001		
Asthma-related Hospitalizations	n (%)	9 (6.5)	5 (3.6)	3 (2.2)	4 (2.9)	37 (7.0)	17 (3.2)	NR	
	Rate over treatment period (95%CI)	0.14	0.04	0.02	0.04	0.19 (0.12, 0.30)	0.03 (0.01, 0.06)		
	Difference v. placebo (95%CI); p-value	REF	0.26 (0.08, 0.92); NR	0.16 (0.04, 0.70); NR	0.26 (0.07, 0.98); NR	REF	0.15 (0.07, 0.33); NR		
Asthma-related ED visits†	n (%)	NR				50 (9.4)	23 (4.4)	NR	
	Rate over treatment period					0.28 (0.20, 0.39)	0.06 (0.04, 0.09)		
	Difference v. placebo (95%CI); p-value					REF	0.21 (0.12, 0.37); NR		
Efficacy outcomes not reported: Post-BD FEV_1 (difference v. placebo), Reduction in OCS use-related outcomes									

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, ED: emergency department, LS mean: least-squares mean, mg: milligrams, n: number, N: total number, NR: not reported, OCS: oral corticosteroids, PBO: placebo, post-BD FEV_1: post-bronchodilator forced expiratory volume in 1 second, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, REF: reference, SE: standard error, TEZ: tezepelumab

* 90% confidence interval

Table D3.9. Efficacy Outcomes: Dupilumab I[16,83]

Trial		Phase 2b		
Follow-up		24 weeks		
Arms		PBO	DUP 200 mg	DUP 300 mg
N		158	150	157
Annualized Rate of Severe Exacerbations	≥1 severe event, n/N (%)	41/158 (26)	13/148 (9)	17/156 (11)
	Event rate estimate (95%CI)	0.897 (0.619, 1.3)	0.269 (0.157, 0.461)	0.265 (0.157, 0.445)
	Difference v. placebo, % (95%CI); p-value	REF	70 (43.5, 84.1); p=0.0002	70.5 (45.4, 84.1); p<0.0001
Pre-BD FEV_1 (% predicted)	N evaluated	125	135	143
	Change from baseline, LS mean	0.13 (0.03)	0.29 (0.03)	0.28 (0.03)
	Difference v. placebo (95%CI); p-value	REF	0.16 (0.07, 0.24); p=0.0005	0.16 (0.07, 0.24); p=0.0004
Pre-BD FEV_1 (Liters)	N evaluated	125	135	143
	Change from baseline, LS mean (SE)	7.01 (1.87)	16.62 (1.88)	17.34 (1.83)
	Difference v. placebo (95%CI); p-value	REF	9.60 (4.47, 14.74); p=0.0003	10.33 (5.26, 15.40); p<0.0001
ACQ-5 Score	N evaluated	127	134	145
	Change from baseline, LS mean	-1.14 (0.8)	-1.49 (0.08)	-1.45 (0.08)
	Difference v. placebo (95%CI); p-value	REF	-0.35 (-0.57, -0.15)*; p=0.0015	-0.31 (-0.52, -0.09)*; p=0.0049
AQLQ Score	N evaluated	127	132	141
	Change from baseline, LS mean	0.88 (0.09)	1.20 (0.09)	1.24 (0.08)
	Difference v. placebo (95%CI); p-value	REF	0.31 (0.08-0.55); 0.009	0.36 (0.12-0.59); 0.0027
Efficacy outcomes not reported: AAER, post-BD FEV_1, asthma-related hospitalizations and/or emergency department visits				

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, ED: emergency department, DUP: dupilumab, LS mean: least-squares mean, mg: milligrams, n: number, N: total number, NR: not reported, OCS: oral corticosteroids, PBO: placebo, post-BD FEV_1: post-bronchodilator forced expiratory volume in 1 second, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, REF: reference, SE: standard error

* 95% CI are digitized, interpret with caution

Table D3.10. Efficacy Outcomes: Dupilumab II[17,75,76,82,84-86]

Trial		LIBERTY ASTHMA QUEST				LIBERTY ASTHMA VENTURE	
Follow-up		52 weeks				24 weeks	
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO	DUP 300 mg
N		317	631	321	633	107	103
Annualized Rate of Severe Exacerbations	Events per patient year (95%CI)	0.87 (0.72, 1.05)	0.46 (0.39, 0.53)	0.97 (0.81, 1.16)	0.52 (0.45, 0.61	NR	NR
	Estimate (95%CI)	NR	NR	NR	NR	1.60 (1.25,2.04)	0.65 (0.44, 0.96)
	Difference v. placebo, % (95%CI); p-value	REF	47.7 (33.8, 58.7); p<0.001	REF	46.0 (32.0, 57.0); p<0.001	REF	59.3 (37, 74); p<0.0001
Pre-BD FEV_1 (% predicted)	N evaluated	307	611	313	610	NR	NR
	Change from baseline, LS mean	12.11 (1.56)	21.34 (1.13)	13.67 (1.56)	23.08 (1.13)		
	Difference v. placebo (95%CI); p-value	REF	9.23 (5.54, 12.92); NR	REF	9.41 (5.74, 13.07); p<0.001		
Pre-BD FEV_1 (Liters)	N evaluated	240	477	250	488	NR	NR
	Change from baseline, LS mean (SE)	0.16 (0.02)	0.36 (0.02)	0.22 (0.02)	0.35 (0.02)	0.01 (0.05)	0.22 (0.05)
	Difference v. placebo (95%CI); p-value	REF	0.20 (0.14-0.25); <0.0001	REF	0.13 (0.08-0.19); <0.0001	REF	0.22 (0.09 to 0.34); p<0.001
Post-BD FEV_1 (Liters)	N evaluated	239	499	255	494	NR	NR
	Change from baseline, LS mean	-0.04 (0.02)	0.15 (0.02)	0.01 (0.02)	0.14 (0.02)		
	Difference v. placebo (95%CI); p-value	REF	0.19 (0.14-0.24); <0.0001	REF	0.13 (0.08-0.18); <0.0001		
ACQ-5 Score*	N evaluated	NR	NR	NR	NR	NR	NR
	Change from baseline, LS mean	-1.15 (0.06)	-1.54 (0.04)	-1.30 (0.06)	-1.52 (0.04)	NR	NR
	Difference v. placebo (95%CI); p-value	REF	-0.39 (-0.53, -0.25)	REF	-0.22 (-0.36, -0.08)	REF	-0.47 (-0.76, -0.18)
AQLQ Score	N evaluated	NR	NR	NR	NR	NR	NR
	Change from baseline, LS mean	0.99 (0.06)	1.28 (0.04)	1.03 (0.06)	1.29 (0.04)		
	Difference v. placebo (95%CI); p-value	REF	0.29 (0.15, 0.44); NR	REF	0.26 (0.12, 0.40); NR		

Trial		LIBERTY ASTHMA QUEST				LIBERTY ASTHMA VENTURE	
Follow-up		52 weeks				24 weeks	
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO	DUP 300 mg
Asthma-related Hospitalizations and ED Visits	Arm	Combined PBO		Combined DUP		NR	NR
	Rate over treatment period (95%CI)	0.065 (0.047, 0.090)		0.035 (0.025, 0.048)			
	Difference v. placebo (95%CI); p-value	REF		46.8 (18.4, 65.3); NR			
Reduction in OCS dose without losing asthma control	Change from baseline, LS mean (SE)	N/A		N/A		-41.9 (4.6)	-70.1 (4.9)
	Difference v. placebo (95%CI); p-value					REF	-28.2 (-40.7, -15.8); p<0.001
≥50% Reduction in OCS dose	Proportion, n (%)					57 (53.3)	82 (79.6)
	Odds ratio v. placebo (95%CI); p-value					REF	3.98 (2.06, 7.67); p<0.001
100% Reduction in OCS dose	Proportion, n (%)					31 (29.2)	54 (52.4)
	Odds ratio v. placebo (95%CI); p-value					REF	2.74 (1.47, 5.10); p=0.002
Efficacy outcomes not reported: AAER, ≥1 severe asthma exacerbation, asthma-related emergency department visits, hospitalization events (n)							

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, ED: emergency department, DUP: dupilumab, LS mean: least-squares mean, mg: milligrams, ml: milliliter, n: number, N: total number, N/A: not applicable, NR: not reported, OCS: oral corticosteroids, PBO: placebo, post-BD FEV_1: post-bronchodilator forced expiratory volume in 1 second, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, REF: reference, SE: standard error

* For LIBERTY ASTHMA QUEST: ACQ-5 evaluated at 24 weeks

Table D3.11. Efficacy Outcomes: Dupilumab III[32,68,84,87]

Trial		TRAVERSE							
Arms		TRAVERSE		from Phase 2b		from QUEST		from VENTURE	
		PBO/DUP	DUP/DUP	PBO/DUP	DUP/DUP	PBO/DUP	DUP/DUP	PBO/DUP	DUP/DUP
Follow-up		48-96 weeks							
N		223	448	111	421	517	1013	97	90
AAER	Events per patient year (95%CI)	0.26	0.27	0.314	0.33	0.351	0.331	0.25	0.25
	Relative reduction v. placebo, % (95%CI); p-value	NR	NR	NR	NR	NR	NR	NR	NR
Annualized Rate of Severe Exacerbations	Events per patient year (95%CI)	NR	NR	0.314 (NR)	0.330 (NR)	0.351 (NR)	0.331 (NR)	NR	NR
	Difference v. placebo, % (95%CI); p-value			NR	NR	NR	NR		
Pre-BD FEV_1 (Liters)	N evaluated	NR	NR	NR	NR	NR	NR	NR	NR
	Change from baseline, LS mean (SE)	1.75 (0.55)	1.81 (0.60)						
	Difference v. placebo (95%CI); p-value	NR	NR						
100% Reduction in OCS dose*	Proportion, n (%)	21 (100)	31 (94)	NR	NR	NR	NR	29 (29.9)	48 (53.3)
	Odds ratio v. placebo (95%CI); p-value	NR	NR					NR	NR
Efficacy outcomes not reported: ≥1 asthma exacerbation, ≥1 severe exacerbation, pre-BD FEV_1 (% predicted), post-BD FEV_1, ACQ-5 score, AQLQ score, asthma-related hospitalizations and/or emergency department visits, reduction in OCS dose without losing asthma control, ≥50% Reduction in OCS dose									

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, ED: emergency department, DUP: dupilumab, LS mean: least-squares mean, n: number, N: total number, NR: not reported, OCS: oral corticosteroids, PBO: placebo, post-BD FEV_1: post-bronchodilator forced expiratory volume in 1 second, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, REF: reference, SE: standard error

* Patients that remained OCS-free in TRAVERSE

Table D3.12. Efficacy Outcomes: Omalizumab[21,23,69]

