NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761224
Priority or Standard	Priority
Submit Date(s)	May 7, 2021
Received Date(s)	May 7, 2021
PDUFA Goal Date	January 7, 2022
Division/Office	Division of Pulmonology, Allergy, and Critical Care
Review Completion Date	December 17, 2021
Established/Proper Name	Tezepelumab
(Proposed) Trade Name	Tezspire
Pharmacologic Class	Thymic stromal lymphopoietin (TSLP) blocker
Applicant	AstraZeneca
Dosage form	Injectable, single dose vial and single dose prefilled syringe
Applicant proposed Dosing Regimen	210 mg every 4 weeks
Applicant Proposed Indication(s)/Population(s)	For the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma, (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.
Recommended Dosing Regimen	210 mg every 4 weeks

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Linda Ebonine, Ladan Jafari
Nonclinical Reviewer	Anup Srivastava
Nonclinical Team Leader	Carol Galvis
Clinical Pharmacology Reviewer	Jing Niu
Clinical Pharmacology Team Leader	Yunzhao Ren
Pharmacometrics Reviewer	Jing Niu
Pharmacometrics Team Leader	Jerry (Jingyu) Yu
Clinical Reviewer	Jennifer Lan
Clinical Team Leader	Miya Paterniti
Statistical Reviewer	Susan Mayo
Statistical Team Leader	Yongman Kim
Cross-Disciplinary Team Leader	Miya Paterniti
Division Director (DPACC)	Sally Seymour
Division Director (DPT-II)	Andrew Goodwin
Division Director (OCP)	Suresh Doddapaneni
Division Director (OB)	Laura Lee Johnson
Office Director (or designated signatory authority)	Julie Beitz

Additional Reviewers of Application

Clinical Data Scientist	DeAngelo McKinley, Yongqi Li
OPQ Regulatory Business Project Manager	Anita Brown, CDR Hamet Touré
OBP Application Technical Lead	Leslie Rivera-Rosado
OBP Reviewer	Andrea Franco
OBP Labeling	James Barlow
OPMA Facility Team Lead	Zhong Li
Microbiology	Max Van Tassell, Jeanne Ringer, Wendy Tan
OPDP	Kyle Snyder, Twyla Thompson
DMPP	Maria Nguyen, Marcia Williams
OSI	Suyoung Chang, Karen Bliech,
OSE/DEPI	Yan Li,Efe Eworuke
OSE/DMEPA	Lissa Owens, Idalia Rychlik
OSE/DPV	Scott Janiczak, Lisa Wolf
OSE/DRM	Donna Fitzgerald, Jackie Sheppard
OSE SRPM	Cristina Attinello, Nichelle Rashid
CDRH	Michaela Schulman, Suzanne Hudak
DCOA	Onyekachukwu Illoh, David Reasner
OCP	Issam Zineh
Genomics	Bart Rogers, Christia Grimstein

OPQ=Office of Product Quality
OBP=Office of Biotechnology Products

OPMA= Office of Pharmaceutical Manufacturing Assessment
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DPV= Division of Pharmacovigilance
DRM= Division of Risk Management
SRPM= Safety Regulatory Project Managers
CDRH= Center for Devices and Radiological Health
DCOA= Division of Clinical Outcome Assessment
OCP=Office of Combination Products

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Anup Srivastava	Office of New Drugs (OND)/Office of Immunology and Inflammation (OII)/Division of Pharmacology Toxicology for Immunology and Inflammation (DPTII)	Sections: 5	**Select one:** _X__ Authored ___ Approved
	Signature:			
Nonclinical Supervisor	Carol Galvis	OND/OII/DPTII	Sections: 5	**Select one:** ___ Authored _X__ Approved
	Signature:			
Nonclinical Division Director	Andrew Goodwin	OND/OII/DPTII	Sections: 5	**Select one:** ___ Authored __X_ Approved
	Signature:			
Clinical Pharmacology Reviewer	Jing Niu	Office of Translational Sciences (OTS)/Office of Clinical Pharmacology (OCP)/Division of Inflammation and Immune Pharmacology (DIIP)	Sections: 6, 16.2	**Select one:** __X_ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader	Yunzhao Ren	OTS/OCP/DIIP	Section: 6, 16.2	**Select one:** ___ Authored _X__ Approved
	Signature:			
Pharmacometrics Reviewer	Jing Niu	OTS/OCP/Division of Pharmacometrics (DPM)	Section: 6, 16.2	**Select one:** _X__ Authored ___ Approved
	Signature:			
Pharmacometrics Team Leader	Jerry (Jingyu) Yu	OTS/OCP/DPM	Section: 6, 16.2	**Select one:** ___ Authored __X_ Approved
	Signature:			
Division Director (Clinical Pharmacology)	Suresh Doddapaneni	OTS/OCP/DIIP	Section: 6, 16.2	**Select one:** ___ Authored _X__ Approved
	Signature:			
Clinical Reviewer	Jennifer Lan	OND/OII/Division of Pulmonology, Allergy, and Critical Care (DPACC)	Sections:1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 16.1	**Select one:** _X__ Authored ___ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Miya Paterniti	OND/OII/DPACC	Sections: all	**Select one:** ___ Authored _X__ Approved
	Signature:			
Division Director (Clinical)	Sally Seymour	OND/OII/DPACC	Section: 14 Sections: all	**Select one:** _X__ Authored _X__ Approved
	Signature:			
Office Director	Julie Beitz	OND/OII	Section: 15 Sections: all	**Select one:** _X__ Authored _X__ Approved
	Signature:			
Statistical Reviewer	Susan Mayo	OTS/Office of Biometrics (OB)/Division of Biometrics III (DBIII)	Sections:8.1, 8.3	**Select one:** _X__ Authored ____ Approved
	Signature:			
Statistical Team Leader	Yongman Kim	OTS/OB/DBIII	Sections: 8.1, 8.3	**Select one:** ___ Authored _X__ Approved
	Signature:			
Division Director (OB)	Laura Lee Johnson	OTS/OB/DBIII	Sections:8.1, 8.3	**Select one:** ___ Authored _X__ Approved
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1 Executive Summary

1.1. Product Introduction

Tezepelumab is a thymic stromal lymphopoietin (TSLP) blocker that binds TSLP and prevents the interaction of TSLP with the heterodimeric TSLP receptor. Tezepelumab is the first-in-class anti-TSLP monoclonal antibody. Tezepelumab is proposed as add-on maintenance treatment in patients with (b) (4) severe asthma aged 12 years and older, (b) (4) . The application supports the indication of add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. The Applicant also proposes tezepelumab for (b) (4) The proposed indication of (b) (4) The Applicant proposes a 210 mg every 4 week injection, presented in a single dose vial and single dose prefilled syringe via subcutaneous (SC) injection given in a healthcare setting. Tezepelumab was granted Breakthrough Drug Designation for severe asthma without an eosinophilic phenotype on September 4, 2018 as it showed preliminary efficacy in asthmatics across eosinophilic populations. (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval of tezepelumab 210 mg subcutaneous every 4 weeks for use as add-on maintenance treatment in adult and pediatric patients 12 years of age and older with severe asthma.

To support this application, the Applicant completed a 1-year dose ranging trial (PATHWAY) and a 1-year efficacy and safety trial (NAVIGATOR). Results of these two adequate and well-controlled trials demonstrated substantial evidence of effectiveness[2] by demonstrating a statistically significant and clinically relevant reduction in asthma exacerbations in patients with severe asthma. Improvements in secondary endpoints of lung function and PROs (AQLQ(6)+12 and ACQ-6) were also supportive. Both trials enrolled subjects regardless of baseline blood eosinophil level or FeNO level in which tezepelumab demonstrated efficacy across all levels. The adolescent subgroup was not powered to demonstrate statistical significance, but did show numerical and clinically meaningful reductions in asthma exacerbations and an improvement in lung function compared to placebo. This review team recommends approval in this pediatric age group, given the same pathophysiology for asthma in adults and adolescent, no age-related

[1] Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics; May 2014
[2] Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

differences in the pharmacokinetics (PK), and no safety concerns for the use of tezepelumab in this age group. The Applicant did conduct a third pivotal oral corticosteroid sparing (OCS) trial (SOURCE), but the trial did not demonstrate efficacy in oral corticosteroid reduction.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Tezepelumab is a TSLP blocker that binds TSLP, preventing it from interacting with the TSLP receptor, thereby modulating the downstream pathway involved in the Th2 immune response. Tezepelumab is a first-in-class biologic and the first biologic to demonstrate evidence of effectiveness (b) (4) The Applicant proposes tezepelumab for the add-on maintenance treatment of (b) (4) severe asthmatics in patients ≥12 years of age (b) (4) (b) (4) The submission supports modifying the proposed indication to add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

The efficacy and safety of tezepelumab was evaluated in two well-controlled and adequately designed trials including a 1-year dose-ranging trial and a 1-year efficacy and safety trial. Both trials demonstrated a statistically significant and clinically relevant reduction in asthma exacerbations and improvement in lung function in patients with severe asthma treated with the 210 mg Q4W dose of tezepelumab. Reduction in asthma exacerbation was demonstrated across all baseline eosinophilic levels and across all baseline levels of a related marker (FeNO). The adolescent subgroup showed a numerical and clinically meaningful reduction in asthma exacerbations along with improvement in FEV1 when compared to placebo. Given the same pathophysiology for asthma in adolescents along with the demonstrated positive trend, no age-related differences in the PK and PD, and no safety concerns for tezepelumab in adolescent patients, this review team recommends approval in the adolescent age group. The oral corticosteroid reduction trial did not demonstrate a reduction in daily OCS dose with use of tezepelumab.

The program included an assessment of safety concerns related to immunomodulatory therapy and biologics including infections, malignancy, hypersensitivity events, and immunogenicity. Injection site reactions were not common and overall equal in placebo and tezepelumab groups. There were no episodes of anaphylaxis reported related to tezepelumab and hypersensitivity reactions overall were equal in the placebo and tezepelumab groups. There was no increase in serious infections in the tezepelumab group. A third trial, which failed on efficacy assessing oral corticosteroid reduction, provided supplementary safety data and did not show any additional safety signals. No safety concerns were identified that offset the efficacy benefits provided by tezepelumab in both the adult and adolescent populations.

This review team recommends approval of tezepelumab in patients 12 years of age and older with severe asthma. No safety concerns were identified that would preclude approval in this population and safety findings seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction leading to chronic symptoms despite current standard of care treatment. While many exacerbations may be managed as an outpatient with the use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death. Severe asthma, a subset of asthma with uncontrolled symptoms despite maximal optimized therapy, accounts for approximately 4% of asthma patients[3]. Although the prevalence of severe asthma is low, it accounts for more than 60% of healthcare costs related to asthma.	Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma population continues to experience significant morbidity and the potential for mortality from this condition.
Current Treatment Options	Current available treatment options for patients with severe asthma who require add-on therapy to their existing asthma treatment regimen are limited to specific asthma phenotypes. These include omalizumab (anti-IgE), mepolizumab (anti-IL5), reslizumab (anti-IL5), benralizumab (anti-IL5), and dupilumab (anti-IL4Ra). Omalizumab is indicated for the add on maintenance treatment of patients ≥6 years and older with allergic asthma. The remaining biologics are approved for treatment of eosinophilic asthma. Dupilumab and mepolizumab are both approved down to 6 years of age. Benralizumab is approved down to 12 years of age and reslizumab is approved in patients ≥ 18 years of age.	The currently approved biologics are indicated for either those with allergic asthma or those with asthma with an eosinophilic phenotype. [redacted] (b) (4)

[3] Global Initiative for Asthma (GINA), 2020, Global Strategy for Asthma Management and Prevention, accessed July 16, 2021: http://www.ginasthma.org/.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In two well-designed and well-controlled trials, tezepelumab demonstrated a statistically significant and clinically relevant reduction in asthma exacerbations and improvement in lung function in patients with severe asthma. Both trials enrolled subjects regardless of eosinophil levels; efficacy was seen consistently across all baseline eosinophilic levels, although a larger treatment effect was seen in those with higher baseline eosinophilic levels. Tezepelumab addresses an unmet need for patients with severe asthma without an eosinophilic phenotype. • The adolescent subgroup showed numerical and clinically meaningful reductions in asthma exacerbations along with a clinically meaningful improvement in FEV1 compared with placebo. This subgroup, however, did not demonstrate statistically significant improvement which may be due to insufficient sample size to demonstrate a statistical difference. This review team recommends approval in this age group, due to the similar pathophysiology compared to adults, no age-related differences in the PK, and no safety concerns for the use of tezepelumab in adolescent patients.	Tezepelumab reduces asthma exacerbations and improves lung function in patients ≥12 years of age with severe asthma, regardless of eosinophilic level. (b) (4)
Risk and Risk Management	• Review of the safety data from the clinical development program did not identify any serious safety issues with tezepelumab. • No dose related adverse events were found. • Pharyngitis was the most common adverse event. • No increase in severe infections was found. • Injection site reactions were of equal frequency in tezepelumab and placebo groups.	The program does not demonstrate any safety findings that offset the efficacy findings. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• No episodes of anaphylaxis related to tezepelumab were reported. • Overall hypersensitivity reaction frequency was equal in tezepelumab and placebo groups.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8 and 11
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing caused by underlying airway inflammation and airway hyper-responsiveness. It is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction. The diagnosis and management of this common condition are outlined in the NAEPP[4] and Global Initiative for Asthma (GINA)[5] guidelines, which include a treatment approach of escalating daily maintenance therapy in accordance with a patient's symptoms. While the majority of patients are successfully managed with this step-wise treatment approach, a subset of patients remains uncontrolled despite maximal medical management.