Trial		EXTRA		INNOVATE	
Follow-up		48 weeks		28 weeks	
Arms		PBO	OMA	PBO	OMA
N		421	427	210	209
Asthma Exacerbation Rate*	≥1 exacerbation, n (%)	179 (42.5)	152 (35.6)	NR	NR
	Rate (95%CI)	0.88	0.66	0.91 (0.73, 1.14)	0.68 (0.53, 0.87)
	Relative reduction v. placebo, % (95%CI); p-value	REF	25 (8-39); p=0.006	REF	26.2 (0.02, 44.8); p=0.042
Severe Exacerbation Rate	≥1 severe event, n (%)	NR	NR	55 (26.2)	35 (16.8)
	Rate (95%CI)			0.48 (0.36, 0.64)	0.24 (0.17, 0.35)
	Difference v. placebo, % (95%CI); p-value			REF	50 (NR); p=0.002
Pre-BD FEV_1 (% predicted)	N evaluated	NR	NR	NR	NR
	Change from baseline, LS mean			NR	NR
	Difference v. placebo (95%CI); p-value			REF	2.8 (NR); p=0.043
Pre-BD FEV_1 (Liters)	N evaluated	NR	NR	NR	NR
	Change from baseline, LS mean (SE)			0.096 (NR)	0.19 (NR)
	Difference v. placebo (95%CI); p-value			NR	NR
AQLQ Score	N evaluated	NR	NR	205	204
	Change from baseline, LS mean	0.92	1.15	0.46	0.91
	Difference v. placebo (95%CI); p-value	REF	0.29 (0.15, 0.43); p=0.005	REF	0.45 (NR); p<0.001
Asthma-related Hospitalizations, n (%)	n (%)	NR	NR	25	13
	Rate over treatment period (95%CI)			0.12 (NR)	0.06 (NR)
	Difference v. placebo (95%CI); p-value			REF	0.540 (0.250, 1.166); p=0.117
Asthma-related ED visits, n (%)	n (%)	NR	NR	14	9
	Rate over treatment period			0.06	0.04
	Difference v. placebo (95%CI); p-value			REF	0.659 (0.208, 2.094); p=0.480

Efficacy outcomes not reported: Post-BD FEV_1 (liters) and ACQ-5 score

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, ED: emergency department, LS mean: least-squares mean, mg: milligrams, ml: milliliter, n: number, N: total number, NR: not reported, OCS: oral corticosteroids, OMA: omalizumab, PBO: placebo, post-BD FEV_1: post-bronchodilator forced expiratory volume in 1 second, pre-BD FEV_1: prebronchodilator forced expiratory volume in 1 second, REF: reference, SE: standard error

* For EXTRA: Rate of "protocol-defined" asthma exacerbations. For INNOVATE: Rate of "clinically significant" asthma exacerbations.

Table D3.13. Safety Outcomes: Tezepelumab [6-8,29,73,74,77-81]

Trial		PATHWAY									
Follow-up		64 weeks									
Arms		PBO		TEZ 70 mg		TEZ 210 mg		TEZ 280 mg		TEZ Overall	
N		138		138		137		137		412	
Type of Events		Overall	Non-Asthma-Related	Overall	Non-Asthma-Related	Overall	Non-Asthma-Related	Overall	Non-Asthma-Related	Overall	Non-Asthma-Related
Adverse Events, n (%)	Overall	91 (65.9)	82 (59.4)	93 (67.4)	83 (60.1)	90 (65.7)	86 (62.8)	89 (65.0)	82 (59.9)	272 (66.0)	251 (60.9)
	Serious	18 (13.0)	11 (8)	17 (12.3)	13 (9.4)	13 (9.5)	12 (8.8)	18 (13.1)	15 (10.9)	48 (11.7)	40 (9.7)
	Grade 3/4	28 (20.3)	16 (11.6)	26 (18.8)	20 (14.5)	29 (21.2)	23 (16.8)	21 (15.3)	13 (9.5)	76 (18.4)	56 (13.6)
Treatment-related Adverse Events, n (%)	Overall	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Serious	0 (0)	NR	2 (1.4)	NR	1 (0.7)	NR	0 (0)	NR	3 (0.7)	NR
Discontinuation, n (%)	Overall	8 (5.8)	NR	11 (8.0)	NR	15 (10.9)	NR	22 (16.1)	NR	56 (13.6)	NR
	AE-related	1 (0.7)	1 (0.7)	0 (0)	0 (0)	2 (1.5)	2 (1.5)	3 (2.2)	3 (2.2)	5 (1.2)	5 (1.2)
Mortality, n (%)	Overall	0 (0)	0 (0)	1 (0.7)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	1 (0.2)
	Asthma-related			0 (0)	0 (0)					0 (0)	0 (0)
	AE-related			0 (0)	0 (0)					0 (0)	0 (0)
	Treatment-related			1 (0.7)	1 (0.7)					1 (0.2)	1 (0.2)
Adverse Events of Special Interest											
Asthma, n (%)		50 (36.2)	NR	35 (25.4)	NR	27 (19.7)	NR	38 (27.7)	NR	100 (24.3)	NR
Nasopharyngitis, n (%)		16 (11.6)	NR	19 (13.8)	NR	19 (13.9)	NR	15 (10.9)	NR	53 (12.9)	NR
Bronchitis, n (%)		7 (5.1)	NR	8 (5.8)	NR	5 (3.6)	NR	9 (6.6)	NR	22 (5.3)	NR
Headache, n (%)		6 (4.3)	NR	6 (4.3)	NR	11 (8.0)	NR	5 (3.6)	NR	22 (5.3)	NR
Injection site reactions*, n (%)		5 (3.6)	NR	4 (2.9)	NR	4 (2.9)	NR	2 (1.5)	NR	NR	NR

Trial	PATHWAY				
Follow-up	64 weeks				
Arms	PBO	TEZ 70 mg	TEZ 210 mg	TEZ 280 mg	TEZ Overall
Safety outcomes not reported: Treatment-related discontinuation, sinusitis, influenza, upper respiratory tract infection, conjunctivitis					

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, TEZ: tezepelumab

* 1 ml syringe size

Table D3.14. Safety Outcomes: Tezepelumab II[6-8,29,73,74,77-81]

Trial		NAVIGATOR		SOURCE*	
Follow-up		52 weeks		48 weeks	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg
N		531	528	NR	NR
Adverse Events, n (%)	Overall	429 (80.8)	407 (77.1)	NR	NR
	Serious	73 (13.7)	52 (9.8)	NR	NR
	Grade 3/4	NR	NR	NR	NR
Discontinuation, n (%)	Overall	57 (10.7)	36 (6.8)	NR	NR
	AE-related	19 (3.6)	11 (2.1)	NR	NR
	Treatment-related	NR	NR	NR	NR
Mortality, n (%)	Overall	2 (0.4)	0 (0.0)	NR	NR
	Asthma-related	NR	NR	NR	NR
	AE-related	2 (0.4)	0 (0.0)	NR	NR
	Treatment-related	NR	NR	NR	NR
Adverse Events of Special Interest					
Asthma, n (%)		59 (11.1)	27 (5.1)	NR	NR
Nasopharyngitis, n (%)		114 (21.5)	113 (21.4)	NR	NR
Bronchitis, n (%)		33 (6.2)	25 (4.7)	NR	NR
Headache, n (%)		45 (8.5)	43 (8.1)	NR	NR
Sinusitis, n (%)		19 (3.6)	40 (7.5)	NR	NR
Influenza, n (%)		19 (3.6)†	22 (4.1)†	NR	NR
Upper respiratory tract infection, n (%)		87 (16.4)	59 (11.2)	NR	NR
Injection site reactions, n (%)		14 (2.6)	19 (3.6)	NR	NR
Safety outcomes not reported: Treatment-related adverse events, conjunctivitis					

AE: adverse event, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo, TEZ: tezepelumab

* No safety data reported for SOURCE to date

† Influenza-like illness

Table D3.15. Safety Outcomes: Dupilumab I[9,16,17,76]

Trial		Phase 2b			LIBERTY ASTHMA QUEST				VENTURE	
Follow-up		24 weeks			66 weeks				24 weeks	
Arms		PBO	DUP 200 mg	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO	DUP 300 mg
N		158	148	156	313	631	321	632	107	103
Adverse Events, n (%)	Overall	118 (75)	119 (80)	121 (78)	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	69 (64)	64 (62)
	Serious	9 (6)	10 (7)	13 (8)	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	6 (6)	9 (9)
Discontinuation, n (%)	Overall	12 (8)*	11 (7)*	7 (4)*	38 (12.1)	70 (11.1)	35 (10.9)	85 (13.4)	5 (5)	2 (2)
	AE-related	5 (3)	6 (4)	4 (3)	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	4 (4)	1 (1)
Mortality, n (%)	Overall	NR	NR	NR	3 (1.0)	1 (0.2)	0 (0)	4 (0.6)	0 (0)	0 (0)
	Asthma-related	NR	NR	NR	NR	NR	NR	NR	0 (0)	0 (0)
	AE-related	0	0	0	3 (1.0)	1 (0.2)	0 (0)	4 (0.6)	0 (0)	0 (0)
	Treatment-related	NR	NR	NR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse Events of Special Interest										
Nasopharyngitis, n (%)		15 (9)	15 (10)	16 (10)	NR	NR	NR	NR	NR	NR
Bronchitis, n (%)		16 (10)	11 (7)	19 (12)	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	6 (5.6)	7 (6.8)
Headache, n (%)		20 (13)	17 (11)	17 (11)	26 (8.3)	46 (7.3)	25 (7.8)	40 (6.3)	NR	NR
Sinusitis, n (%)		11 (7)	5 (3)	6 (4)	27 (8.6)	36 (5.7)	29 (9.0)	26 (4.1)	4 (3.7)	7 (6.8)
Influenza, n (%)		5 (3)	6 (4)	9 (6)	29 (9.3)	36 (5.7)	22 (6.9)	38 (6.0)	6 (6)	3 (3)
Upper respiratory tract infection, n (%)		28 (18)	22 (15)	20 (13)	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	NR	NR
Injection site reactions, n (%)		21 (13)	29 (20)	41 (26)	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	4 (4)	9 (9)
Conjunctivitis, n (%)		NR	NR	NR	all PBO: NR (2.3)		all DUP: NR (3.3)		NR (0.9)	NR (1.0)
Safety outcomes not reported: Grade 3/4 adverse events, treatment-related adverse events, treatment-related discontinuation, asthma										

AE: adverse event, DUP: dupilumab, mg: milligram, n: number, N: total number, NR: not reported, PBO: placebo

* Discontinued by week 24

Table D3.16. Safety Outcomes: Dupilumab II[32,68,87]