Although the presenting symptoms may be similar, asthma is a heterogenous disease with different underlying processes driving the inflammation. The current thinking proposes that asthma may be categorized with four primary phenotypes. These include (1) early onset mild allergic asthma, (2) early-onset allergic moderate to severe remodeled asthma, (3) late-onset nonallergic eosinophilic asthma, and (4) late onset noneosinophilic asthma[6]. Currently, the approved biologics for moderate-to-severe and severe asthma target subjects with asthma categorized as eosinophilic phenotype or those who have an allergic trigger. There are no therapies for add-on maintenance therapy for moderate to severe or severe asthma which include non-eosinophilic asthma.

Tezepelumab, a human immunoglobulin (IgG2λ) monoclonal antibody targeting TSLP, is a new biologic and the first anti-TSLP proposed for the treatment of asthma, with or without an eosinophilic phenotype. TSLP is an epithelial cell-derived cytokine that occupies an upstream position in the asthma inflammatory cascade and therefore plays a central role in airway inflammation seen in asthma[7]. The mechanism of action of tezepelumab involves modulation of Th2 signaling that does not rely solely on inhibition of the IL-5 pathway and eosinophils and therefore, tezepelumab's clinical program enrolled patients regardless of eosinophil level given that it is an upstream mediator of the inflammatory cascade. TSLP has been found to be induced by both allergic and non-allergic triggers and therefore blocking this pathway may be beneficial for a wide population instead of a specific population.

[4] National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute (NHLBI), 2007, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, NIH publication no. 07-4051.
[5] Global Initiative for Asthma (GINA), 2020, Global Strategy for Asthma Management and Prevention, accessed July 16, 2021: http://www.ginasthma.org/.
[6] Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: Moving toward precision medicine. J Allergy Clin Immunol. 2019;144 (1):1-12.
[7] Gauvreau GM, O'Byrne PM, Boulet L-P, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. New Engl J Med. 2014;370:2102-10.

2.2. Analysis of Current Treatment Options

There are currently various approved biologics for add-on maintenance treatment of asthma which are summarized in Table 1. However, of those approved, each biologic targets a specific population of asthma patients (b) (4) Omalizumab, an anti-IgE, was the first approved biologic for asthma; however, the indication is limited to allergic asthma defined by a positive skin test or in vitro reactivity to a perennial aeroallergen. Then there are the biologics targeting the IL-5 pathway (i.e., mepolizumab, reslizumab, benralizumab), and antil-IL4Ra (dupilumab) which are indicated for treatment of asthma with an eosinophilic phenotype. (b) (4)

Table 1. Summary of Treatments Relevant to Proposed Indication

Product Name	Indication	Dose	Efficacy Information & Population Studied
Omalizumab (Approved 2003)	Moderate-to-severe persistent asthma in patients ≥6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with inhaled corticosteroids	75 to 375 mg SC every 2 to 4 weeks depending on weight and serum IgE	*Exacerbations* Omalizumab demonstrated a significantly lower rate of asthma exacerbations when compared to placebo in two trials in pediatric subjects ages 6 to <12 years. *Lung function* FEV1 was not significantly different in omalizumab-treated subjects compared to placebo.
Mepolizumab (Approved 2015)	Add-on maintenance treatment in patients ≥6 years of age with severe asthma with an eosinophilic phenotype	100 mg SC every 4 weeks	*Exacerbations* One phase 2b exacerbation trial demonstrated a reduction in exacerbations. The population was enriched with subjects meeting criteria believed to identify an eosinophilic phenotype. These criteria included peripheral blood eosinophil counts ≥ 300 cells/uL, sputum eosinophil counts > 3%, FeNO >50 ppm or loss of control with OCS dose reduction.

			One pivotal exacerbation trial demonstrated a reduction in exacerbations in severe asthma subjects on background standard of care with peripheral blood eosinophil count ≥150 cells/µl (within 6 weeks of dosing) or historical count ≥300 cells/µl (within 12 calendar months of enrollment) with a history of two exacerbations in the prior 12 months. *Adolescents* 28 adolescents were evaluated in the program with a trend toward exacerbation reduction. *Oral Corticosteroid Reduction* One trial demonstrated an ability to reduce oral corticosteroids dosage in severe asthma subjects with peripheral blood eosinophil count ≥150 cells/µl or historical count ≥300 cells/µl. *Lung function* No consistent improvement in lung function was seen in this development program. *Approval in subjects 6 to < 12 years of age* Based on 1-year PK/PD/safety in 36 pediatric subjects with severe eosinophilic asthma.
Reslizumab (Approved 2016)	Add-on maintenance therapy in patients ≥18 years old with severe asthma with	3 mg/kg IV every 4 weeks	*Exacerbations* Two pivotal trials demonstrated a reduction in exacerbations and improvements in lung function

	an eosinophilic phenotype		in severe asthma patients with a peripheral blood eosinophil count ≥400 cells/µl and a history of at least one asthma exacerbation in the prior 12 months. *Lung function* The two exacerbation trials and a third lung function trial in severe asthma patients with a peripheral blood eosinophil count ≥400 cells/ µl demonstrated an improvement in lung function. One trial evaluated lung function in asthma patients unselected for blood eosinophil levels. A lung function benefit was demonstrated in the overall population. No association between a treatment effect and blood eosinophil levels was seen. *Adolescents* 39 adolescents were evaluated in the program with point estimates favoring placebo in two exacerbation studies. Reslizumab is approved for use in patients 18 years of age and older given an unfavorable risk benefit
Benralizumab (Approved 2017)	Add-on maintenance treatment in patients ≥12 years of age with severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks x 3 doses, then every 8 weeks	*Exacerbations* Two pivotal trials demonstrated a reduction in exacerbations in severe asthma subjects with a peripheral blood eosinophil count ≥300 cells/µl within 3-4 weeks of dosing (primary analysis population) and a history of ≥2

			asthma exacerbations in the prior year. OCS use was allowed. Subjects with a baseline eosinophil count of ≥ 300 cells/µL showed a numerically greater response than those with <300 cells/µL . The exacerbation benefit was not statistically significant in those with < 300 cells/µL. *Lung function* One dose-ranging and two exacerbation trials demonstrated an improvement in lung function in subjects with a baseline eosinophil count ≥ 300 cells/uL. *Adolescents* 108 adolescents were evaluated in the program with similar PK and PD to adults. *Oral corticosteroid reduction* One trial demonstrated an ability to reduce oral corticosteroid dosage in severe asthma subjects with peripheral blood eosinophil count ≥150 cells/µl (within 6 weeks of dosing).
Dupilumab (Approved 2018)	Add-on maintenance treatment in 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.	Age ≥12 year old and older: 200 mg every 2 weeks with a 400 mg loading dose or 300 mg every 2 weeks with a 600 mg loading dose 6-11 year old:	*Exacerbations* Two pivotal trials demonstrated a reduction in exacerbations in severe asthma patients. In the primary analysis population (subjects with blood eosinophil count of ≥300 cells/µL in Trial 1 and the overall population in Trial 2), subjects receiving dupilumab 200 mg or 300 mg every 2

		100 mg every 2 weeks or 300 mg every 4 weeks subcutaneous for 15 to < 30 kg 200 mg every 2 weeks for ≥ 30 kg	weeks had a significant reduction in asthma exacerbations compared to placebo. Prespecified subgroup analyses of the trials demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. *Lung function* Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for both pivotal trials in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in Trial 1 and the overall population in Trial 2). Subgroup analysis of Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils. *Oral Corticosteroids Reduction* An oral corticosteroid reduction trial demonstrated that subjects receiving dupilumab achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. *Approval in 6-11 year old* Safety and efficacy for this age group was based on a 1-year, randomized, double-blind, placebo-controlled safety and efficacy trial in 408 subjects with moderate-to-severe

			asthma. The primary endpoint was annualized rate of severe exacerbations with key secondary endpoint of change from baseline in pre-bronchodilator percent predicted FEV1 at Week 12.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The key regulatory history is summarized in Table 2.

Table 2. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
IND 103031 filed	August 8, 2008	First in Human trial
EOP2 meeting	July 10, 2017	Agreed on adolescent enrollment and dosing
Breakthrough Drug Designation Granted	September 4, 2018	Based on results of their phase 2b Pathway trial. For patients with severe asthma without an eosinophilic phenotype as the drug showed preliminary efficacy in high and low eosinophil population and there are no approved therapies for patients who require add-on maintenance treatment of severe asthma without an eosinophilic phenotype.
Agreed Pediatric Study Plan	December 30, 2020	Amended PSP comprises 4 studies: • A phase 3 efficacy and safety study in adolescents and adults • A Phase 1 PK/safety study in children 5-11 years old • A phase 3 efficacy and safety study in children 5-11 years old • Phase 1 PK/PD safety study in children 2-4

		years old.
Pre-BLA meeting comments	February 28, 2021	Division agreed with pooling PATHWAY and NAVIGATOR trials for safety. Division relayed indication will be a review issue.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An Office of Scientific Investigations consult was requested due to the large clinical development program. The inspections qualified as Mission Critical as tezepelumab is a breakthrough therapy drug and that it also meets an unmet medical need to treat life-threatening disease. Initially, five sites were selected (Sorocaba, Brazil; Edmond, OK; Boerne, TX; Zaporizhzhia, Ukraine; Kyiv, Ukraine) due to higher enrollment, no previous inspections, high treatment responders, and previous site complaints. During assessment, the team determined that there were significant issues with the Kyiv site (data generated by Dr. Melnyk) as it failed to maintain source records. Furthermore, the central reader raised issues regarding the site's PFT measurements in addition tolab values that appeared suspicious as results looked similar amongst various subjects. (b) (4) OSI relayed they are unable to verify the reliability of the data from this site and therefore OSI recommended conducting a sensitivity analysis to assess the validity and robustness of the results from the primary analysis by excluding data generated by this site (See 8.1.4.8 Efficacy Results – Primary Endpoint). As OSI was unable to verify the reliability of the data from Dr. Melnyk's site, OSI identified an additional site to conducta clinical inspection in Charlotte, NC. OSI also conducted an Applicant/CRO inspection to understand study oversight, which showed compliance with Good Clinical Practice (GCP). After review of the clinical inspection in Charlotte, NC along with the previous sites, OSI did not find further issues with the development program.