Trial		TRAVERSE					
Follow-up		96 weeks					
Arms		from Phase 2b		from QUEST		from VENTURE	
		PBO/DUP	DUP/DUP	PBO/DUP	DUP/DUP	PBO/DUP	DUP/DUP
N		111	421	517	1013	97	90
Adverse Events, n (%)	Overall	88 (79.3)	369 (87.6)	414 (80.1)	789 (77.9)	74 (76.3)	70 (77.8)
	Serious	14 (12.6)	42 (10.0)	48 (9.3)	106 (10.5)	12 (12.4)	10 (11.1)
Discontinuation, n (%)	Overall	NR	NR	NR	NR	NR	NR
	AE-related	3 (2.7)	19 (4.5)	12 (2.3)	31 (3.1)	4 (4.1)	5 (5.6)
	Treatment-related	NR	NR	NR	NR	NR	NR
Mortality, n (%)	Overall	0 (0)	3 (0.7)	0 (0)	1 (0.1)	0 (0)	0 (0)
	Asthma-related	NR	NR	NR	NR	NR	NR
	AE-related	0 (0)	3 (0.7)	0 (0)	1 (<0.1)	0 (0)	0 (0)
	Treatment-related	NR	NR	NR	NR	NR	NR
Adverse Events of Special Interest							
Nasopharyngitis, n (%)		27 (24.3)	109 (25.9)	99 (19.1)	191 (18.9)	17 (17.5)	16 (17.8)
Bronchitis, n (%)		15 (13.5)	80 (19.0)	63 (12.2)	118 (11.6)	9 (9.3)	14 (15.6)
Headache, n (%)		13 (11.7)	47 (11.2)	47 (9.1)	74 (7.3)	4 (4.1)	5 (5.6)
Influenza, n (%)		5 (4.5)	45 (10.7)	30 (5.8)	69 (6.8)	9 (9.3)	7 (7.8)
Upper respiratory tract infection, n (%)		18 (16.2)	60 (14.3)	65 (12.5)	130 (12.8)	8 (8.2)	6 (6.7)
Injection site reactions*, n (%)		38 (34.2)	65 (16.9)	50 (9.7)	57 (5.6)	7 (7.3)	2 (2.2)
Safety outcomes not reported: Grade 3/4 AEs, treatment-related AEs, asthma as an adverse event, sinusitis, conjunctivitis							

AE: adverse event, DUP: dupilumab, DUP/DUP: patients receiving dupilumab in the parent study receiving 300 mg Q2W of dupilumab in TRAVERSE, n: number, N: total number, NR: not reported, PBO: placebo, PBO/DUP: patients receiving placebo in the parent study receiving 300 mg Q2W of dupilumab in TRAVERSE

* Erythema and pruritis

Table D3.17. Safety Outcomes: Omalizumab[21,23]

Trial		EXTRA		INNOVATE	
Follow-up		48 weeks		28 weeks	
Arms		PBO	OMA	PBO	OMA
N		420	428	237	245
Adverse Events, n (%)	Overall	334 (79.5)	344 (80.4)	179 (75.5)	177 (72.2)
	Serious	44 (10.5)	40 (9.3)	37 (15.6)	29 (11.8)
Treatment-related Adverse Events, n (%)	Overall	NR	NR	22 (9.3)	29 (11.8)
	Serious	NR	NR	NR	NR
Discontinuation, n (%)	Overall	94 (22.3)	83 (19.4)	22 (9.3)	30 (12.2)
	AE-related	10 (2.4)	16 (3.7)	4 (1.7)	11 (4.5)
	Treatment-related	NR	NR	NR	NR
Mortality, n (%)	Overall	3 (0.7)*	0 (0)	NR	NR
	Asthma-related	NR	NR	NR	NR
	AE-related	NR	NR	NR	NR
	Treatment-related	1 (0.2)	0 (0)	NR	NR
Adverse Events of Special Interest					
Nasopharyngitis, n (%)		NR	NR	22 (9.3)	24 (9.8)
Headache, n (%)		NR	NR	22 (9.3)	17 (6.9)
Sinusitis, n (%)		NR	NR	18 (7.6)	14 (5.7)
Influenza, n (%)		NR	NR	13 (5.5)	11 (4.5)
Upper respiratory tract infection, n (%)		NR	NR	13 (5.5)	11 (4.5)
Injection site reactions, n (%)		13 (3.1)	5 (1.2)	3 (1.3)	13 (5.3)
Safety outcomes not reported: Grade 3/4 adverse events, asthma as an adverse event, bronchitis, conjunctivitis					

AE: adverse event, n: number, N: total number, NR: not reported, OMA: omalizumab, PBO: placebo

* 2 deaths occurred after the treatment period

Table D3.18. Blood Eosinophil Count Subgroup Outcomes: Tezepelumab I[6,29,77,79]

Trial		PATHWAY							
Blood Eosinophil Count, cells/µL		EOS ≥300		EOS <300		EOS ≥150		EOS <150	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
AAER*	N	71	68	67	69	105	103	33	34
	Events per patient year (95%CI)	0.65 (0.48, 0.87)	0.26 (0.15, 0.42)	0.80 (0.59, 1.04)	0.15 (0.07, 0.28)	0.66 (0.52, 0.84)	0.23 (0.15, 0.35)	0.92 (0.61, 1.32)	0.12 (0.03, 0.31)
	Diff v. placebo, % (95%CI); p-value	REF	0.40 (0.19, 0.85); NR	REF	0.19 (0.08, 0.46); NR	REF	0.34 (0.18, 0.65); NR	REF	0.17 (0.05, 0.64); NR
Pre-BD FEV_1* (liters)	N	69	58	58	63	102	90	29	31
	LS Mean	-0.10	0.11	-0.04	0.01	-0.10	0.07	-0.01	-0.02
	Diff vs. placebo (95%CI); p-value	REF	0.21 (0.06, 0.35); NR	REF	0.05 (-0.08, 0.19); NR	REF	0.18 (0.06, 0.29); NR	REF	-0.02 (-0.23, 0.19); NR
ACQ-6*	N	60	53	52	57	87	83	25	27
	LS Mean	-0.99	-1.45	-0.83	-1.09	-0.93	-1.27	-0.76	-1.06
	Diff vs. placebo (95%CI); p-value	REF	-0.46 (-0.79, -0.13); NR	REF	-0.26 (-0.57, 0.05); NR	REF	-0.35 (-0.61, -0.08); NR	REF	-0.30 (-0.75, 0.14); NR
AQLQ*	N	58	47	47	50	82	72	23	25
	LS Mean	1.04	1.38	0.86	1.18	0.93	1.22	0.89	1.33
	Diff vs. placebo (95%CI); p-value	REF	0.34 (-0.03, 0.71); NR	REF	0.32 (-0.01, 0.65); NR	REF	0.29 (0.00, 0.59); NR	REF	0.44 (-0.02, 0.89); NR

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, EOS: blood eosinophil count, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference, TEZ: tezepelumab

* Assessed at week 52

Table D3.19. Blood Eosinophil Count Subgroup Outcomes: Tezepelumab II[7,29,73,74,80,81]

Trial		NAVIGATOR							
Blood Eosinophil Count, cells/µL		EOS ≥300		EOS <300		EOS ≥150		EOS <150	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
AAER*	N	[2]	219	309	309	393	390	138	138
	Events per patient year (95%CI)	2.66 (2.18, 3.23)	0.79 (0.63, 1.00)	1.73 (1.46, 2.05)	1.02 (0.84, 1.23)	2.24 (1.93, 2.60)	0.89 (0.74, 1.05)	1.70 (1.32, 2.19)	1.04 (0.79, 1.37)
	Reduction v. placebo, % (95%CI); p-value	REF	70 (60, 78); NR	REF	41 (25, 54); p<0.001	REF	61 (51, 68); NR	REF	39 (12, 58); NR
Pre-BD FEV_1* (liters)	N	189	189	264	282	332	347	121	124
	LS Mean (SE)	0.14 (0.03)	0.37 (0.03)	0.06 (0.02)	0.13 (0.02)	0.11 (0.02)	0.28 (0.02)	0.07 (0.04)	0.10 (0.04)
	Diff vs. placebo (95%CI); p-value	REF	0.23 (0.15, 0.31)	REF	0.07 (0.00, 0.13)	REF	0.17 (0.11, 0.23)	REF	0.03 (−0.07, 0.13)
ACQ-6*	N	198	201	274	284	352	362	120	123
	LS Mean (SE)	-1.26 (0.07)	-1.78 (0.07)	-1.15 (0.06)	-1.36 (0.06)	-1.25 (0.05)	-1.66 (0.05)	-1.08 (0.09)	-1.17 (0.09)
	Diff vs. placebo (95%CI); p-value	REF	-0.50 (-0.69, 0.31); NR	REF	-0.21 (-0.37, -0.05); NR	REF	-0.41 (-0.56, -0.27); NR	REF	-0.09 (-0.33, -0.16); NR
AQLQ*	N	196	198	271	282	348	358	119	122
	LS Mean (SE)	1.21 (0.08)	1.71 (0.08)	1.10 (0.06)	1.31 (0.06)	1.21 (0.06)	1.62 (0.06)	0.96 (0.10)	1.07 (0.10)
	Diff vs. placebo (95%CI); p-value	REF	0.51 (0.30, 0.71); NR	REF	0.21 (0.04, 0.39); NR	REF	0.41 (0.26, 0.57); NR	REF	0.11 (-0.16, 0.37); NR

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, EOS: blood eosinophil count, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference, SE: standard error, TEZ: tezepelumab

* Assessed at week 52

Table D3.20. Blood Eosinophil Count Subgroup Outcomes: Tezepelumab III[8,29]

Trial		SOURCE							
Blood Eosinophil Count, cells/µL		EOS ≥300		EOS <300		EOS ≥150		EOS <150	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg	PBO	TEZ 210 mg
Daily OCS Dose*	N	24	28	52	46	52	47	24	27
	Cumulative odds ratio (95%CI)	REF	3.49 (1.16, 10.49)	REF	0.70 (0.33, 1.47)	REF	2.58 (1.16, 5.75)	REF	0.40 (0.14, 1.13)

95%CI: 95% confidence interval, EOS: blood eosinophil count, mg: milligram, N: total number, NR: not reported, OCS: oral corticosteroid, PBO: placebo, REF: reference, TEZ: tezepelumab

* Assessed at week 48

Table D3.21. Blood Eosinophil Count Subgroup Outcomes: Dupilumab I[16,83]

Trial		Phase 2b					
Blood Eosinophil Count, cells/µL		EOS ≥300			EOS <300		
Arms		PBO	DUP 200 mg	DUP 300 mg	PBO	DUP 200 mg	DUP 300 mg
Annualized Severe Asthma Exacerbation Rate*	N	68	65	64	90	85	93
	Estimate (95%CI)	1.044 (0.572, 1.904)	0.300 (0.133, 0.678)	0.201 (0.078, 0.517)	0.779 (0.493, 1.231)	0.253 (0.124, 0.516)	0.313 (0.170, 0.576)
	Relative risk reduction v. placebo, % (95%CI); p-value	REF	71.2 (24.3, 89.1); p=0.0116	80.7 (44.1, 93.3); p=0.0024	REF	67.6 (24.4, 85.9); p=0.0081	59.9 (16.1, 80.8); p=0.0152
Pre-BD FEV_1* (liters)	N	52	59	58	73	76	85
	LS Mean	0.22 (0.05)	0.38 (0.05)	0.38 (0.05)	0.09 (0.04)	0.23 (0.04)	0.23 (0.04)
	Diff vs. placebo (95%CI); p-value	REF	0.16 (0.02, 0.31); p=0.0264	0.16 (0.01, 0.30); p=0.0345	REF	0.14 (0.03, 0.25); p=0.0104	0.14 (0.03, 0.24); p=0.0109
ACQ-5*	N	52	59	58	75	75	87
	LS Mean	-1.17 (0.13)	-1.59 (0.12)	-1.72 (0.13)	-1.13 (0.10)	-1.46 (0.10)	-1.29 (0.10)
	Diff vs. placebo (95%CI); p-value	REF	-0.42 (-0.76, -0.07); p=0.0171	-0.55 (-0.90, -0.20); p=0.0021	REF	-0.33 (-0.61, -0.05); p=0.0201	-0.17 (-0.44, 0.10); p=0.2259
AQLQ*	N	53	58	56	74	74	85
	LS Mean (SE)	0.79 (0.13)	1.46 (0.13)	1.57 (0.13)	1.01 (0.11)	1.06 (0.11)	1.07 (0.11)
	Diff vs. placebo (95%CI); p-value	REF	0.67 (0.31, 1.03); p=0.0003	0.78 (0.42, 1.15); p<0.0001	REF	0.05 (-0.26, 0.36); p=0.74	0.06 (-0.24, 0.36); p=0.6899