4.2. Product Quality

Tezepelumab will be distributed in solution as a single-dose glass vial along with a single-dose pre-filled syringe. The data provided in this application support the conclusion that the proposed presentations combined with in process, release, and stability testing ensure process

consistency and drug substance, (b) (4) and drug product with appropriate quality attributes. The Office of Biotechnology Products recommends approval. For further details, see the review by Leslie Rivera Rosado.

4.3. Clinical Microbiology

The Division of Microbiology Assessment recommends approval based on review of the product quality microbiology and sterility assurance. For further details, see the reviews by Wendy Tan and Jeanne Fringer.

4.4. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health reviewed the device constituent of the combination product and recommends approval. The tezepelumab pre-filled syringe is supplied as a ready-to-use, single dose, prefilled and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange. See the CDRH review by Michaela Schulman for additional details.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Introduction
The Applicant has submitted a complete nonclinical pharmacology and toxicology program for tezepelumab. BLA 761224 is recommended for approval from the nonclinical pharmacology and toxicology perspective. There are no outstanding nonclinical issues.

Brief Discussion of Nonclinical Findings
The completed nonclinical studies support the approval of 210 mg tezepelumab to be administered once every four weeks subcutaneously as proposed in the labeling for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

The current review includes a detailed evaluation of the relevant nonclinical Pharmacology and Pharmacokinetics/ADME studies. The results of the general repeat-dose toxicology studies in monkeys ranging from 1-month to 6-month duration are summarized along with the complete review of the enhanced pre- and post-natal development (ePPND) toxicology study in monkeys. The carcinogenic risk assessment associated with long-term use of tezepelumab is also summarized.

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine produced in response to pro-inflammatory stimuli that drive allergic inflammatory responses mainly through its activity on dendritic and mast cells and thus, plays an important role in the pathophysiology of

diseases such as asthma and atopic dermatitis. TSLP signals through heterodimeric receptors that contain TSLPR and IL-7R alpha chains. TSLP first interacts with the cognate TSLPR thus potentiating recruitment of IL-7R alpha and forming an extracellular ternary complex leading to activation of intracellular signaling by the JAK/STAT and PI3K pathways.[8]

Tezepelumab is a high affinity antibody that binds to human TSLP (K_D=15.8 pM) and cynomolgus monkey TSLP (K_D=32.2 pM) at comparable binding affinities, thereby, prevents its interaction with the heterodimeric TSLP receptor (IL-7Rα and TSLPR human chains). Tezepelumab does not bind to non-primate species including mouse, rat, and rabbit. TSLP-induced phosphorylation of STAT5 was inhibited by tezepelumab in whole human blood ex vivo. M702 (anti-mouse TSLP surrogate antibody) decreased airway hyperresponsiveness and total leukocytes (neutrophils and eosinophils) in the bronchoalveolar lavage fluid (BALF) of animals treated with M702 in a mouse model of OVA-induced asthma. There were no treatment-related mortalities or treatment-related effects on cardiovascular function, respiratory rate, and neurological behavior following a single dose of 300 mg/kg IV tezepelumab in cynomolgus monkeys.

The Established Pharmacologic Class (EPC) for tezepelumab is "Thymic Stromal Lymphopoietin Blocker", as tezepelumab binds to the ligand TSLP and prevents its interaction with the heterodimeric TSLP receptor composed of TSLPR and IL-7R alpha chains.

Tezepelumab is absorbed slowly following subcutaneous administration in humans and monkeys and the SC bioavailability is also similar in humans (77% estimated based on population PK analysis) and monkeys (~73%). Tezepelumab distribution was confined to blood volume in both monkeys and humans. Tezepelumab $t_{1/2}$ was approximately 24-26 days in humans and 7-14 days in monkeys. These are consistent with expected $t_{1/2}$ values for hIgG1 mAbs.

Based on comparable binding affinities of tezepelumab to human and cynomolgus monkey TSLP, and lack of binding to other species, cynomolgus monkey was chosen as the most relevant toxicological species for nonclinical safety assessment. Tezepelumab was well tolerated in all the repeat-dose toxicity studies up to 6 months in duration via the SC or intravenous (IV) routes of administration and there were no dose—limiting toxicities across any of these studies. A 6-month SC and IV study in cynomolgus monkeys (once weekly dosing) represented the pivotal toxicology study to support the marketing approval of tezepelumab. No dose-limiting toxicities were identified. The target organs of toxicity were limited to injection site findings that were not always dose-dependent. The injection site findings were not considered dose-limiting because these are monitorable in the clinical setting. The mean $AUC_{0\text{-}168h}$ at the no observed adverse effect level (NOAEL) of 300 mg/kg/week SC (the highest dose tested) was 30,200 µg*day/mL. This exposure supports the clinical tezepelumab exposure at the maximum recommended human dose (MRHD) of 210 mg every 4 weeks (Table 13).

[8] Marković I and Savvides NS. Modulation of Signaling Mediated by TSLP and IL-7 in Inflammation, Autoimmune Diseases, and Cancer. Frontiers in Immunology 2020;11:1557.

The conduct of carcinogenicity studies in rodents was not feasible as tezepelumab does not bind to rodents' TSLP. Therefore, a carcinogenicity risk assessment was conducted. Based on the results of the 6-month study in monkeys as well as evidence from the available scientific literature, the malignancy risk in humans by chronic inhibition of TSLP via tezepelumab treatment is currently unknown.

In an enhanced pre- and post-natal development (ePPND) study, pregnant female cynomolgus monkeys were treated with 50 mg/kg or 300 mg/kg tezepelumab (IV) once every 7 days from GD20-22 until the end of gestation. There were no effects of tezepelumab on maintenance of pregnancy or delivery. Moreover, there were no effects of maternal tezepelumab treatment on behavioral, physical, or neurological measurements in F1 infants that were followed for 6.5 months postnatally. Therefore, the maternal NOAEL and the fetal/infant NOAEL in this study were determined at 300 mg/kg.

5.2. Referenced NDAs, BLAs, DMFs

- IND 103031: Tezepelumab for the add-on maintenance treatment of (b) (4) (b) (4) severe asthma (b) (4)
  - All nonclinical studies in support of approval of BLA 761224 were submitted to IND 103031.

5.3. Pharmacology

Tezepelumab is a fully humanized monoclonal immunoglobulin (IgG2λ) that is directed against thymic stromal lymphopoietin (TSLP). TSLP is an epithelial cell derived cytokine produced in response to pro-inflammatory stimuli that drives allergic inflammatory responses through its activity on dendritic and mast cells. The Applicant proposes that inhibition of TSLP may inhibit multiple biological pathways, including those involving IL-4 and IL-13, which will reduce asthma. In support of this hypothesis, the Applicant conducted a series of in vitro and in vivo studies using tezepelumab and a constructed surrogate mouse anti-TSLP (M702) (Table 3). Tezepelumab bound to cynomolgus monkey and human TSLP with high affinity. However, it did not bind to mouse, rat, or rabbit TSLP. In an in vivo safety pharmacology study conducted in the cynomolgus monkey, single dose IV injection of tezepelumab up to 300 mg/kg did not affect hemodynamic parameters, body temperature, respiration rate, ECG, or neurological behavior.

The Established Pharmacologic Class (EPC) was discussed with Dr. Paul Brown (Pharm-Tox Associate Director) and the final EPC was determined as "Thymic Stromal Lymphopoietin (TSLP) Blocker" based on the pharmacology of TSLP and the mechanism of action of tezepelumab. Generally, the term "blocker" is used for molecules that prevent a ligand receptor interaction not only by binding to the receptor but also by binding to the ligand. In this case, tezepelumab binds to TSLP (ligand), thereby, prevent its interaction with the TSLP receptor. Therefore, TSLP blocker is the most appropriate EPC for tezepelumab.

Table 3. Summary of pharmacology studies with tezepelumab or M702 (mouse anti-TSLP surrogate)

Study	Methods	Results
In vitro/non-GLP studies		
Inhibition of ^{125}I-recombinant human TSLP binding to cell surface expressed human TSLP receptor complex on BAF/HTR cells (mouse IL-3 dependent pro-B cell line) by unlabeled human TSLP, mouse anti-human TSLP receptor (M505) or tezepelumab (Study: R20070415)	Saturation binding and inhibition curves using radiolabeled ligand (^{125}I-labeled rhTSLP) Biacore Analysis	▪ ^{125}I-rhTSLP bound to BAF/HTR cells with a K_d= 324 pM and at 855 sites/cell ▪ K_i of unlabeled rhTSLP=157pM ▪ The K_is for M505 or tezepelumab inhibition of ^{125}I-rhTSLP binding to BAF/HTR cells were 360 pM and 28.7 pM, respectively. ▪ Data shows that tezepelumab has good characteristics for inhibiting binding of rhTSLP to TSLP receptor at very high affinity.
In vitro characterization of anti-human TSLPmAB tezepelumab: Recombinant and native binding affinities, IC_{50} values and Species Cross Reactivity (Study: R20070150)	Three assays were conducted: BAF:HuTSLPR proliferation, BAF:CynoTSLPR proliferation, and Primary human dendritic cell osteoprotegerin production assays Pre-determined EC_{90} amounts of TSLP were used in each assay as appropriate and incubated with serially diluted tezepelumab for 30 minutes at room temp prior to addition to assay. IC_{50} values were calculated. Binding affinity data were generated using BIAcore.	▪ Primary human dendritic cells IC_{50} for tezepelumab: 48 to 422 pM ▪ Primary Cynomolgus PBMC IC_{50} for tezepelumab: 97 to 411 pM ▪ IC_{50} of tezepelumab in BAF:Hu TSLP proliferation assay against recombinant and native human TSLP is 37 and 33 pM, respectively. ▪ IC_{50} of tezepelumab in BAF:Hu TSLP proliferation assay against recombinant and native cynomolgus TSLP is 91 pM and 582 pM, respectively. ▪ IC_{50} of tezepelumab in BAF:Cyno TSLP proliferation assay against recombinant Cynomolgus TSLP=268 pM ▪ Human TSLP to tezepelumab K_D=15.8 pM ▪ Cynomolgus TSLP to tezepelumab K_D= 32.2 pM ▪ Mouse TSLP to tezepelumab K_D=0 ▪ Based on comparable binding affinities (< 10-fold difference in potency) of tezepelumab to human and cynomolgus monkey TSLP, cynomolgus monkey was chosen as the most relevant toxicological species for nonclinical safety assessment.
Binding of tezepelumab to rat and rabbit TSLP	ELISA	▪ Tezepelumab did not bind to rat or rabbit TSLP.

Study	Methods	Results
(Study: 154365)		▪ Human TSLP was included as a positive control and binding to tezepelumab was readily detected.
Activity of tezepelumab in whole blood assays (Study: R20070151)	Dendritic cells (DC) isolated from a leukopak were spiked into whole blood collected at the time of leukopheresis from the same donor. Tezepelumab (2µg/mL to 8 pg/mL) was added to whole blood or combined with TSLP (15 pg/mL and 75 pg/mL) ex vivo for 1 h. A dilution series of TSLP was added to the DC-spiked whole blood. Phosphoprotein signaling was stopped 15 min after addition of the TSLP using Phosflow buffer and the extent of STAT5 phosphorylation was measured using a flow cytometer.	▪ Tezepelumab inhibited TSLP induced phosphorylation in DCs in whole blood. ▪ Stimulations with 15 pg/mL of TSLP were calculated to be half maximally inhibited by 22.65 ng/mL of tezepelumab when the mAb was preincubated 2 h in blood prior to TSLP addition. ▪ TSLP/tezepelumab complex preformed prior to its addition to DC spiked whole blood was calculated to be half maximally inhibited by 0.48 ng/mL of tezepelumab. ▪ When STAT5 phosphorylation was induced with TSLP at 75 pg/mL half maximal inhibition was calculated to occur at 27.08 ng/mL of tezepelumab. Preexisting complex at this concentration of TSLP were half maximally inhibited at 0.36 ng/mL of tezepelumab. ▪ Tezepelumab is able to bind TSLP and prevent signal transduction induced by added ligand (TSLP) in ex vivo whole blood stimulations and it indicates that presence of serum did not affect the ability of tezepelumab to bind to its target and to block signaling.
In vitro characterization of the anti-mouse TSLP Surrogate antibody M702 (Study: R20080116)	Two methods were used: Pre-determined EC_{90} amounts of TSLP were utilized in each bioassay as appropriate and incubated with serially diluted M702 for 30 minutes at room temp prior to addition to the assay. IC_{50} values were determined using the GraphPad PRISM program. Binding affinity data were generated via BIAcore.	▪ M702 inhibited recombinant mouse TSLP induced activity in the BAF:MuTSLPR proliferation assay with an IC_{50} value of 209 pM. ▪ In the primary mouse dendritic cell assay, M702 inhibited mouse TSLP with an IC_{50} value of 229 pM. ▪ M702 was found to bind mouse TSLP with a binding affinity (K_D) of 41 pM as determined via BIAcore. ▪ These data show that M702 is an active surrogate of tezepelumab in mice and could be potentially

Study	Methods	Results
		used for nonclinical in vivo pharmacology studies.
In vivo/non-GLP studies		
Treatment with anti-mouse TSLP antibody M702 inhibits inflammation parameters in mouse OVA asthma model (Study: R20070146)	BALB/c and C57BL/6 mice were sensitized to OVA antigen and treated with IV and intranasal (IN) doses of M702 at various doses to determine : airway hyperresponsiveness (AHR), serum IgE concentrations bronchoalveolar lavage fluid (BALF) cellularity and differentials, BALF IL5 and IL13, IL4, IL5, IL13 production in lung lymph node cell cultures, total lung lesion scores and lung mucus production	▪ M702 reduced BAL fluid cellularity and AHR when administered IV throughout OVA priming and OVA challenging phases. ▪ M702 reduced serum IgE concentrations when administered IN during OVA challenge phase. ▪ Inhibition of TSLP with mAB inhibits inflammatory cell influx into lung and BALF and increased serum IgE concentrations in mouse. ▪ This indicates the potential of tezepelumab in mitigating the characteristics of airway disease by blocking the pharmacological actions of TSLP.
Effect of M702 in the FITC- induced contact hypersensitivity response (Study: R2007147)	Female C57BL/6 or BALB/c mice (5 mice/group and 3 groups) sensitized to hapten fluorescein isothiocyanate (FITC) were challenged with FITC on the left ear and vehicle on the right ear. Mice were treated with M702 or isotype control at various times throughout the challenges. Then, 24 and 48 h later the thickness of the ears was measured.	▪ M702 reduced the 24 h inflammatory response by 60% in C57BL/6 mice and 36% in BALB/c mice, respectively. ▪ This model was used due to its similarity to atopic dermatitis in humans and it suggests that TSLP blockade impacts the initiation of the FTIC immune response.
Intranasal TSLP instillation induces pulmonary inflammation and is inhibited by anti-TSLP mAb M702 and Anti-IL-4Rα mAb Mu317RaXMu (BAL Cellularity, histology) (Study: R20070148)	BALB/c mice were IN challenged daily with TSLP for 2 weeks. Cohorts of mice were treated once weekly with mAB against TSLP or anti-IL-4Rα during week 2 of challenge. Mice were assessed for changes in BALF cells and BALF analytes, lung histopathology and lung collagen.	▪ 2 weeks of TSLP challenge resulted in an increase in inflammatory cells in the BALF and lung tissue and in goblet cell hyperplasia. ▪ Treatment with M702 or Mu317RaXMu prevented accumulation of inflammatory cells in the BALF (-53% of CD40 and -63% of VCAM-1) and lung tissue, and completely (M702) or partially (Mu317RaXMu) inhibited goblet cell hyperplasia as observed histologically.

Study	Methods	Results
		▪ Only treatment with Mu317RaXMu but not M702, reduced CD40 in BALF relative to control. ▪ Data suggest a phenotype induced by TSLP and mediated through IL-4Rα pathway which can be only partially attenuated by blocking TSLP.
Effects of intradermally injected murine TSLP protein into Wild Type (WT), STAT6 knockout (KO) and IL-4Rα KO mice (Study: R20070149)	BALB/c or IL4Rα KO or STAT6 KO female mice received 10 µg TSLP or MSA (mouse serum albumin) as a protein control intradermally 3 times per week for 2 weeks. At the end, the skin was histologically analyzed, assessed for mRNA expression, draining LNs were harvested for in vitro restimulation and analysis of cytokine production, and blood was taken for determination of serum IgE levels by ELISA.	▪ TSLP injected intradermally induces skin inflammation, and increased Th2 cytokine and chemokine gene expression in WT mice. ▪ Mice lacking IL4Rα or STAT6 reduced these TSLP-induced effects but did not ablate TSLP effects. ▪ Therefore, TSLP may induce skin inflammation via different pathways independent of IL4 or IL13.
Safety pharmacology/GLP		
Effects of single dose IV tezepelumab on cardiovascular, respiratory, and neurobehavioral endpoints in cynomolgus monkeys (Study: 109453)	4 male telemetry-instrumented cynomolgus monkeys were dosed intravenously with vehicle and 300 mg/kg tezepelumab IV on Day 1 and Day 3, respectively.	▪ No treatment-related mortalities or treatment-related effects on cardiovascular function, respiratory rate, neurological behavior, and body temperature were noted.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
A Pharmacokinetic Study of AMG 157 in Male Cynomolgus Monkeys Following Single-Dose Intravenous (5 mg/kg) or Subcutaneous (5 and 50 mg/kg) Administration (Study: 108662) (non-GLP)	▪ Mean $T_{1/2}$ for both IV and SC administration of tezepelumab ranged from 7 to 10 days. ▪ Systemic exposure to tezepelumab increased in a slightly less than dose proportional manner from 5 to 50 mg/kg SC doses (~8.26 fold instead of 10-fold). ▪ Anti-tezepelumab antibody was observed in 2/3 males at 50 mg/kg SC and in 1/3 males at 5 mg/kg IV. These animals were excluded from PK analysis. ▪ At 5 mg/kg SC dose, bioavailability was ~73%. This is generally consistent with bioavailability values reported for approved SC therapeutic mAbs.[9] ▪ In humans, estimated bioavailability after SC administration based on population PK was 76.8%, consistent with bioavailability values in monkeys and other approved SC mAbs.
A Single-Dose Pharmacokinetic Study of AMG 157 in Naïve Female Cynomolgus Monkeys Following Subcutaneous Dose Administration (0.1, 0.3, 1.0, and 3.0 mg/kg) *(Study: 109742) (non-GLP)*	▪ Systemic exposure to tezepelumab following SC administration was increased in an approximately dose-dependent manner. ▪ T_{max} was ~3.0 days in both males and females. ▪ Mean $T_{1/2}$ ranged from 9.7 to 14 days. ▪ In humans, SC tezepelumab absorption rate constant (k_a) from population PK analyses was estimated to be 0.316 day^{-1} which is consistent with the k_a values for approved SC therapeutic antibodies. [10] ▪ C_{max} and $AUC_{0\text{-}168\ h}$ values at the NOAEL dose in the 6-month SC cynomolgus monkey study exceed the clinical values at the maximum recommended human dose of 210 mg Q4W by 128-fold and 134-fold, respectively.

[9] Keizer RJ, Huitema ADR, Schellens JHM and Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinetics 2010;49:493-507
[10] Keizer RJ, Huitema ADR, Schellens JHM and Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinetics 2010;49:493-507

Type of Study	Major Findings
Distribution	▪ Mean steady state tezepelumab volume of distribution (V_{ss}) in cynomolgus monkeys following a single IV dose (5 mg/kg) was approximately 50 mL/kg. This is approximately equivalent to the cynomolgus monkey total blood volume, [11] and it indicates limited extravascular distribution. This is expected V_{ss} for a monoclonal antibody.[12] ▪ In humans, tezepelumab V_d ranged from 5.5 to 6.0 L at doses between 35 mg to 280 mg in study D5180C00003. These values were within the total blood volume in humans (~5 L), suggesting that tezepelumab has limited extravascular distribution in humans.
Metabolism	▪ Metabolism studies were not conducted with tezepelumab as the metabolic pathways of a therapeutic mAb are expected to be consistent with other endogenous antibodies (e.g. proteolysis in liver and phagocytic cells of the immune system).
Excretion	▪ Tezepelumab clearance in male and female monkeys ranged from 3.67 to 6.83 mL/day/kg. These values are consistent with published values for 13 other humanized IgG antibodies in cynomolgus monkeys.[13] ▪ Tezepelumab clearance in humans ranged from 2.33 to 2.95 mL/day/kg, comparable to the values observed in monkeys. These values are generally consistent with clearance values reported for other approved therapeutic mAbs on a human IgG1 framework.[14] ▪ Mean $T_{1/2}$ in monkeys after SC administration ranged from 7-14 days. Mean $T_{1/2}$ in humans was slightly higher (24-26 days). These are consistent with expected $T_{1/2}$ values for hIgG1 mAbs. • Long $T_{1/2}$ may be related to the binding of IgG to FcRn (protects against endosomal degradation) in endothelial cells.

[11] Ageyama N, Shibata H, Narita H, Hanari K, Kohno A, Ono F, Yoshikawa and Terao K. Specific gravity of whole blood in cynomolgus monkeys, squirrel monkeys, and tamarins and total blood volume in cynomolgus monkeys. Contemporary Topics in Laboratory Animal Science. 2001; 40:33 – 35.
[12] Ryman JT, Meibohm B. Pharmacokinetics of Monoclonal Antibodies. CPT Pharmacometrics Syst Pharmacol. 2017 Sep;6(9):576-88.
[13] Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, and Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: What have we learned? mAbs. 2011;3:1:61–66.
[14] Lobo ED, Hansen RJ, and Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. Journal of Pharmaceutical Sciences. 2004; 93:2645-2668.

Type of Study	Major Findings
TK data from general repeat-dose toxicology studies in monkeys (GLP)	Monkey No target organs of toxicity were identified in any of these studies except for injection site findings that are considered clinically monitorable.
1-month SC toxicity study with 4-month recovery period (Study: 108823) Doses- 0, 30, 100, 300 SC QW	▪ *T1/2: Not reported* ▪ *Accumulation: Ranged from 1.72 to 2.34 across all doses from Day 1 to 22, indicating ~2.0-fold accumulation over time.* ▪ *Dose proportionality: Systemic exposure to tezepelumab increased dose proportionally from 30 to 100 mg/kg and slightly less than dose proportionally from 100 to 300 mg/kg, (increased by 2.5-fold instead of 3.0-fold).* ▪ NOAEL was determined at 300 mg/kg, SC and corresponding $AUC_{0\text{-}168h}$ of 29,000 µg*day/mL.
1-month IV toxicity study with 4-month recovery period (Study: 111874) Doses-0, 50, 300 IV QW	▪ *T1/2: Not reported* ▪ *Accumulation: Ranged from 1.41 to 1.55 across all doses from Day 1 to 22, indicating slight accumulation over time.* ▪ *Dose proportionality: Systemic exposure to tezepelumab increased approximately dose-proportionally from 50 to 300 mg/kg.* ▪ *NOAEL was initially determined at 50 mg/kg due to kidney vascular findings at 300 mg/kg and an IR was sent to the Applicant to justify the kidney findings. Based on the lack of correlative evidence of disease, the kidney vascular finding in this animal was considered pre-existing. Because no findings of concern were observed in the kidney in the 6-month study, the reviewer agreed with the Applicant and therefore the NOAEL could be determined at 300 mg/kg with corresponding $AUC_{0\text{-}168h}$ of 38,900 µg*day/mL.*
3-month SC toxicity study with 5-month recovery period (Study: 108448) Doses-0, 50, 100, 300 SC QW	▪ *T1/2: Not reported* ▪ *Accumulation: Ranged from 1.8 to 3.2 across all doses from Day 1 to 85, indicating significant accumulation over time.* ▪ *Dose proportionality: Systemic exposure to tezepelumab increased approximately dose proportionally from 50 to 300 mg/kg.* ▪ *NOAEL was determined at 300 mg/kg, SC with corresponding $AUC_{0\text{-}168h}$ of 31,125 µg*day/mL.*

Type of Study	Major Findings
6 months, SC and IV (Study: 108824) Doses- 0, 50 IV QW; 0, 50, 300 SC QW	▪ *T1/2: Not reported* ▪ *No difference in tezepelumab exposure between males and females* ▪ *Accumulation: Ranged from 1.74 to 2.44-fold and ~1.73-fold after SC and IV administration, respectively.* ▪ *Dose proportionality: Systemic exposure to tezepelumab increased approximately dose proportionally on Day 1 and less than dose proportionally on Day 176.* ▪ *NOAEL was determined at 300 mg/kg, SC with corresponding AUC_{0-168h} of 30,200 µg*day/mL.*
TK data from reproductive toxicology studies Enhanced Prenatal and Postnatal Development Study (ePPND) (Study: 108825) Doses- 0, 50, 300 mg/kg QW SC	Monkey ▪ *As there were no drug-related effects, the NOAELs for maternal and fetal/infant were determined at 300 mg/kg, SC with corresponding AUC_{0-168h} of 38,000 µg*day/mL.* ▪ Tezepelumab crossed the placenta in cynomolgus monkeys and its' serum concentrations were 0.5 to 6.7-fold higher in infants relative to maternal animals.