Trial	Phase 2b					
Blood Eosinophil Count, cells/µL	EOS ≥300			EOS <300		
Arms	PBO	DUP 200 mg	DUP 300 mg	PBO	DUP 200 mg	DUP 300 mg

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, DUP: dupilumab, EOS: blood eosinophil count, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference

* Assessed at week 24

Table D3.22. Blood Eosinophil Count Subgroup Outcomes: Dupilumab II[17,75,76,82,86,88]

Trial		LIBERTY ASTHMA QUEST							
Blood Eosinophil Count, cells/µL		≥300 EOS				<300, ≥150 EOS			
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg
AAER*	N	148	264	142	277	84	173	95	175
	Estimate (95%CI)	1.081 (0.846, 1.382)	0.370 (0.289, 0.475)	1.236 (0.972, 1.571)	0.403 (0.317, 0.512)	0.867 (0.592, 1.271)	0.559 (0.416, 0.751)	0.844 (0.578, 1.234)	0.471 (0.347, 0.638)
	Relative risk v. placebo, % (95%CI); p-value	REF	0.342 (0.244, 0.480); NR	REF	0.326 (0.234, 0.454); p<0.001	REF	0.644 (0.407, 1.019); NR	REF	0.557 (0.350, 0.888); NR
Pre-BD FEV_1* (liters)	N	113	206	111	207	80	169	90	168
	LS Mean	0.17 (0.04)	0.47 (0.03)	0.23 (0.04)	0.48 (0.03)	0.17 (0.04)	0.28 (0.03)	0.25 (0.04)	0.25 (0.03)
	Diff vs. placebo (95%CI); p-value	REF	0.30 (0.21-0.39); <0.0001	REF	0.25 (0.16, 0.33); <0.0001	REF	0.11 (0.01, 0.21); NR	REF	0.00 (-0.10, 0.10); NR
ACQ-5*	N	NR	NR	NR	NR	NR			
	LS Mean (SE)	-1.15 (0.06)	-1.54 (0.04)	-1.30 (0.06)	-1.52 (0.04)				
	Diff vs. placebo (95%CI); p-value	REF	-0.39 (-0.53, -0.25)	REF	-0.22 (-0.36, -0.08)				
AQLQ†	N	NR	NR	NR	NR	NR			
	LS Mean (SE)	0.96 (0.09)	1.37 (0.06)	0.98 (0.09)	1.32 (0.06)				
	Diff vs. placebo (95%CI); p-value	REF	0.41 (0.20, 0.62)	REF	0.34 (0.13, 0.54)				

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-5: Asthma Control Questionnaire-5, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, DUP: dupilumab, EOS: blood eosinophil count, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, ml: milliliter, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference

* Assessed at week 52

† Assessed at week 24

Table D3.23. Blood Eosinophil Count Subgroup Outcomes: Dupilumab III[17,75,76,82,86,88]

Trial		Liberty Asthma QUEST							
Blood Eosinophil Count, cells/µL		EOS ≥150				EOS <150			
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg
AAER*	N	NR	NR	NR	NR	85	193	83	181
	Estimate (95%CI)	NR	NR	NR	NR	0.511 (0.346, 0.755)	0.472 (0.358, 0.623)	0.642 (0.445, 0.927)	0.737 (0.575, 0.946)
	Relative risk v. placebo, % (95%CI); p-value	NR	NR	NR	NR	REF	0.925 (0.580, 1.474); NR	REF	1.149 (0.747, 1.767); NR
Pre-BD FEV_1* (liters)	N	175	341	185	347	83	185	83	176
	LS Mean	0.15 (0.03)	0.40 (0.02)	0.23 (0.03)	0.39 (0.02)	0.13 (0.04)	0.19 (0.03)	0.11 (0.04)	0.20 (0.03)
	Diff vs. placebo (95%CI); p-value	REF	0.25 (0.18-0.32); <0.0001	REF	0.15 (0.09-0.22); <0.0001	REF	0.06 (-0.04, 0.15); NR	REF	0.09 (-0.01, 0.18); NR
Outcomes not reported: Asthma Control Questionnaire-5 (ACQ-5), Asthma Quality of Life Questionnaire (AQLQ)									

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, Diff: difference, DUP: dupilumab, EOS: blood eosinophil count, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, ml: milliliter, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference

* Assessed at week 52

Table D3.24. Blood Eosinophil Count Subgroup Outcomes: Dupilumab IV[9,85]

Trial		LIBERTY ASTHMA VENTURE							
Blood Eosinophil Count, cells/µL		EOS ≥300		EOS <300		EOS ≥150		EOS <150	
Arms		PBO	DUP 300 mg	PBO	DUP 300 mg	PBO	DUP 300 mg	PBO	DUP 300 mg
AAER*	N	41	48	66	55	69	81	38	22
	Estimate (95%CI)	1.74 (1.20, 2.53)	0.50 (0.26, 0.98)	1.44 (1.05, 1.98)	0.78 (0.50, 1.22)	1.55 (1.14, 2.07)	0.64 (0.43, 0.97)	1.54 (1.01, 2.34)	0.61 (0.28, 1.34)
	Diff v. placebo, % (95%CI)	REF	0.29 (0.14, 0.60)	REF	0.55 (0.32, 0.94)	REF	0.42 (0.25, 0.69)	REF	0.40 (0.17, 0.95)
Reduction in OCS dose from baseline (mg/day)*	N	41	48	66	55	69	81	38	22
	LS Mean change (SE)	-42.71 (6.77)	-79.54 (6.36)	-44.98 (6.00)	-66.31 (6.47)	-46.51 (5.21)	-75.91 (4.76)	-36.87 (8.60)	-63.77 (11.14)
	Diff v. placebo, % (95%CI); p-value	REF	-71.1 (40, 86)	REF	-45.5 (NR)	REF	-58.2 (NR)	REF	-60.4 (5, 83)

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, Diff: difference, DUP: dupilumab, EOS: blood eosinophil count, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, OCS: oral corticosteroids, PBO: placebo, REF: reference

* Assessed at week 24

Table D3.25. Allergic Status Subgroup Outcomes: Tezepelumab I[78-80]

Trial		PATHWAY			
Allergic Status Subgroup		Allergic		Non-allergic	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg
AAER*	N	64	71	66	57
	Events per patient year (95%CI)	0.69 (0.50, 0.93)	0.15 (0.07, 0.28)	0.73 (0.54, 0.97)	0.22 (0.12, 0.39)
	Reduction v. placebo, % (95%CI); p-value	REF	0.20 (0.07, 0.56); NR	REF	0.34 (0.16, 0.72); NR
Pre-BD FEV_1* (liters)	N	59	64	64	49
	LS Mean (SE)	-0.04	0.10	-0.04	0.12
	Diff vs. placebo (95%CI); p-value	REF	0.14 (0.00, 0.29)	REF	0.16 (0.01, 0.31)
ACQ-6*	N	51	59	54	44
	LS Mean (SE)	-1.13	-1.23	-0.69	-1.28
	Diff vs. placebo (95%CI); p-value	REF	-0.10 (-0.42, 0.22)	REF	-0.59 (-0.94, -0.25)
AQLQ*	N	49	54	49	38
	LS Mean (SE)	1.13	1.20	0.60	1.25
	Diff vs. placebo (95%CI); p-value	REF	0.07 (-0.27, 0.41)	REF	0.66 (0.28, 1.03)

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference, SE: standard error, TEZ: tezepelumab

* Assessed at week 52

Table D3.26. Allergic Status Subgroup Outcomes: Tezepelumab II[78-80]

Trial		NAVIGATOR			
Allergic Status Subgroup		Allergic		Non-allergic	
Arms		PBO	TEZ 210 mg	PBO	TEZ 210 mg
AAER*	N	341	339	177	184
	Events per patient year (95%CI)	2.03 (1.73, 2.39)	0.85 (0.71, 1.03)	2.21 (1.78, 2.75)	1.09 (0.86, 1.38)
	Reduction v. placebo, % (95%CI); p-value	REF	0.42 (0.33, 0.53); NR	REF	0.49 (0.36, 0.67); NR
Pre-BD FEV_1* (liters)	N	296	298	148	170
	LS Mean (SE)	0.14	0.22	0.01	0.24
	Diff vs. placebo (95%CI); p-value	REF	0.07 (0.01, 0.14); NR	REF	0.23 (0.14, 0.31); NR
ACQ-6*	N	309	310	154	171
	LS Mean (SE)	-1.25	-1.54	-1.1	-1.52
	Diff vs. placebo (95%CI); p-value	REF	-0.29 (-0.45, -0.13); NR	REF	-0.42 (-0.63, -0.20); NR
AQLQ*	N	307	306	151	170
	LS Mean (SE)	1.21	1.55	1.01	1.37
	Diff vs. placebo (95%CI); p-value	REF	0.34 (0.17, 0.51); NR	REF	0.36 (0.13, 0.59); NR

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference, SE: standard error, TEZ: tezepelumab
* Assessed at week 52

Table D3.27. Allergic Status Subgroup Outcomes: Dupilumab [76]

Trial		LIBERTY ASTHMA QUEST							
Allergic Status Subgroup		Allergic				Non-Allergic			
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg
AAER*	N	183	360	179	361	134	271	142	272
	Events per patient year (95%CI)	0.736 (0.572, 0.948)	0.465 (0.378, 0.572)	0.975 (0.768, 1.238)	0.531 (0.434, 0.650)	1.077 (0.818, 1.417)	0.430 (0.335, 0.552)	0.924 (0.702, 1.215)	0.511 (0.404, 0.647)

Trial		LIBERTY ASTHMA QUEST							
Allergic Status Subgroup		Allergic				Non-Allergic			
Arms		PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg	PBO 1.14 ml	DUP 200 mg	PBO 2.0 ml	DUP 300 mg
	Reduction v. placebo, % (95%CI); p-value	REF	36.9 (13.4, 54.0); p=0.004	REF	45.5 (26.0, 59.9); p<0.001	REF	60.0 (42.7, 72.1); p<0.001	REF	44.6 (21.5, 60.9); p<0.001
Pre-BD FEV_1‡ (liters)	**N**	NR	NR	NR	NR	NR	NR	NR	NR
	LS Mean (SE)	NR	NR	NR	NR	NR	NR	NR	NR
	Diff vs. placebo (95%CI); p-value	REF	0.13 (0.05, 0.20); p<0.001	REF	0.16 (0.09, 0.23); p<0.001	REF	0.14 (0.07, 0.22); p<0.001	REF	0.09 (0.01, 0.16); p=0.02
ACQ-6†	**N**	NR	NR	NR	NR	NR	NR	NR	NR
	LS Mean (SE)	NR	-1.39 (0.05)	NR	-1.42 (0.05)	NR	-1.51 (0.06)	NR	-1.35 (0.06)
	Diff vs. placebo (95%CI); p-value	REF	-0.28 (-0.46, -0.11); p<0.01	REF	-0.26 (-0.44, -0.08); p<0.01	REF	-0.44 (-0.65, -0.22); p<0.0001	REF	-0.08 (-0.29, 0.12); p=0.43
Efficacy outcomes not reported: AQLQ									