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 6-Month (one weekly) subcutaneous and intravenous injection toxicity study of tezepelumab in Cynomolgus monkeys with a 5-Month treatment-free phase (Study: 108824)

- No dose-limiting toxicities were identified. The target organs of toxicity were limited to injection site findings that were not always dose-dependent. The injection site findings were not considered dose-limiting because these are clinically monitorable.
- NOAEL was determined at 300 mg/kg/week SC and was associated with a mean AUC_{0-168h} of 30,200 µg*day/mL (male and female combined).
- *A more detailed review of this study can be found in the IND 103031 nonclinical review dated September 24, 2013*.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (vehicle control using SC injection), 0 (vehicle control using IV injection), 50 mg/kg SC, 50 mg/kg IV, or 300 mg/kg SC; Once weekly for 26 doses.
Route of administration:	Subcutaneous (scapular region) or Intravenous Injection (saphenous vein)
Formulation/Vehicle:	(b) (4) polysorbate (b) (4) (pH = 5.2)
Species/Strain:	Cynomolgus monkey (*Macaca fascicularis*)
Number/Sex/Group:	6/sex/group at 50 mg/kg IV, 300 mg/kg SC, and the vehicle control SC; 4/sex at 50 mg/kg SC; 2/sex at the vehicle control IV
Age:	Males: 5-7 years Females: 3-5 years
Satellite groups/ unique design:	2 animals/sex in groups 1 (control-SC), 4 (50 mg/kg IV), and 5 (300 mg/kg SC) were maintained in the study for a 5-month recovery period
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	▪ One animal at the 50 mg/kg IV dose (animal number I00505) was euthanized on study day 156 due to poor clinical condition. The cause of death in this animal was considered to be development of anti-tezepelumab antibodies that formed immune complexes and caused vascular inflammation. Therefore, this animal's death was not attributed to tezepelumab treatment.
Clinical Signs	None
Body Weights	None
Ophthalmoscopy	None
ECG	None

Hematology	▪ Females only: transient increase in WBCs (+41% to +43% at 50 mg/kg SC and +42% to +66% at 300 mg/kg SC) and monocytes (+22% to +58% at 50 mg/kg, SC and +35% to +92% at 300 mg/kg, SC). Both parameters were normalized by dosing day 169. ▪ Males only: transient decrease in eosinophils starting on dosing day 162 and until dosing day 176 (-37% to -54% at 50 mg/kg SC and -38% to -76% at 300 mg/kg SC). After 50 mg/kg IV dose, transient decrease in eosinophil levels was also observed (-53% to -68%). ▪ As these changes were not always dose-related, therefore, its relationship to tezepelumab treatment is unclear.
Clinical Chemistry	▪ Decreased cholesterol was observed in males treated with 300 mg/kg SC tezepelumab (-19% to -23%); and in females treated with 50 mg/kg IV tezepelumab (-23% to -33%) and with 300 mg/kg SC tezepelumab (-26% to -32%). ▪ Non-dose dependent/transient increase in ALP in famles at all doses (+26% to +45% at 50 mg/kg SC, +30% to +54% at 50 mg/kg IV, and +51% to +57% at 300 mg/kg SC). ▪ These finds were not considered dose-limiting as these were not associated with histopathology or other findings of concern.
Urinalysis	None
Gross Pathology	None
Organ Weights	None
Histopathology Adequate battery: Yes	▪ Treatment-related histological findings included only the injection sites characterized by perivascular lymphocytes/macrophages infiltrates. ▪ These findings were not dose-related and were reversible after a 5-month recovery period. ▪ Further, these injection site findings are considered clinically monitorable and, therefore, not dose-limiting.

Special Evaluation Male reproductive assessment	▪ No drug-related changes were observed in percent motility, density, or sperm morphology in drug-treated animals compared to vehicle controls.
Female reproductive assessment	▪ No drug-related changes were observed on menstrual cycle length.
Immunophenotyping	▪ Tezepelumab treatment resulted in increased B cell counts (absolute and relative) at two SC doses with no clear dose-dependent trend. NKC count (absolute and relative) was increased dose-dependently at all doses in males but not in females. Total T cell count (%), primarily CD8 T cells were slightly decreased at 50 mg/kg IV and 300 mg/kg SC.
Antibody analysis	▪ 5/32 and 2/8 monkeys treated with tezepelumab developed anti-tezepelumab binding antibodies during the dosing phase and during the recovery phase, respectively. ADAs were non-neutralizing and development of ADAs did not affect tezepelumab systemic exposure.
Immune complex analysis	▪ Only animal I00505 (euthanized on study day 156 due to poor clinical condition) was found positive for circulating immune complexes (CIC) on study day 156, with a concentration of > 32 µg/mL. All the other samples were negative for CIC. Detection of CIC in monkey is not predictive of CIC formation in humans (as per ICH S6(R1) guideline) and thus, does not contribute to the human risk profile assessment.

-: indicates reduction in parameters compared to control
+: indicates increment in parameters compared to control

General toxicology; additional studies

5.5.2. Genetic Toxicology

Genetic toxicology studies are not applicable to mAbs and were not conducted with tezepelumab.

5.5.3. Carcinogenicity

The Applicant submitted an assessment of carcinogenic risk associated with long-term inhibition of TSLP using a weight-of-evidence approach. This approach entailed a thorough review of nonclinical and clinical data generated till date with tezepelumab and also literature data related to TSLP mechanism of action and biology. Based on the available data, lack of binding of tezepelumab to rodents' TSLP, and lack of human TSLP transgenic mice, a standard 2-year rodent bioassay is considered unfeasible and not needed for the safety assessment of

tezepelumab. Further, as per ICHS6(R1), studies with murine surrogates would not be able to provide meaningful information about the carcinogenicity risk of tezepelumab. Overall, it can be concluded that the malignancy risk in humans by chronic inhibition of TSLP via tezepelumab treatment is currently unknown. *A more detailed review of the carcinogenicity assessment can be found in the IND 103031 nonclinical review dated March 20, 2018.*

5.5.4. Reproductive and Developmental Toxicology

Enhanced Prenatal and Postnatal Development Study (ePPND)

Study title/ number: Maternal, Embryo-Fetal, and Neonatal Toxicity Study of AMG 157 Administered by Intravenous Injection to Pregnant Cynomolgus Monkeys with 6.5-Month Postnatal Evaluation (Study number: 108825)

Key Study Findings

- ADAs were detected in the plasma of a subset of maternal animals and infants.
  - Maternal animals: 50 mg/kg- 4/24 (16.7%); 300 mg/kg- 11/17 (64.7%)
  - Infants: 1/11 infants delivered from 1 maternal animal at 300 mg/kg who tested positive for ADA.
  - Systemic exposure to tezepelumab was not affected by the presence of ADAs in maternal animals and infant.
- Tezepelumab was detected in maternal milk up to ~0.5% of the maternal plasma concentration.
- As there were no drug-related effects, the NOAELs for maternal and fetal/infant were determined at 300 mg/kg (high dose).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	Pregnant females- 0, 50, and 300 mg/kg IV. See below (Table 4, excerpted from Applicant's submission). Once on GD20-GD22 (based on the day of pregnancy confirmation) and once every 7 days until the end of gestation.
Route of administration:	Intravenous (IV)- slow bolus injection via saphenous vein (cephalic vein was used on 7 dosing occasions)
Formulation/Vehicle:	(b) (4) polysorbate (b) (4), pH 5.2
Species/Strain:	Cynomolgus monkeys (*Macaca fascicularis*)
Number/Sex/Group:	0 mg/kg-14 pregnant females; 50 mg/kg-23 pregnant females; 300 mg/kg-16 pregnant females
Satellite groups:	NA

Animal age:	4.4 to 11.5 years of age
Animal weight:	2.6 to 4.1 kg on Day -2 of the study
Study design:	▪ Sexually mature and experimentally naïve males were used for breeding ▪ Adult female was paired with male for 3 days during the anticipated time of ovulation ▪ Pregnancy was determined by ultrasound once b/w GD18-GD20 and confirmed within 2 to 4 days b/w GD20-GD22. ▪ Note that the dosing period is consistent with the guidelines for ePPND studies in the ICH S6 addendum ▪ During gestation, pregnancy status was monitored via ultrasound conducted biweekly starting on GD32. ▪ C-sections were not performed as all deliveries had occurred by GD175. (GD175 is the maximum acceptable length of normal gestation in cynomolgus monkeys (normal range: 160±10 days)[15] ▪ Infants were euthanized on BD180±2 days (single KLH challenge; 6 infants) or BD195±1 day (dual KLH challenge; 28 infants). ▪ All adult females assigned to study will be released from study and returned to the animal colony on PPD180 ± 2 days at the time of the infant necropsy.
Deviation from study protocol affecting interpretation of results:	No

[15] Hendrie TA, Peterson PE, Short JJ, Tarantal AF, Rothgarn E, Hendrie MI and Hendrickx AG. Frequency of prenatal loss in a macaque breeding colony. Am. J. Primatol. 1996;40:41-53

Table 4. Experimental Study Design for the ePPND Study

Group No.	Number of Pregnant Females[a]	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Solution Concentration (mg/mL)
1	14	0 (control)	4.3	0
2	23	50	4.3	12
3	16	300	4.3	70

[a] Includes 2 females in each of Groups 2 and 3 that were enrolled onto study to replace early pregnancy losses prior to GD50. One additional female in each group (1-3) was replaced that was presumed to have aborted but was subsequently found not to be pregnant by mCG analysis. Includes 7 females in Group 2 that were enrolled onto study to ensure an adequate group size for data interpretation.

Observations and Results

F_0 Dams

Pregnancy outcome

Initially 14 pregnant females per group were planned for study enrollment. However, due to early abortions (prior to GD50), 2 additional pregnant females were added to each of groups 2 and 3 to maintain the group total at 14 pregnant females dosed through parturition. It is to be noted that pregnancy losses after GD50 (late losses) were not replaced. Additionally, Applicant included 7 pregnant females to Group 2 to ensure that sufficient number of infants are available for post-natal data interpretation. One additional female in each group (1-3) was replaced that was earlier presumed to have aborted but was later found to be not pregnant as revealed by mCG analysis. The reason for adding 7 pregnant females exclusively to Group 2 has not been specified by the Applicant.