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, DUP: dupilumab, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, ml: milliliter, N: total number, NR: not reported, PBO: placebo, pre-BD: prebronchodilator, REF: reference, SE: standard error

* Assessed at week 52

† Assessed at week 24

‡ Assessed at week 12

Table D3.28. Oral Corticosteroid Dependent Subgroup Outcomes: Tezepelumab[74]

Trial		NAVIGATOR	
Subgroup		OCS-Dependent Patients	
Arms		PBO	TEZ 210 mg
AAER*	N	51	49
	Events per patient year (95%CI)	2.94 (1.40, 3.20)	2.12 (2.00, 4.32)
	Reduction v. placebo, % (95%CI); p-value	REF	28 (-26, 59)
Pre-BD FEV_1* (liters)	N	51	49
	LS Mean (SE)	0.20 (0.62)	0.29 (0.62)
	Diff vs. placebo (95%CI); p-value	REF	0.27 (0.1, 0.44)
ACQ-6*	N	51	49
	LS Mean (SE)	-0.85 (0.16)	-1.50 (0.16)
	Diff vs. placebo (95%CI); p-value	REF	-0.65 (-1.08, -0.22)
AQLQ*	N	51	49
	LS Mean (SE)	0.81 (0.17)	1.32 (0.17)
	Diff vs. placebo (95%CI); p-value	REF	0.50 (0.04, 0.97)

95%CI: 95% confidence interval, AAER: annualized asthma exacerbation rate, ACQ-6: Asthma Control Questionnaire-6, AQLQ: Asthma Quality of Life Questionnaire, Diff: difference, FEV_1: forced expiratory volume in one second, LS mean: least-squares mean, mg: milligram, N: total number, NR: not reported, OCS: oral corticosteroid, PBO: placebo, pre-BD: prebronchodilator, REF: reference, SE: standard error, TEZ: tezepelumab

* Assessed at week 52

D4. Ongoing Studies

Table D4.1. Ongoing Studies

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population Criteria	Key Outcomes	Estimated Completion
Tezepelumab					
A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents With Severe Uncontrolled Asthma (DESTINATION) AstraZeneca NCT03706079	MC, BD, PC, Phase 3 RCT Actual enrollment: N = 951	**Arm 1:** Tezepelumab 210 mg Q4W + SoC **Arm 2:** Placebo Q4W + SC	**Inclusions:** - Adult and adolescent subjects who did not meet IP discontinuation criteria and attended the EOT visit for either NAVIGATOR or SOURCE - Informed consent by the Addendum for Extended Follow-up - Assent by adolescent subjects where applicable **Exclusions:** - Pulmonary disease other than asthma - Disorders including cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that are not stable - History of alcohol or drug abuse within 12 months	**Primary:** - Exposure adjusted incidence rates of AEs/SAEs [up to week 104] **Secondary:** - Annualized asthma exacerbation rate [up to week 104]	**Primary:** October 18, 2021 **Study:** May 12, 2022
A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults With Severe Uncontrolled Asthma	MC, DB, PC, Phase 3 RCT Est. enrollment: N = 396	**Arm 1:** Tezepelumab 210 mg Q4W + SC **Arm 2:** Placebo Q4W + SC	**Inclusions:** - Adults ages 18-80 - Physician-diagnosed asthma for ≥12 months - Controller medication of medium or high dose ICS for ≥6 months + one additional controller for ≥3 months - History of ≥2 asthma exacerbations withing 12 months and ≥1 exacerbation during treatment of medium-to-high dose ICS - ACQ-6 score ≥1.5	**Primary:** - Annualized asthma exacerbation rate [up to week 52] **Secondary:** - Change in prebronchodilator FEV_1, AQLQ(S)+12, and ACQ-6 [up to 52 weeks]	**Primary & Study:** May 30, 2025

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population Criteria	Key Outcomes	Estimated Completion
AstraZeneca NCT03927157			**Exclusions:** - Pulmonary disease other than asthma - History of cancer, clinically significant infection, chronic drug, or alcohol abuse within 12 months - Current smokers or history of smoking ≥10 pack-years		
A Phase I, Open-label Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age With Mild, Moderate, or Severe Asthma AstraZeneca NCT04673630	OL, Phase I pharmacokinetic study Est. enrollment: N = 14	**Single Arm:** single dose tezepelumab	**Inclusions**: - Age 5 to 11 - Diagnosis of asthma for ≥6 months - Treatment with low, medium, high dose ICS for ≥6 months with stable dose for ≥3 months **Exclusions:** - History of clinically significant disease other than asthma - History of asthma deterioration or exacerbation resulting in systemic corticosteroid use within 3 months of visit 1 - History of hospitalization within 6 months or systemic corticosteroid use within 3 months of visit 1	**Primary**: - Maximum serum concentration (Cmax), time to reach Cmax, area under the concentration-time curve	**Primary & Study**: December 22, 2021
Dupilumab (Dupixent®)					
A Randomized, Placebo-controlled, Parallel Group Study Designed to Assess the Change in Mucociliary Clearance After 12 Weeks of Treatment With Dupilumab in Patients With Moderate to Severe Asthma	PC, Phase IV RCT Est. enrollment: N = 30	**Arm 1**: Dupilumab 200 mg **Arm 2**: Placebo	**Inclusions:** - Moderate to severe Type 2 High asthma (FEV_1 <90% predicted and on medium to high dose ICS with or without a second controller) - Age >18 - Blood eosinophils (EOS) >300 cells/mm^3 - Exhaled Nitric Oxide (FeNO) >25 ppb **Exclusions:** - Current smoker or >10 pack year smoking history - Drug or alcohol addiction in last 5 years	**Primary**: - Change in mucociliary clearance rate [12 weeks] **Secondary**: - Change in % predicted FEV_1 and ACT [12 weeks]	**Primary**: March 1, 2024 **Study**: September 1, 2024

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population Criteria	Key Outcomes	Estimated Completion
Sally E. Wenzel MD NCT04743791			- Lung disease other than asthma including Chronic Obstructive Pulmonary Disease (COPD) or other uncontrolled disease		
Randomized, Double Blind, Placebo Controlled Study to Evaluate the Effect of Dupilumab on Airway Inflammation Through Assessments of Lung Function, Mucus Plugging and Other Lung Imaging Parameters in Patients With Asthma Sanofi **NCT04400318**	DB, PC, Phase IV RCT Est. enrollment: N = 153	**Arm 1**: Dupilumab Q2W **Arm 2**: Placebo	**Inclusions**: - Ages 18 to 70 - Diagnosis of asthma based on GINA 2019 - Uncontrolled moderate to severe asthma - History of ≥1 exacerbation in the prior year - Blood eosinophil ≥300 cells /µL and FeNO ≥25 ppb during screening - Treatment with medium to high dose ICS with a second controller +/- a third controller **Exclusions**: - Current smoker or cessation of smoking within 1 year or >10 pack year smoking history - Asthma exacerbation or hospitalization during screening - Diagnosed pulmonary (non-asthma) or systemic disease associated with elevated peripheral eosinophil count - History of COPD or another significant lung disease - OCS within 2 weeks of visit 1	**Primary**: - Change in prebronchodilator FEV_1 [up to week 24] - Change in regional airway volumes corrected for lung volume at total lung capacity [up to week 24] **Secondary**: - Change in lobar volumes, internal airflow distribution, image-based ventilation/perfusion [week 24] - Change in ACQ-7 [week 24]	**Primary & Study**: October 2022
A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Effect of Dupilumab on Exercise Capacity in Patients With Moderate-to-Severe Asthma	DB, PC, Phase IV RCT Est. enrollment: N = 140	**Arm 1**: Dupilumab Q2W via pre-filled syringe **Arm 2**: Placebo	**Inclusions**: - Physician diagnosis of asthma - Stable background therapy for ≥3 months with stable dose of medium-to-high ICS with at least a second controller medication - Blood eosinophil count ≥300 cells/µL or on maintenance OCS at screening - ACQ-5 score ≥1.5 at screening **Exclusions**:	**Primary**: - Change in constant work rate exercise endurance time [up to week 12] **Secondary**: - Change in average number of steps walked per day,	**Primary**: February 8, 2022 **Study**: April 19, 2022

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population Criteria	Key Outcomes	Estimated Completion
Regeneron Pharmaceuticals NCT04203797			- Current smoking, vaping, tobacco chewing within 6 months or >10 pack years smoking history - Clinically significant cardiac disease or uncontrolled hypertension - Participation in exercise or physical rehabilitation programs within 6 months - Prior dupilumab use or anti-IgE therapy within 130 days or any other biologic therapy	energy expenditure, mean duration of moderate to vigorous physical activity [up to week 12]	
Omalizumab (Xolair®)					
A Multicenter, Open-Label, Single-Arm Study to Assess the Impact of Omalizumab on Exercise Capacity, Physical Activity, and Sleep Quality in Patients With Moderate to Severe Allergic Asthma Genentech, Inc. NCT04195958	MC, OL, Phase IV RCT Est. enrollment: N = 118	**Single Arm:** Omalizumab (150-375 mg Q2W or Q4W)	**Inclusions** - Diagnosed asthma for ≥12 months - Positive skin test or in vitro reactivity to perennial aeroallergen - ICS dose ≥500 micrograms and ≥1 second controller for ≥3 months prior to screening - Uncontrolled asthma (ACQ-5 ≥0.75) - Sleep disturbance dur to asthma **Exclusions** - Treatment with investigational drug within 12 weeks, monoclonal antibodies within 6 months, oral corticosteroid within 3 months of screening - History of interstitial lung disease, COPD, clinically significant non-asthma pulmonary disease - Current smoker or >10 pack years history - History of alcohol, drug, chemical abuse within 6 months of screening	**Primary**: - Change in endurance time during cardio-pulmonary exercise testing (CPET) [week 24] **Secondary**: - Change in physical activity, dynamic hyperinflation, sleep efficiency [week 24] - Adverse events [week 28]	**Primary & Study**: September 30, 2022
Impact of Omalizumab Withdrawal After a 3 Year Duration Treatment in Well Controlled Severe	MC, OL, Phase IV RCT Est. enrollment: N = 234	**Arm 1**: Omalizumab withdrawal **Arm 2**: Omalizumab continuation of	**Inclusions**: - Patient participating in the RAMSES cohort - Adults >18 years old - Treated with omalizumab for 36-60 months for severe allergic asthma	**Primary**: - Number of exacerbations [12 months]	**Primary**: January 1, 2025

Title / Trial Sponsor	Study Design	Treatment Arms	Patient Population Criteria	Key Outcomes	Estimated Completion
Allergic Asthma: a Multicentric Randomized Controlled Trial Assistance Publique - Hôpitaux de Paris NCT04763447		same pre-study dose	- Well controlled with treatment with ≤1 exacerbation in the year prior **Exclusions**: - Patients refusing or with reasons other than good asthma control to stop omalizumab - Not covered by health insurance - Patients with poor adherence to treatment	**Secondary**: - Changes in asthma control, AQLQ, inhaled and oral steroid dose, FEV_1 [up to 12 months]	**Study**: February 1, 2025
Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)					

ACQ-6: Asthma Control Questionnaire-6, AQLQ(S)+12: Standardized Asthma Quality of Life Questionnaire for 12 years and older, Cmax: maximum serum concentration, DB: double blind, EOT: end of trial, Est: estimated, FEV_1: forced expiratory volume in 1 second, GINA: Global Strategy for Asthma Management and Prevention, ICS: inhaled corticosteroids, IP: investigational product, MC: multicenter, mg: milligrams, N: total number, OCS: oral corticosteroids, OL: open-label, PC: placebo-controlled, ppb: parts per billion, Q2W: every two weeks, Q4W: every four weeks, RCT: randomized controlled trial, SC: standard care

D5. Previous Systematic Reviews and Technology Assessments

We identified two ongoing health technology assessments by the National Institute for Health and Care Excellence (NICE) of tezepelumab and dupilumab and one assessment of omalizumab by the Canadian Agency for Drugs and Technologies in Health (CADTH). We also identified and summarized the most recent and relevant systematic reviews of dupilumab and omalizumab in patients with severe asthma below.