Table 5. Summary of Pregnancy Outcome

Group No.	Dose Level (mg/kg)	No. of Pregnant Females [a]	No. of Live Infants (M/F)			No. of Pregnancy/Fetal Losses (M/F/U)	Mean Gestation Length of Live Births (Days)
			Total	Males	Females		
1	0 (control)	14	11	7	4	3 (2/1/0)	158.8
2	50	23	15	8	7	8 (2/3/3)	156.0
3	300	16	12	5	7	4 (1/1/2)	157.7
Total		**53**	**38**	**20**	**18**	**15**	**-**
Historical Control Data [b]		149	112			37	159.0 ± 6.4

M-male; F-female; U-unknown

[a] Includes 2 females in each of Groups 2 and 3 that were enrolled onto study to replace early pregnancy losses prior to GD50. One additional female in each group (1-3) was replaced that was presumed to have aborted but was subsequently found not to be pregnant by mCG analysis. Includes 7 females in Group 2 that were enrolled onto study to ensure an adequate group size for data interpretation.

[b] Based on control data from 8 ePPND studies conducted at the Testing Facility from 2008 to present.

Salient features of pregnancy outcome data summarized in Table 5, are as follows:

- In total 38 live-births from 53 pregnancies (~71.7%) were recorded across all the dose groups. Around 71.7% live births in this study were comparable to results from control pregnancies in eight ePPND studies of similar design occurring at the Testing Facility (112 live births out of 149 pregnancies [~75.2%]; range from 61.1% to 93.3%).
- The number of male: female live infants in each group was 7:4 (Group 1); 8:7 (Group 2); and 5:7 (Group 3). Although the number of males in the control group was disproportionately higher (~63.6%) as compared to the number of males in Group 2 (~53.3%) and Group 3 (~41.6%), it was not considered outside the wide range of normal variation in M:F infant ratios in these studies in nonhuman primates.
- The mean gestational length of live births ranged between 156-158 days across all groups, and this was within the historical control range (139-175 days; mean 159.0 days) for the Testing Facility.

Fetal Losses

Fetal losses prior to GD140 were considered as abortions, and those on or after GD140 were considered stillbirths because infants born on or after GD140 can be expected to survive.[16]

The overall incidence of embryonic or fetal loss ranged from 21.4% to 34.8% across all dose groups and was within the historical control range for this type of study. In the 300 mg/kg dose group, the mortality rate of 12.5% in first trimester was higher than the historical control range (0 to 11.8%). However, these losses are unlikely to be related to tezepelumab treatment because fetal exposure to monoclonal antibodies is expected to be low during first trimester in both non-human primates (NHPs) and humans. Generally, in NHPs and humans, the IgG placental transfer is low in the period of organogenesis and begins to increase in early second trimester, reaching highest levels late in third trimester.[17] As the fetal loss in drug-treated groups were within the historical control data for second and third trimester, it was not attributed to tezepelumab treatment (Table 6).

[16] Hendrie TA, Peterson PE, Short JJ, Tarantal AF, Rothgarn E, Hendrie MI and Hendrickx AG. Frequency of prenatal loss in a macaque breeding colony. *Am. J. Primatol*. 1996;40:41-53.
[17] Pentsuk N, Van der Laan JW. 2009. An interspecies comparison of placental antibody transfer: new insights into developmental toxicity testing of monoclonal antibodies. Birth Def Res B 86: 328-344.

Table 6. Summary of Fetal Losses

Dose Level (mg/kg)	No. of Pregnant Females	Overall loss	1st trimester (GD20-50) loss-	2nd trimester (GD51-100) loss-	3rd trimester (GD101-term) loss	3rd trimester (GD140-term) loss- Stillbirth	Total surviving offspring
0	14	3/14 (21.4%)	0/14 (0%)	0/14 (0%)	3/14 (21.4%)	1/14 (7.1%)	11
50	23	8/23 (34.8%)	2/23 (8.7%)	1/23 (4.3%)	5/23 (21.7%)	4/23 (17.4%)	15
300	16	4/16 (25.0%)	2/16 (12.5%)	0/16 (0%)	2/16 (12.5%)	1/16 (6.3%)	12
Historical control data [b] Range		37/148 (25%) 6.7 to 38.9%	12/148 (8.1%) 0 to 11.8%	2/148 (1.4%) 0 to 10.0%	22/148 (14.9%) 0 to 28.6%	14/148 (9.5%) 0 to 16.7%	

[b] Based on control data from 8 ePPND studies conducted at the Testing Facility from 2008 to present.

Clinical signs

Cage side observations were conducted twice daily throughout the study. There were no treatment-related changes in clinical signs or qualitative food consumption during gestation through 6.5 months postpartum.

Body weight

Body weights were measured on initial day of mating, GD10, and GD18 and weekly thereafter through delivery. Following parturition, body weights were measured weekly along with infant body weights on PPD1 through PPD180±2 or PPD195±1. There were no treatment-related changes in body weights during gestation and postpartum.

Embryo/Fetal measurements by ultrasound during gestation

There were no drug-related changes in following fetal measurements by ultrasound during gestation- crown rump length (mm), biparietal diameter (mm), occipitofrontal diameter (mm), head circumference (mm), abdominal circumference (mm), humerus length (mm), femur length (mm), heart rate (bpm), and gestational sac mean (mm).

Postpartum/Birth Day (BD1) observations

The mother and infant were observed during the morning after birth was detected (BD1), or ~4 to 8 hours after birth when the birth occurred during the day. There were no drug-related postpartum observations. Adult female number 3513 at 300 mg/kg showed signs of rejecting the infant (infant number 3131) on BD1. As a result, the infant was euthanized on BD3 because of logistical challenges of hand-rearing the infant.

Toxicokinetics

Blood

Blood samples were collected from all maternal animals on GD20-GD22 and on GD139-GD141 at pre-dose, 12, 24, 48, 96, 168 hrs post dose. Blood samples were also collected at pre-dose on GD48-GD50, GD97-GD99, on day of abortion/stillbirth, and at time of unscheduled necropsy (Table 7).

Table 7. Summary of TK data in maternal monkey plasma in ePPND study

	50 mg/kg (n=24)		300 mg/kg (n=17)	
Gestation day	**C_0 (µg/ml)**	**AUC_{0-168} (µg*day/ml)**	**C_0 (µg/ml)**	**AUC_{0-168} (µg*day/ml)**
GD20-GD22	1370	4570	8640	25000
GD139-GD141	1880	8720	10600	38000

There was a dose proportional increase in the exposure to tezepelumab from 50 to 300 mg/kg following first dose on GD20-GD22 and eighteenth dose on GD139-GD141. Mean accumulation ratios on GD139-GD141 were 1.9 and 1.51 at 50 and 300 mg/kg, respectively. Although anti-drug antibodies (ADA) were detected in the plasma of a subset of animals (see below), there was a no effect of ADA on tezepelumab exposure.

Milk

Milk samples were collected from maternal females on PPD7, PPD28, and PPD91. Additionally, blood was collected on PPD7, PPD28, PPD91, and PPD180±2 or PPD195±1 days. Blood samples were collected from all infants on BD7, BD28, BD91, BD180±2 or BD195±1 days, and at time of unscheduled necropsy.

Tezepelumab was detected in maternal milk on PPD7 at mean concentrations approximately 300-fold lower than the concentration detected in the plasma. Similarly, tezepelumab was detected in maternal milk at PPD28 at concentrations around 180-fold lower at 50 mg/kg and 908-fold lower at 300 mg/kg. In animals at 50 mg/kg, percent drug concentration in milk was ~0.4% and 0.5% on PPD7 and PPD28, respectively. Similarly, in animals at 300 mg/kg, percent drug concentration in milk was ~0.3% and 0.1% on PPD7 and PPD28, respectively (Table 8). Similar results were obtained after excluding monkeys with positive anti-tezepelumab antibodies indicating that presence of ADAs had no effect on drug concentration in milk. These are notable findings given that tezepelumab dosing was stopped at the time of infant delivery and the data also suggests that tezepelumab has a potential long half-life in blood/plasma.

Table 8. Mean tezepelumab values in plasma and milk of female monkeys during lactation period. Pregnant monkeys were administered tezepelumab from GD20-22 (based on pregnancy confirmation) until parturition

Maternal Tezepelumab dose	50 mg/kg				300 mg/kg			
	Plasma (ng/ml)	Milk (ng/ml)	Plasma: milk ratio	Percent in milk	Plasma (ng/ml)	Milk (ng/ml)	Plasma: milk ratio	Percent in milk
PPD7	555,600	2445	227	0.4%	1,800,000	4843	372	0.3%
PPD28	133,000	738	180	0.5%	356,000	392	908	0.1%
PPD91	4,517	BLQ	NR	NR	10,717	BLQ	NR	NR
BLQ: below limit of quantitation; NR: not reported								

Anti-drug antibodies (ADA)

For antibody analysis, blood was collected from all maternal females at predose on GD20-GD22, GD48-GD50, GD97-GD99, GD139-GD141, and on PPD28, and PPD180 ± 2 or PPD195 ± 1 days, on day of abortion/stillbirth, and at time of unscheduled necropsy.

Anti-tezepelumab binding antibodies were not detected in the control group as expected but were detected in 4/24 adult animals at 50 mg/kg; and 11/17 adult animals and 1/11 infants at 300 mg/kg. Overall, 15/41 tezepelumab treated adult animals and 1/25 infants tested positive for antibodies capable of binding to tezepelumab (Table 9, excerpted from Applicant's submission). All ADA positive animals tested negative for antibodies capable of neutralizing tezepelumab. Presence of ADAs did not have any effect on tezepelumab exposure.

Table 9. Percentage of antibody-positive animals per dose group

Group (Dose)	Positive for Binding Antibodies		Positive for Neutralizing Antibodies	
	Adults	Infants	Adults	Infants
1 (0 mg/kg)	0/15 (0.0%)	0/11 (0.0%)	0/15 (0.0%)	0/11 (0.0%)
2 (50 mg/kg)	4/24 (16.7%)	0/14 (0.0%)	0/24 (0.0%)	0/14 (0.0%)
3 (300 mg/kg)	11/17 (64.7%)	1/11 (9.1%)	0/17 (0.0%)	0/11 (0.0%)
All Animals	15/56 (26.8%)	1/36 (2.8%)	0/56 (0.0%)	0/36 (0.0%)
AMG 157-treated Animals	15/41 (36.6%)	1/25 (4.0%)	0/41 (0.0%)	0/25 (0.0%)

Dosing Solution Analysis

AMG157 dosing solutions were within ±10% of the target theoretical concentration for Groups 2 and 3. The percent relative standard deviation (%RSD) between each set of 3 aliquots/dilutions for each dosing solution aliquot (Groups 2 and 3) was acceptable at ≤5%.

F1 Generation

Each treatment group had at least 11 infants on BD7 (Table 10). This is within the minimum recommended value of at least 6-8 per group in the ICH S6 Addendum.

Table 10. Total number of F1 animals per treatment group in tezepelumab ePPND study

Maternal Tezepelumab dose (mg/kg)	# of dams	Total surviving offspring at PND 7
0	14	11
50	23	14
300	16	11

Mortality of infants

There were no infant losses in the control group whereas there were 3 and 1 infant losses in 50 mg/kg and 300 mg/kg groups, respectively. In infants #2096 at 50 mg/kg and #3131 at 300 mg/kg, the cause of infant death was attributed to lack of maternal care that is considered as an incidental finding in primigravid cynomolgus monkeys.[18] In infant #2106 (at 50 mg/kg) found dead on BD33, microscopic findings included necrosis, inflammation, and intralesional bacteria in tail and skeletal muscle. These correlated with macroscopic findings of firm iliac artery and skeletal muscle of left thigh, dry stiff discolored tail, and red discoloration of lungs (no microscopic correlate). In infant #2136 (at 50 mg/kg) found dead on BD5, all examinations and observations on BD1-BD4 were within the range of normal variability for neonatal cynomolgus monkeys and the death of animal was attributed to pneumonia. Both the deaths of infants-#2106 and #2136, were not considered treatment related because there was lack of dose response effect and deaths were attributed to postnatal infection (in animal #2106) and pneumonia (in animal #2136), respectively (Table 11). Overall, 4/38 (10.5%) infants died/euthanized within 33 days postnatal development and this was within the range of historical control data for the Testing Facility (0 to 20%).