NICE Technology Assessments

Tezepelumab for treating severe asthma [ID3910]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of tezepelumab in people with severe asthma inadequately controlled by standard therapy. Comparators in the draft scope include dupilumab, omalizumab, reslizumab, benralizumab, and mepolizumab. The expected publication date is to be confirmed.

Dupilumab for treating severe asthma [ID1213]

NICE is currently conducting an appraisal of the clinical and cost effectiveness of dupilumab in people older than 12 years with severe asthma inadequately controlled by standard therapy. Comparators in the draft scope include omalizumab, reslizumab benralizumab, and mepolizumab. The expected publication date is to be confirmed.

Omalizumab for treating severe persistent allergic asthma [TA278]

NICE evaluated omalizumab for the treatment of severe persistent allergic asthma in 2013. They recommend it as an option for treating severe persistent allergic IgE mediated asthma as an add-on to optimized standard therapy in people aged 6 and older who need continuous or frequent treatment with oral steroids (four or more courses in the previous year). Optimized standard therapy includes inhaled high-dose corticosteroids, long-acting beta agonists leukotriene receptor antagonists, theophylline, oral corticosteroids, and smoking cessation.

CADTH Technology Assessments

Omalizumab Treatment for Adults and Children with Allergic Asthma: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

CADTH conducted a review of omalizumab treatment for adults and children with allergic asthma in 2015. They published a summary with a critical appraisal. They concluded that omalizumab decreases the risk of asthma exacerbations in patients with moderate to severe allergic asthma

inadequately controlled by standard therapies. They acknowledged that one evidence-based guideline recommended its use for the treatment of individuals aged 6 and older who had severe persistent confirmed allergic IgE mediated asthma as an add on to optimized standard therapy for those who need frequent treatment with oral corticosteroids.

Previous Systematic Reviews

Agache I, Song Y, Rocha C, et al. Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma. Allergy. 2020 May;75(5):1058-1068.

Through a systematic review, investigators identified three randomized controlled trials (RCTs) of dupilumab in patients with severe, uncontrolled asthma to assess its efficacy and safety. The 2735 included patients across the three trials (LIBERTY ASTHMA QUEST, VENTURE, and the Phase 2b study) were ages twelve and older with severe asthma uncontrolled by ICS or OCS plus two additional controllers. In this population, dupilumab decreased the annualized rate of severe exacerbations with high certainty of evidence compared to placebo across all trials (IRR: 0.51, 95% CI 0.45-0.59) with no difference between the 200 mg and 300 mg doses. In the subgroup of patients with high blood eosinophil count (>300 cells/µL) the rate of severe exacerbations decreased significantly more than those with <300 cells/µL (IRR: 0.63 vs. 0.35; p = 0.001). The pooled ACQ-5 score in the three RCTs showed improvement in asthma control with dupilumab compared to placebo, although not by the minimally important difference (MID) of 0.5. The pooled result of the two RCTs that evaluated AQLQ was similar, showing improvement with dupilumab versus placebo but again not reaching the MID. As for safety, investigators determined with moderate certainty that dupilumab increases drug-related adverse events at 24 weeks. Additionally, pooled analysis showed with high certainty that dupilumab reduces the percentage use of OCS (reaching the MID) and rescue medication (without reaching the MID) as compared to placebo and improves FEV_1 at 24 weeks (without reaching the MID). Overall, this systematic review concludes that as an add-on treatment in patients with severe, uncontrolled asthma using ICS plus a second controller, dupilumab reduces the rate of asthma exacerbations and use of OCS; somewhat improves asthma control, quality of life, and FEV_1; but may increase short-term drug-related adverse events.

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

Investigators conducted a systematic review to assess the efficacy of omalizumab in patients with severe allergic asthma. 22 published papers were identified in adults with severe asthma treated with omalizumab including 12 randomized controlled trials. From five RCTs with data on reduction in annual exacerbations, omalizumab was favorable with an absolute risk reduction of 37% compared to placebo. As for improvement in asthma control, data from five studies of 2287 patients showed a statistically significant improvement in ACQ and ACT scores, although the improvements were below the minimal clinically important difference (MCID) of 0.5 points. Statistically significant improvements in AQLQ above the MCID of 0.5 were seen in four studies of 1852 patients on omalizumab compared to placebo. Safety was assessed from 13 studies and was not significantly different in terms of serious adverse events between omalizumab and placebo groups. Overall, evidence quality was low for important outcome measures due to evolving definitions of severe asthma, however omalizumab appears safe and demonstrates significant reductions in exacerbation rate and OCS dose. The effect on lung function, asthma control and quality of life remains uncertain. More studies on patients with true, severe asthma are needed.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	

Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[89]

There are multiple definitions of moderate and severe asthma and some definitions have evolved over time. The Global Initiative for Asthma (GINA) defines severe asthma as a type of difficult-to-treat asthma that is 1) uncontrolled despite management of modifiable disease factors and despite adherence to maximally optimized high dose ICS-LABA treatment, or 2) asthma that worsens when high dose treatment is decreased.[3] The European Respiratory Society (ERS)/American Thoracic Society (ATS) Management of Severe Asthma guideline defines severe asthma as asthma that requires or remains uncontrolled despite treatment with high dose ICS plus a second controller medication and/or OCS. In scenario analyses, we estimated cost-effectiveness estimates in two main subgroups: 1) allergic asthma and 2) eosinophilic asthma. These analyses compare relevant agents in each indication versus SoC (i.e., placebo arms of clinical trials).

E2. Model Inputs and Assumptions

Health State Utilities

Health state utilities were derived from publicly available literature and/or manufacturer submitted data and applied to health states. The 2018 review used the St George's Respiratory Questionnaire (SGRQ) instrument and mapping algorithm. The AQLQ was measured across all biologics in this review which include the sub-group analyses in allergic and eosinophilic asthma whereas the SGRQ was not measured across all biologics. While the SGRQ was administered in tezepelumab trials, the utility values from both mapping algorithms produce similar differences in utility between tezepelumab plus SoC and SoC alone (<0.01 difference in utility for non-exacerbation health state). Further, when using the AQLQ mapping instrument, the non-exacerbation health state utility value at baseline is consistent with recent cost-effectiveness publications on other biologic therapies in asthma.[90]

Given a dearth of data on the utility associated with an asthma-related ED visit, we assumed the mid-point between the values for hospitalization and oral steroid burst events. We assigned the pre-post decrement in utilities observed in Lloyd et al. for exacerbation-related events. Two weeks

duration was assumed for all exacerbation health states, consistent with the model cycle. Although an oral steroid burst or ED visit does not typically last two weeks, the stress and anxiety related to these events may remain over a two-week period.

Severe asthma flare-ups are commonly treated through prescribed bursts of oral corticosteroids (OCS), ranging in intensive treatment periods from five days to two weeks. While consistent use of OCS is associated with a greater likelihood of side effects, we note that there is a distinction between chronic OCS use and a steroid burst.[91,92]

The disutility of chronic OCS for the proportion of patients using >5 mg of prednisone daily or its equivalent (-0.023)[93] will be assumed to be equivalent to the disability-adjusted life years (DALYs) that were weighted by the proportion of chronic oral corticosteroid user who developed the following adverse events: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke. Table E2.2 displays the disutilities present in the model. This disutility for chronic OCS use is assumed to not apply for those individuals who are able to reduce their chronic OCS use to at or below 5 mg.

Table E2.1. Asthma Patient-Reported Outcome Response and Non-Exacerbation Utility

Characteristic	Tezepelumab plus SoC	SoC (placebo arm)	Source
Asthma Patient-Reported Outcome Measure	AQLQ	AQLQ	Pooled PATHWAY and NAVIGATOR trials[6,7]
Asthma Patient-Reported Outcome Mean Change Difference vs. SoC (95% CI)	0.34 (0.17, 0.49)	Reference	Pooled PATHWAY and NAVIGATOR trials[6,7]
Non-Exacerbation Mean Health State Utility for Biologic plus SoC vs. SoC Alone (95% CI for tezepelumab mean difference vs. placebo)	0.788 (0.774, 0.801)	0.75	Pooled PATHWAY and NAVIGATOR trials[6,7]

CI: confidence interval, SoC: standard of care

Table E2.2. Disutilities

Characteristic	Disutility	Source
Steroid Burst*	-0.1	Lloyd et al. 2007[52]
ED Visit*	-0.15	Lloyd et al. 2007[52] and assumption
Hospitalization*	-0.20	Lloyd et al. 2007[52]
Chronic Oral Corticosteroid Use**	-0.023	Norman et al. 2013[93]

*2-week duration

**Lifetime duration

Drug Utilization

Treatment Regimen

Table E2.3 indicates inputs corresponding to the regimen for the specific intervention. Table E2.3 also includes findings for tezepelumab as compared to SoC alone on the proportion of patients who are on oral corticosteroids at the end of the study, generally from oral steroid sparing studies (i.e., SOURCE). Consistent with prior ICER reports, we assumed 100% compliance and adherence to biologic add-on therapy.[31,37] Given that the model does not include progressive aspects of the disease and given the treatment benefits are held constant over time, changes to the compliance/adherence assumption are not thought to greatly impact the results.

Table E2.3. Treatment Regimen

Characteristic	Tezepelumab	Omalizumab	Dupilumab
Treatment Dose	210 mg every 4 weeks	75-375mg every 2 to 4 weeks (vial wastage included)	200mg or 300mg every 2 weeks
Route of Administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection

Cost Inputs

All costs used in the model were updated to first quarter of 2021 US dollars or the most recently available data using the health care component of the personal consumption expenditure index, in accordance with the ICER Reference Case.

Drug Costs

Treatment Costs and Details

The unit cost for each intervention is reported in Table E2.4. We used estimates of net price from the SSR Health database for dupilumab. The net price for omalizumab was provided to us by the manufacturer using the following statement, "average annual net cost of treatment for adults with allergic asthma (Q1 Jan - Mar 2021) based on average utilization of 2.85 units of 150 mg prefilled syringe per month. Methodology intended to represent an average prescribed dosing. Net cost assumption is an average cost reflecting all price concessions given to customers, and inclusive of all statutory discounts and rebates. This calculation is an estimate for the purposes of financial modeling. Cost treatment per patient varies as dosing depends on age, weight, IgE level and pricing differs by provider and payer (commercial insurance or government program)."[94] Further, threshold prices will be calculated at the three cost-effectiveness thresholds ($50,000, $100,000, and $150,000 per QALY gained).

Treatment-related costs (SoC and asthma biologics) will be assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states).

Table E2.4. Drug Costs

Drug	WAC per Dose	Discount from WAC	Net Price per Dose	Net Price per Year
Tezepelumab	Placeholder based on Dupilumab WAC price	Placeholder based on Dupilumab WAC price	Placeholder based on Dupilumab net price	Placeholder based on Dupilumab net price
Dupilumab (300mg)	$1601.70	33.1%*	$1071.50	$27,859.88
Omalizumab (150mg)	$1162.34	27.5%†	$784.56	$26,832.00

WAC: wholesale acquisition cost

*SSR Health, LLC, was used for estimating discount from wholesale acquisition cost

†The net-price/year provided by Genentech was used for estimating the discount from whole sale acquisition cost (data on file)[94]

Non-Drug Costs

Table E2.5 details the health care utilization costs that were used in the model. Unit costs for health care utilization were the same across different treatments and populations. Unit costs for health care utilization are consistent with the previous 2018 review. Unit costs for asthma-related hospital stays, emergency department (ED) visits, and exacerbations requiring an OCS burst were estimated using a cohort of 222,817 US patients with asthma from the Clinformatics DataMart Multiplan dataset. Costs were estimated for 30-day periods after an exacerbation and were summarized as mean health care cost per exacerbation and inflated to the most recent available evidence on inflation up to early 2021 US Dollars.

The annual cost of SoC in an incremental analysis compared to SoC alone has an approximate incremental difference of $0. We assumed the same annualized cost of SoC from the prior 2018 ICER review and consistent with Whittington et al. 2018.

The chronic use of oral corticosteroids likely results in adverse clinical events and their associated costs. We assumed that doses of daily oral corticosteroids above 5 mg were potentially harmful to the patient in terms of adverse events and could impact day-to-day living. Annual US costs associated with an individual using oral corticosteroids chronically above the 5 mg dose level was $8,326. This annual estimate compared chronic oral steroid users to asthma patients who did not use oral steroids.

The cost associated with biologic administration is also displayed in Table E2.5. We assume that four office visits each year would be associated with standard of care. Therefore, administration

costs were assigned to the listed therapies in Table E2.3 for each administration in a year above four.

Societal Perspective Inputs

A recent nationally representative cross-sectional analysis of the Medical Expenditure Panel Survey (MEPS) from 2010 – 2017 provided indirect cost inputs for the modified societal perspective (Table E2.8).[53] We made the assumption that patients would benefit from biologic treatment enough that indirect costs would be consistent with moderate asthma rather than severe asthma. We operationalized this reduction through a multiplier that reduced indirect costs each cycle. This reduction in indirect cost was consistent with an analysis by Corren et al. from 2019 which found significant reductions in lost time at work from initiating dupilumab.[83] The MEPS analysis includes both school or work in their cost calculations over a seven year period in a nationally representative population.

Table E2.5. Health Care Utilization Cost Inputs

Health Care Cost Category	Unit Cost	Source
Exacerbation-Related Steroid Burst (SD)	$1,604 ($2,738)	Suruki et al. 2017[95]
Exacerbation-Related ED Visit (SD)	$2,161 ($2,869)	Suruki et al. 2017[95]
Exacerbation-Related Hospitalization (SD)	$9,442 ($7,568)	Suruki et al. 2017[95]
Annual Cost for SoC (95% interval)	$6,494 ($5,297, $7,827)	Whittington et al. 2018[49]
Annual Cost of Long-Term Oral Corticosteroid Use with Adverse Events (SD assumed)	$8,326 ($8,326)	Lefebvre et al. 2017[46]
Office Visit Treatment Administration for Subcutaneous Office-Administered Tezepelumab (assumed to be self-administered after loading dose)	$74	Physicians' Fee and Coding Guide (HCPCS code 99213)[96]

Scenario Analysis Inputs

Table E2.6. Key Inputs for Eosinophilic Asthma Scenario Analysis

Parameter	Tezepelumab plus SoC	Dupilumab plus SoC	SoC Alone
Annualized Exacerbation Rate, end of study (95% CI)	1.91 (95% CI: 1.63, 2.23)		
Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	0.38 (95% CI: 0.29, 0.52)	AIC	Reference group
Rate Ratio for Exacerbations Resulting in ED Visit (without hospitalization)	0.38 (95% CI: 0.29, 0.52)	AIC	Reference group
Rate Ratio for Exacerbations Resulting in Hospitalization	0.38 (95% CI: 0.29, 0.52)	AIC	Reference group
Non-Exacerbation Mean Health State Utility for Biologic plus SoC vs. SoC Alone (95% CI for tezepelumab mean difference vs. placebo)	0.80	0.78	0.75
Sources	Pooled PATHWAY and NAVIGATOR Subgroup ≥ 150 cells/µL	Academic in confidence;[17]	Pooled PATHWAY and NAVIGATOR Subgroup ≥ 150 cells/µL

Table E2.7. Key Inputs for Allergic Asthma Scenario Analysis

Parameter	Tezepelumab plus SoC	Omalizumab plus SoC	SoC Alone
Annualized Exacerbation Rate, end of study (95% CI)	1.82 (95% CI: 1.54, 2.16)		
Rate Ratio for Exacerbations Resulting in Steroid Burst (without ED visit or hospitalization)	0.39 (95% CI: 0.29, 0.54)	0.52 (95% CI: 0.37, 0.73)	Reference group
Rate Ratio for Exacerbations Resulting in ED Visit (without hospitalization)	0.39 (95% CI: 0.29, 0.54)	0.49 (95% CI: 0.25, 0.97)	Reference group
Rate Ratio for Exacerbations Resulting in Hospitalization	0.39 (95% CI: 0.29, 0.54)	0.16 (95% CI: 0.06, 0.42)	Reference group
Non-Exacerbation Mean Health State Utility for Biologic plus SoC vs. SoC Alone (95% CI for tezepelumab mean difference vs. placebo)	0.79	0.78	0.75
Sources	Pooled PATHWAY and NAVIGATOR Allergic Subgroup	Bousquet et al. 2005; Normansell et al. 2014	Pooled PATHWAY and NAVIGATOR Allergic Subgroup

Table E2.8. Key Inputs for Modified Societal Perspective Analysis

Category	Mean	Source
Incremental Indirect Costs per Person per Year (Severe asthma vs. no asthma)	$1000	Song et al. 2020[53]
Multiplier for Biologic Impact on Indirect Costs per Year	0.32	Song et al. 2020[53]; equivalent to comparison between severe and moderate asthma

E3. Results

Description evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1. First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[97]

2. For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

3. We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.

4. If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.

5. The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

6. We use the same calculations in the comparator arm to derive its evLY.

Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

Description Health Improvement Distribution Index Calculations (Results presented in Chapter 5)

The Health Improvement Distribution Index identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The Health Improvement Distribution Index is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if the disease prevalence was 10% in poor Americans whereas the disease prevalence across all Americans was 4%, then the Health Improvement Distribution Index would be 10% / 4% = 2.5. For interventions known to increase health in this disease and that accomplish equal access across the entire population, poor Americans would receive 2.5 times the health improvements as compared to the same sized group of Americans without regard to economic status. Health Improvement Distribution Indexes above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits.

For this evaluation, asthma disease prevalence (2019) among black adults was 9.7% whereas the asthma disease prevalence (2019) among all US adults was 8.0%. Therefore, the Health Improvement Distribution Index for black adults equals 9.7% / 8.0% = 1.21.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors or plausible parameter ranges). Figure E4.1 presents the tornado diagram resulting from the one-way sensitivity analysis for tezepelumab plus SoC versus Soc alone. Key drivers of cost-effectiveness

estimates include the utility for non-exacerbation state for tezepelumab plus Soc and SoC alone, severe asthma exacerbation risk of death, annualized exacerbation rate for SoC alone, and exacerbation rate ratio for tezepelumab plus SoC.

Probabilistic sensitivity analyses were also be performed by jointly varying multiple model parameters over at least 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

Figure E4.1. Tornado Diagrams

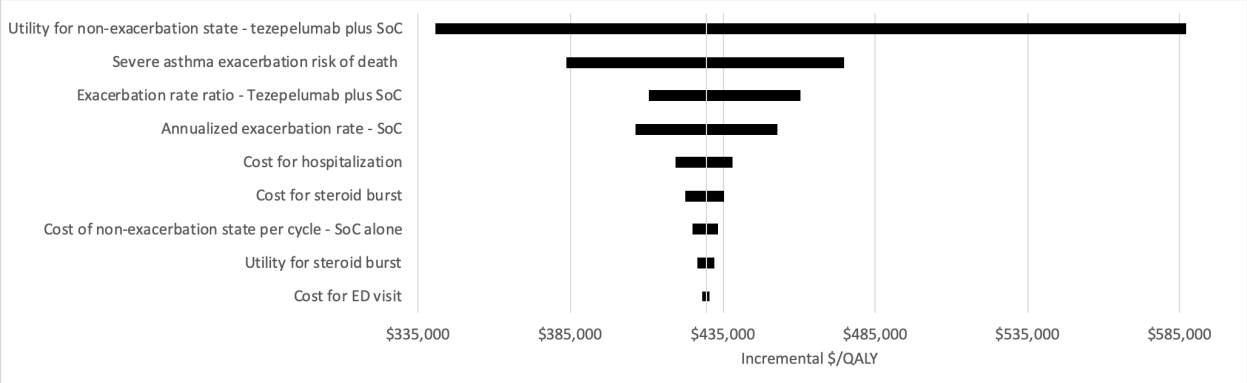


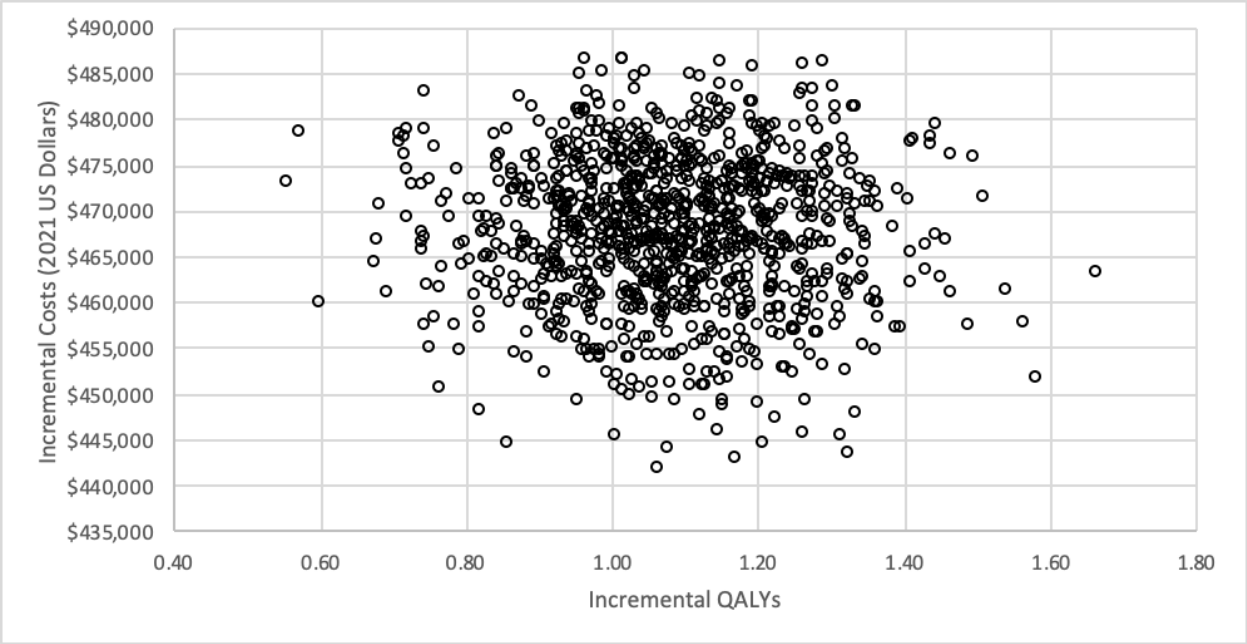
Table E4.1. Tornado Diagram Inputs and Results for Tezepelumab plus Standard of Care vs. Standard of Care Alone