[18] Gardin, JF, Jerome CP, Jayo MJ, Weaver DS. Maternal factors affecting reproduction in a breeding colony of cynomolgus macaques (Macaca fascicularis). *Lab Anim Sci.*1989;39:205-212.

Table 11. Summary of infant losses in the ePPND study

Dose Level (mg/kg)	Total No. of Live Infants	Infant#	Adult Female #	BD of Loss	GD at birth	Comment	Percent Infant death
0	11	No infant losses					0 %
50	15	2096	2059	BD9	GD160	Mother rejected infant on BD7, rejected from foster mother. Infant euthanized on BD9.	20%
		2106	2510	BD33	GD146	Infant found dead on BD33	
		2136	2513	BD5	GD158	Infant found dead on BD5	
300	12	3131	3513	BD3	GD165	Mother rejected infant on BD1, Infant euthanized on BD3	8.3%
Historical control data		10.4% (11/106)		range (0 to 20%)			

Clinical signs

Clinical signs noted twice daily starting from BD1 through BD180±2 or BD195±1. There were no effects of maternal drug treatment on clinical signs.

Body weight

Body weights were recorded on BD1, BD3, BD7, BD14, and weekly thereafter. There were no effects of maternal drug treatment on body weights.

Clinical pathology

Blood was collected from femoral vein of all infants for assessment of hematology parameters on BD14, 28, 91, and 180±2 (6 infants) or BD195±1 (28 infants). There were no effects of maternal drug treatment on hematology parameters of infants exposed to the drug *in utero*.

Toxicokinetics

Blood samples were collected from all lactating females on PPD7, PPD28, PPD91, and PPD180±2 or PPD195±1 days. Additionally, blood samples were collected from all infants on BD7, BD28, BD91, BD180±2 or BD195±1 days, and at time of unscheduled necropsy.

F1 monkeys were exposed to tezepelumab at a concentration up to 4.76-fold and 6.65-fold higher relative to maternal animals on BD91 for 50 mg/kg and on BD180 for 300 mg/kg. This indicates that tezepelumab crosses the placenta. Maternal serum concentrations on PPD91 were <1% of PPD7 for both doses whereas infant serum concentrations on BD91 were ~2.7% and ~3.3% of BD7 for 50 and 300 mg/kg, respectively. Both maternal and infant serum concentrations on PPD180/195 and BD180/195 were <1% of PPD7 and BD7, respectively. Serum ratios on PPD28/PPD7 and BD28/BD7 were ~0.2 for both the doses except the infant serum ratio of 0.6 for 300 mg/kg dose group (Table 12). This suggests that clearance of

tezepelumab occurs at a similar rate from both maternal animals and infants during the treatment-free phase except for infants at 300 mg/kg exhibiting a slower clearance of tezepelumab.

Taken together, the data suggests that tezepelumab transfer from maternal animal to infant occurred both in utero and via milk.

Table 12. Summary of mean tezepelumab plasma concentrations in maternal animals and infants at time points during lactation period

Maternal Tezepelumab dose	50 mg/kg			300 mg/kg		
	Maternal serum (ng/ml)	Infant serum (ng/ml)	Infant: maternal ratio	Maternal serum (ng/ml)	Infant serum (ng/ml) *	Infant: maternal ratio (%)
PPD7/BD7	556,000	784,000	1.41	1,800,000	905,000	0.50
PPD28/BD28	133,000	237,000	1.78	356000	553000	1.55
PPD91/BD91	4520	21500	4.76	10700	30500	2.85
PPD180/BD180	NA	407	NA	129	858	6.65
PPD28/PPD7 ratio or BD28/BD7 ratio	0.24	0.3	NA	0.2	0.6	NA
*In 5 infants (infant numbers- 3016, 3066, 3081, 3101 and 3121) at 300 mg/kg, serum tezepelumab concentration was higher on BD28 relative to BD7.						

Anti-drug antibodies (ADA)
For antibody analysis, blood was collected from all infants on BD28, BD180 ± 2 or BD195 ± 1 days, and at time of unscheduled necropsy.

Only 1/11 infants (infant number: 3066-MF9564F) delivered from maternal female (animal number: 3506-MF37403F) at 300 mg/kg tested positive for binding anti-tezepelumab antibodies at BD28 and tested negative for antibodies at BD195 (Table 9, excerpted from Applicant's submission). This maternal female adult tested positive for binding antibodies on GD99, GD141, PPD28, and PPD195. All binding antibody-positive animals (adults and infants) tested negative for neutralizing antibodies. Therefore, ADA had no impact on tezepelumab exposure in F1 offspring.

Physical examination-BD1
All infants were observed after birth for nursing behavior. There were no effects of maternal drug treatment on heart rates and respiration rates.

External assessment and infant morphological measurements

The external assessment of infants included shape and symmetry of the head and body and was conducted on BD1, BD28, BD56 and BD91 and on the day of necropsy. There were no effects of maternal drug treatment on the external assessments of infants through 6.5 months postnatal.

Neonatal neurobehavioral assessments

Neonatal muscle tone was assessed ~4 to 8 hours after birth on BD1 or next morning if birth occurred later in the day. Neonatal neurobehavioral test battery was assessed on BD3, BD7, and BD14 and it included- righting, palmar grasp, clasp-grasp (monkey infant reflex for clinging to ventrum of the dam), visual following, prone progression, lipsmack orient (test for hearing), oral reflexes (rooting, sucking, snout reflex), eye reflexes (pupil constriction, nystagmus, glabellar tap [blink reflex]), moro reflex, negative geotaxis (test for vestibular function), buildup (increase arousal levels in response to manipulation). There were no effects of maternal drug treatment on neonatal muscle tone or on neurobehavioral evaluations.

Skeletal evaluation (radiographs)

Skeletal radiographs were taken on BD28 when the infant was separated from the mother for body weight measurements. There were no effects of maternal drug treatment on skeletal findings.

Necropsy

Organ weights

There were no tezepelumab-induced effects on mean organ weights or organ weight ratios in F1 animals.

Microscopic findings

Lymphoid tissues (bone marrow-sternum, thymus, spleen and lymph nodes- axillary, mandibular, and mesenteric) of all infants sacrificed at scheduled necropsy (BD180±2 days or BD195±1 day) were examined to assess any immunomodulatory and/or immunotoxic potential of tezepelumab. An independent pathologist peer review was also conducted by the Applicant. There were no tezepelumab-induced lesions in lymphoid tissues examined in animals that survived to study completion.

Lymphocyte phenotyping

Lymphocyte phenotyping was evaluated via flow cytometry of samples collected from infants on BD14, BD28, BD91, and BD179-195 and unscheduled infant necropsies. The following antigen markers and cell populations were quantified: CD20+ B-lymphocytes, CD3+ T-lymphocytes, CD3+/CD4+ T-helper lymphocytes, CD3+/CD8+ T-cytotoxic lymphocytes, CD3-/CD16+ NK cells, and CD3-/CD14+ monocytes.

Although increasing trends in CD20+ B-lymphocytes and CD3+/CD8+ T-cytotoxic lymphocytes cell counts were noted across all groups between BD14 and BD179-195, these values were consistent with historical control data for infant monkeys at this facility. Therefore, there were no tezepelumab-related alterations in lymphocytes subsets or monocytes in F1 animals.

Anti-KLH Antibodies (TDAR assay)
A TDAR (T cell-dependent antibody response) assay was conducted to assess immune function. On BD152 (KLH-immunization-I) and BD166 (KLH-immunization-II), the infants were immunized with 1 mL of KLH injected intramuscularly on the posterior aspect of the thigh to achieve a dose of 5 mg/infant. There were appropriate primary (IgM) and secondary (IgG) humoral immune response following immunization with KLH antigen. There were no tezepelumab-related changes in the anti-KLH IgM or IgG titer values in infants exposed to tezepelumab.

5.5.5. Other Toxicology Studies

Cross-reactivity study of biotinylated tezepelumab with normal human and cynomolgus monkey tissues (Study: 108668) (GLP)

- The cross-reactivity study was considered valid based on the adequacy of the tissue samples from humans and cynomolgus monkeys and due to the positive and the negative controls producing the expected results.
- Tezepelumab weakly bio-stained the cytoplasm of 1/3 human prostate tissues and 1/3 human uterus tissues at the highest concentration examined (50 µg/mL) but not the lower concentration (1 µg/mL). This staining was not associated with inflammation.
- Further, the evidence for cytoplasmic staining of tezepelumab is of limited toxicological significance given that this molecule will not have access to the cytoplasmic compartment in vivo due to its large size (~147 kDa).
- AMG-157 did not cross-react with cynomolgus monkey tissues.

Local tolerance study in male New Zealand rabbits (Study: 109454) (GLP)

- Three male rabbits were administered a single IV injection (1 mL/injection site) of tezepelumab at 70 mg/dose article (right ear vein) and placebo as control (left ear vein) as a slow push bolus.
- No animals died prior to scheduled necropsy.
- Each animal tolerated IV administration well, based on the lack of clinical signs of toxicity, no changes in body weights, and no macroscopic or microscopic observations of toxicity at the injection site.
- No local irritation was observed at the injection site compared to the control treated injection sites.
- As tezepelumab does not bind to rabbit TSLP, thus, the results of the local tolerance study are of little relevance to the safety assessment.

Table 13. Summary table showing tezepelumab systemic exposure values at NOAEL doses in relevant toxicity studies in comparison to the human steady state tezepelumab systemic exposure at the MRHD of 210 mg every 4 weeks

SC Maximum Recommended Human Dose	Human Mean $AUC_{0\text{-}28d}$ value at steady-state (µg*day/mL)[a]	Nonclinical monkey study	$AUC_{0\text{-}168h}$ (µg*day/mL)	$AUC_{0\text{-}4weeks,ss}$ (µg*day/mL)	Safety Margin
210 mg Q4W	901	6-month SC (Study:108824)	30,200	120,800[b]	134
		ePPND (Study:108825)	38,000	152,000[c]	168

a: Simulated human mean values of AUC (over 4 weeks) at steady state following SC administration of tezepelumab 210 mg Q4W to asthma patients (Tezepelumab Population PK report, Module 5.3.3.5).
b: Study 108824 (Day 176) at the SC NOAEL of 300 mg/kg; $AUC_{0\text{-}168hr}$ = 30200 µg*d/mL. A correction factor of 4 was applied to adjust for the difference in dosing frequency between animals (once weekly) and humans (every 4 weeks) to the reported $AUC_{0\text{-}168hr}$ value, resulting in a value of 120,800 µg*d/mL used for ratio calculations.
c: Study 108825 (GD 139-142) at the IV NOAEL of 300 mg/kg; Maternal animal $AUC_{0\text{-}168hr}$ = 38,000 µg*d/mL. A correction factor of 4 was applied to adjust for the difference in dosing frequency between animals (once weekly) and humans (every 4 weeks) to the reported $AUC_{0\text{-}168}$ value, resulting in a value of 152,000 µg*d/mL used for ratio calculations.

6 Clinical Pharmacology

6.1. Executive Summary

AstraZeneca submitted BLA 761224 under the 351 (a) pathway seeking marketing approval for tezepelumab for the indication of "add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma". The proposed dosing regimen is 210 mg for SC injection once every 4 weeks. The dosage form is 210 mg in 1.91 mL (110 mg/mL) solution in a single-dose glass vial/ pre-filled syringe. Tezepelumab was granted Breakthrough Drug Designation in 2018 and priority review on July 7, 2021.

The clinical development program of this submission includes 6 completed phase 1 studies and 5 Phase 2-3 studies. The major clinical pharmacology findings for this application are summarized in Section 6.2.