	Lower Input ICER	Upper Input ICER	Lower Input	Upper Input
Utility for non-exacerbation state - tezepelumab plus SoC	$586,871	$340,556	0.77	0.81
Severe asthma exacerbation risk of death	$474,949	$383,676	0.0039	0.0105
Exacerbation rate ratio - Tezepelumab plus SoC	$410,526	$460,433	0.27	0.51
Annualized exacerbation rate - SoC	$452,908	$406,347	1.58	2.08
Cost for hospitalization	$438,185	$419,419	$6,872	$12,413
Cost for steroid burst	$435,452	$422,578	$1,167	$2,109
Cost of non-exacerbation state per cycle - SoC alone	$433,234	$425,143	$22	$40
Utility for steroid burst	$426,610	$432,367	0.64	0.66
Cost for ED visit	$430,767	$427,996	$1,573	$2,841

Table E4.2. Results of Probabilistic Sensitivity Analysis for Tezepelumab plus Standard of Care vs. Standard of Care Alone

	Tezepelumab plus SoC		SoC Alone		Incremental	
	Mean	Credible Range	Mean	Credible Range	Mean	Credible Range
Total Costs	$696,000	$663,000 - $739,000	$229,000	$190,000 - $273,000	$468,000	$451,000 - $482,000
Total QALYs	14.99	14.69 – 15.27	13.91	13.69 – 14.05	1.09	0.75 – 1.39
ICER					$431,000	$347,000 – $598,000

Figure E4.2. Probabilistic Sensitivity Analysis Results: Cost-Effectiveness Clouds



This panel presents cost-effectiveness clouds from the probabilistic sensitivity analysis.

E5. Scenario Analyses

Scenario Analysis 1

Scenario analysis 1 includes results specific to an allergic asthma population. We relied on pooled baseline data from NAVIGATOR and PATHWAY to estimate cost-effectiveness estimates for tezepelumab plus SoC versus SoC alone within the allergic sub-population (see Table E3.1). Separately we estimated cost-effectiveness estimates for omalizumab plus SoC versus SoC alone using the same baseline allergic asthma inputs. Specific to tezepelumab plus SoC, cost-effectiveness estimates were still above commonly cited cost-effectiveness thresholds and were slightly higher than the base-case estimates mainly due to a lack of differentiation of exacerbation rate ratios across categories of exacerbations (i.e., mild, moderate, severe).

Table E3.1. Scenario Analysis Results

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Tezepelumab plus SoC	SoC alone	$455,000	$1,950,000	$448,000
Omalizumab plus SoC	SoC alone	$494,000	$1,372,000	$481,000

*Placeholder price for tezepelumab assumed the same net pricing for dupilumab

Scenario Analysis 2

Scenario analysis 2 includes results specific to an eosinophilic asthma population. We relied on pooled baseline data from NAVIGATOR and PATHWAY to estimate cost-effectiveness estimates for tezepelumab plus SoC versus SoC alone within the eosinophilic asthma sub-population (see Table E3.2). Separately we estimated cost-effectiveness estimates for dupilumab plus SoC versus SoC alone using the same baseline eosinophilic asthma inputs. Specific to tezepelumab plus SoC, cost-effectiveness estimates were still above commonly cited cost-effectiveness thresholds and were very similar to the base-case estimates.

Table E3.2. Scenario Analysis Results

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Tezepelumab plus SoC	SoC alone	$386,000	$1,854,000	$382,000
Dupilumab plus SoC	SoC alone	$503,000	$1,713,000	$492,000

*Price is a placeholder based on net pricing of dupilumab

Scenario Analysis 3

Table E3.3 presents the results from a modified societal perspective that included productivity losses from both missed school and work. See Table E2.8 for unit costs. Cost-effectiveness results were still above commonly cited cost-effectiveness thresholds when including the impact of tezepelumab on lost productivity.

Table E3.3. Scenario Analysis Results

Treatment	Comparator	Cost per QALY Gained	Cost per Life Year Gained	Cost per evLY Gained
Tezepelumab plus SoC	SoC alone	$424,000	$1,458,000	$416,000

*Price is a placeholder based on net pricing of dupilumab

E6. Heterogeneity and Subgroups

We estimated costs and health outcomes among two relevant subgroups: allergic asthma and eosinophilic asthma. The results for these scenario analyses are available in section E5 of this supplement and describe differences in costs and health outcomes among these subgroups. We also considered additional subgroups such as steroid dependent patients and populations within urban and rural settings. However, at the time of this report posting we are not aware of evidence that would provide inputs for the economic model in these subgroups.

E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

Prior Economic Models

The current ICER model's structure is based on prior asthma model structures including ones developed by Campbell et al. and reviewed in McQueen et al., including the prior ICER report on asthma biologics.[38,41] Since the 2018 review, we found one relevant original research publication in uncontrolled asthma by Sullivan et al. Additionally, there have been two NICE appraisals for benralizumab and dupilumab that are relevant to this ICER review. Sullivan et al. assessed omalizumab plus SoC from a US payer perspective using real-world evidence from PROSPERO.[90] Results suggested over a lifetime, omalizumab add-on therapy was associated an increase in QALYs and costs and met the commonly cited cost-effectiveness threshold of $100,000 per QALY. Inputs such as exacerbations at baseline and mortality were similar or the same as our analysis. However, the non-exacerbation health state utility difference between omalizumab plus SoC versus SoC alone from Sullivan et al. suggest pre-post (uncontrolled) differences close to 0.20 whereas our current and past reviews have a non-exacerbation state utility difference range of 0.03 – 0.06 observed in trial environments. As discussed in the main report, response rates in the SoC arms of trials can be high and therefore, raise concern of real-world analyses that do not include a control group.

Differences between our current modeling analysis and our past 2018 analysis include updates to the proportion of exacerbations resulting in steroid bursts, ED visits, and hospitalizations, asthma-related excess mortality, and the use of the AQLQ mapping instrument to estimate the non-exacerbation state utility value for each arm of the model. First, the 2018 review used a variety of sources to arrive at proportions of exacerbations resulting in steroid bursts, ED visits, and hospitalizations of 90%, 5%, and 5%, respectively. Recent evidence from the CHRONICLE study suggests a different distribution of 79%, 9%, and 14% for exacerbations resulting in steroid bursts, ED visits, and hospitalizations, respectively. CHRONICLE is a prospective real-world study of US patients with confirmed severe asthma not controlled by high-dose inhaled corticosteroids and additional controllers.[98] In CHRONICLE, they were able to identify the distribution of exacerbation categories by setting (e.g., ED or hospital) for patients receiving biologics, maintenance systemic corticosteroids, and not receiving biologics or systemic corticosteroids. In the model we used the distribution of exacerbations from the cohort not receiving biologics or systemic steroids for the SoC alone arm. We then applied the rate ratio reductions for these exacerbation categories from the tezepelumab pooled NAVIGATOR and PATHWAY trials. Given the distribution of visits shifts towards more ED visits and hospitalizations as compared to our previous review, there is more opportunity to increase quality of life and life years, and reduce costs as compared to the SoC arm. The resulting impact is greater incremental QALYs and cost reductions, ultimately leading to lower incremental cost-effectiveness estimates. Second, as discussed in the main report, asthma mortality was calibrated to be consistent with recent United States estimates on asthma deaths. This calibration was done to ensure our previous estimates on asthma mortality stayed consistent with currently available evidence from the United States. This change was necessary largely because of the distribution shift of exacerbations from CHRONICLE described above. Finally, we relied on the AQLQ mapping instrument which is a shift away from the SGRQ from the last review. The resulting non-exacerbation state health utility values were slightly lower than our previous estimates, shifting the incremental cost-effectiveness ratios upward, assuming all else equal.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included individuals ages 12 years and older with severe uncontrolled asthma who are eligible for treatment with tezepelumab. To estimate the size of the potential candidate populations for treatment, we applied a "funnel-based" approach for which we used inputs for the US population size,[99] prevalence estimates for severe asthma,[56-59] and the proportion of patients whose asthma remains uncontrolled.[60,61] Using this approach we derived an estimate of approximately 1.3 million individuals eligible for treatment with tezepelumab. We assumed that 20% of these patients would initiate treatment in each of the five years, or approximately 270,000 patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[40,100] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs, and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that tezepelumab would displace current treatments with standard of care within the eligible patient population.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (https://icer.org/our-approach/methods-process/value-assessment-

framework/), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2021-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $734 million per year for new drugs.

Results

Table F1 illustrates the per-patient budget impact calculations in more detail, based on the annualized placeholder price ($27,860 per year) and the prices to reach $150,000, $100,000, and $50,000 per QALY for tezepelumab ($11,927, $9,077, and $6,226 per year, respectively) compared to standard of care alone.

Table F1. Per-Patient Average Annual Total and Average Net Cost over a Five Year Time Horizon

	Average Annual Per Patient Total and Net Cost			
	Placeholder Price	**$150,000/QALY**	**$100,000/QALY**	**$50,000/QALY**
Tezepelumab	$36,000	$20,300	$17,500	$14,700
Standard of Care	$12,000	$12,000	$12,000	$12,000
Difference (Net)	$24,000	$8,300	$5,500	$2,700

QALY: quality-adjusted life year

Figure F1 illustrates the health care system perspective cumulative per-patient budget impact calculations for tezepelumab compared to standard of care alone, based on the placeholder annualized price of $27,860 per year of treatment.

The average potential budgetary impact for tezepelumab was approximately $24,500 per patient in year one, with the cumulative net cost increasing in years two through five as treatment continues, reaching approximately $120,000 by the end of the five-year horizon. The annual net cost decreased in each subsequent year to approximately $24,000 in year five.

Figure F1. Cumulative Net Cost per Patient with Tezepelumab for Five Years at an Annual Placeholder Price of $27,860 per Year