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) and Pharmacometrics (DPM) have reviewed the clinical pharmacology data submitted in support of BLA 761224 for tezepelumab and found them to be acceptable to support approval from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings of the current review:

1. The pharmacokinetics of tezepelumab were dose-proportional following administration of a single subcutaneous dose over a dose range from 2.1 mg to 420 mg. With a every 4 weeks dosing regimen, tezepelumab achieves steady-state after 12 weeks and the accumulation ratio for C_{trough} is 1.86-fold.
2. Based on population pharmacokinetic analysis, the estimated absolute bioavailability of tezepelumab via SC route was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).
3. The population pharmacokinetic analysis included 1008 volunteers or asthma patients (74%) with normal renal function, 320 volunteers or asthma patients (23%) with mild renal impairment and 38 asthma patients (3%) had moderate renal impairment. Tezepelumab clearance was similar in patients with mild renal impairment, moderate renal impairment and those with normal renal function. Tezepelumab has not been studied in patients with severe renal impairment.
4. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.
5. The influence of body weight (range: 39.3 to 161 kg), age (range: 12 to 80 years), gender and race (White, Black, Asian, Other) on PK were evaluated using population PK analyses. Body weight, age and race were identified as statistically significant predictors

on tezepelumab PK parameters. However, the effect of those factors on exposure had no meaningful impact on efficacy or safety and does not require dose adjustment.

6. The dose-response of tezepelumab was evaluated in PATHWAY at 3 different dose levels of SC tezepelumab (70 mg Q4W, 210 mg Q4W, and 280 mg Q2W) in subjects with severe asthma. Tezepelumab 210 mg Q4W led to numerically improved efficacy compared with 70 mg Q4W, while the 280 mg Q2W dose did not increase efficacy further compared to the 210 mg Q4W dose. No dose-response relationship for safety was observed.
7. In NAVIGATOR, administration of tezepelumab 210 mg SC every 4 weeks reduced inflammatory biomarkers and cytokines from baseline compared with placebo with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5 concentration, and serum IL-13 concentration. Tezepelumab caused a slow but progressive reduction in serum total IgE concentration throughout 52 weeks of treatment. Similar effects were seen in PATHWAY.
8. In all studies of tezepelumab, the incidence and prevalence of ADA and nAb was low. In NAVIGATOR and SOURCE, ADA were detected at any time in 29 (5%) out of 601 patients who received tezepelumab at the 210 mg Q4W dosing regimen during the 48 to 52-week study period. Of these 29 patients, 11 patients (2% of patients treated with tezepelumab) developed treatment-emergent antibodies and 1 patient (0.2% of patients treated with tezepelumab) developed neutralizing antibodies. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.
9. A total of 41 adolescents (age 12-17 years) received tezepelumab treatment in NAVIGATOR. The mean serum trough concentrations in adolescents (age 12 to < 18 years) were approximately 30% higher than those in adults at Week 52. No dose adjustment is needed in adolescents due to the flat exposure-response relationship for efficacy and safety.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dose of tezepelumab is 210 mg administered SC once every 4 weeks. This dose is supported by the totality of the efficacy and safety data. Refer to the clinical review by Dr. Jennifer Lan for more details (Section 8).

Therapeutic Individualization

None.

Outstanding Issues

There was no clinical pharmacology-related outstanding issue for this submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Eleven clinical studies provide data on the clinical pharmacology of tezepelumab in this BLA submission (Table 14).

Table 14. Overview of Tezepelumab Clinical Studies with PK, PD, and Immunogenicity Assessments

Study number (abbreviation)	Study design	Study population	Objectives	Formulation
20070620 (Study 0620)[a]	Phase 1; SAD; RD/DB/PC/DE	Adult healthy subjects	Safety, tolerability, immunogenicity, PK, PD	(b) (4)
20080390 (Study 0390)	Phase 1; MAD; RD/DB/PC/DE	Adult healthy subjects	Safety, tolerability, PK, immunogenicity	
20101183 (Study 1183)	Phase 1; RD/DB/PC	Adult subjects with mild atopic asthma	Late asthmatic response, safety, tolerability, immunogenicity, PK, PD	
D5180C00002 (Study 0002)	Phase 1; OL	Adolescent subjects with mild to moderate asthma	PK, safety, tolerability, immunogenicity, lung function	
D5180C00003 (Japan Study 0003)	Phase 1; SAD; RD/SB/PC/DE	Japanese adult male healthy subjects	Safety, tolerability, PK, immunogenicity	
D5180C00012 (PATH-BRIDGE)	Phase 1; RD/OL	Adult healthy subjects	PK comparability, immunogenicity, safety, and tolerability following SC administration with APFS, AI, and vial-and-syringe	
CD-RI-MEDI9929-1146/D5180C00001 (PATHWAY)	Phase 2b; RD/DB/PC	Adult subjects with severe, inadequately controlled asthma	Efficacy, safety, PK, immunogenicity, PD	
D5180C00007 (NAVIGATOR)	Phase 3; RD/DB/PC	Adult and adolescent subjects with severe uncontrolled asthma	Efficacy, safety, PK, immunogenicity, PD	
D5180C00009 (SOURCE)	Phase 3; RD/DB/PC	Adult subjects with OCS-dependent asthma	Efficacy, safety, PK, immunogenicity, PD	

				(b) (4)
D5180C00013 (CASCADE)	Phase 2; RD/DB/PC	Adult subjects with inadequately controlled asthma on ICS and at least one additional asthma controller	Efficacy, safety, tolerability, PK, immunogenicity, PD	
D5180C00011 (PATH-HOME)	Phase 3;RD/OL	Adult and adolescent subjects with severe asthma	Success of administration, functional testing of device (APFS and AI), efficacy, safety, PK, immunogenicity	

a. For Study 0620, only healthy subject data (Study Part A) are considered in this document; data for subjects with atopic dermatitis (Study Part B) are not considered relevant to this application.

AI, Autoinjector; APFS, Accessorized pre-filled syringe; CSR, Clinical Study Report; DB, Double blind; DE, Dose escalation; ICS, Inhaled corticosteroid; MAD, Multiple ascending dose; OCS, Oral corticosteroid; OL, Open label; PC, Placebo controlled; PD, Pharmacodynamic; PK, Pharmacokinetic; RD, Randomized; SAD, Single ascending dose; SB, Single blind; SC, Subcutaneous.

Source: Revised from Table 2 in Summary of Clinical Pharmacology Studies (Module 2.7.2)

The clinical pharmacology findings for tezepelumab are summarized in Table 15.

Table 15. Clinical Pharmacology Summary

Type of Parameter	Description		
General Information			
Tezepelumab exposure		Mean $C_{max,ss}$ (µg/mL) and SD	Mean AUCss (µg.day/mL) and SD
	(Population PK analysis)	40.9 (14)	901 (328)
Dose proportionality	The pharmacokinetics of tezepelumab showed dose-proportional following SC administration over a dose range of 2.1 mg to 420 mg in healthy adult subjects (Study 0620).		
Accumulation	After repeated SC administration Q4W, serum tezepelumab concentrations achieves steady state by 12 weeks. The mean accumulation ratio was 1.86-fold (population PK analysis).		
Absorption			
T_{max}	The median T_{max} of tezepelumab after SC administration is approximately 3 to 10 days (Study 0620).		
Absolute bioavailability	Absolute bioavailability was estimated to be 81% based on comparison of the mean AUC_{inf} after a single SC 210 mg dose compared with the same dose administered IV (Study 0620). Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 77%. There was no clinically relevant difference in bioavailability when administered to different injection sites (abdomen, thigh, or upper arm).		
Distribution			
Volume of distribution	The estimated central and peripheral volume of distribution of tezepelumab was 3.91 L and 2.17 L, respectively, for a 70 kg individual (population PK analysis).		
Elimination			
Half-life	The elimination half-life was approximately 26 days (population PK analysis).		
Primary metabolic pathways	Tezepelumab is a human monoclonal antibody (IgG2λ) that is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic enzymes.		
Excretion			
Primary excretion pathways	Tezepelumab is eliminated by intracellular catabolism and there is no evidence of target-mediated clearance within the studied dose range (2.1 to 420 mg).		
Intrinsic Factors			
Renal impairment	No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab. The population pharmacokinetic analysis included 1008 volunteers or asthma patients (74%) with normal renal function, 320 volunteers or asthma patients (23%) with mild renal impairment and 38 asthma patients (3%) had moderate renal impairment. Tezepelumab clearance was similar in patients with mild renal impairment (estimated creatinine clearance 60 to 89 mL/min), moderate renal impairment (estimated creatinine clearance 30 to 59 mL/min) and those with normal renal function (estimated creatinine clearance ≥ 90 mL/min). Tezepelumab has not been studied in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min).		

Type of Parameter	Description
Hepatic impairment	No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. Since tezepelumab is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic-specific enzymes, change in hepatic function is not expected to influence tezepelumab clearance. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.
Weight	Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure: patients with body weight of 49 kg and 114 kg (the 5th and 95th percentiles of NAVIGATOR) were expected to have 45% higher and 40% lower steady state exposure (AUCtau), respectively, compared with a typical subject with body weight of 70 kg. However, the effect of body weight on exposure had no meaningful impact on efficacy or safety and does not require dose adjustment. See the pharmacometrics review by Dr. Jing Niu in Section 19.4.1 for further details.
Age, Sex, Race	Based on population pharmacokinetic analysis, age (12 to 80 years), sex and race (White, Black, Asian, Other) had no clinically meaningful effects on the pharmacokinetics of tezepelumab.
Extrinsic Factors and Drug Interactions	
PK of tezepelumab affected	No formal drug interaction studies have been conducted with tezepelumab. A clinically relevant effect of tezepelumab on the pharmacokinetics of co-administered asthma medications is not expected. Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (leukotriene receptor antagonist, theophylline/aminophylline, oral and inhaled corticosteroid) had no clinically meaningful effect on tezepelumab clearance.
Pharmacodynamics	
Biomarkers	In NAVIGATOR, administration of tezepelumab 210 mg subcutaneously every 4 weeks (n=528) reduced inflammatory biomarkers and cytokines from baseline compared with placebo (n=531) with an onset of effect at 2 weeks (the earliest visit during treatment period) and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5 concentration, and serum IL-13 concentration. Tezepelumab caused a slow but progressive reduction in serum total IgE concentration throughout 52 weeks of treatment. Similar effects were seen in PATHWAY.
Immunogenicity	
ADA, TE-ADA, nAb	In NAVIGATOR, anti-drug antibodies (ADA) were detected at any time in 26 (5%) out of 527 patients who received tezepelumab at the recommended dosing regimen during the 52-week study period. Of these 26 patients, 10 patients (2% of patients treated with tezepelumab) developed treatment-emergent antibodies and 1 patient (<1% of patients treated with tezepelumab) developed neutralizing antibodies. ADA titers were generally low and often transient. No evidence of ADA impact on pharmacokinetics, pharmacodynamics, efficacy, or safety was observed.

Source: Module 2.7.2, Summary of Clinical Pharmacology Studies (modified by the reviewer)
Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; C_{tau}, concentration over dosing interval; E-R, exposure-response.

6.3.2. Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen, 210 mg Q4W, is appropriate.

Results from Phase 2 dose finding study PATHWAY showed that tezepelumab 210 mg Q4W dosing was effective in achieving asthma exacerbation through Week 52, with numerically better asthma exacerbation rates compared to tezepelumab 70 mg Q4W and 280 mg Q2W dosing (Table 16). Therefore, tezepelumab 210 mg Q4W dosing regimen was selected in the Phase 3 study.

The efficacy and safety of the 210 mg Q4W dosing regimen has been demonstrated in the Phase 3 study NAVIGATOR.

Table 16. Summary of Annual Asthma Exacerbation Rate Through Week 52 in Study PATHWAY

Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Rate [a]	0.72	0.27	0.20	0.23
95% CI of rate [a]	(0.59, 0.88)	(0.19, 0.38)	(0.13, 0.30)	(0.16, 0.34)
Rate ratio [b]	---	0.38	0.29	0.34
95% CI of rate ratio [b]	---	(0.23, 0.63)	(0.16, 0.51)	(0.20, 0.58)
p-value [c]	---	< 0.001	< 0.001	< 0.001

CI = confidence interval; ITT = intent to treat; Q2W = every 2 weeks; Q4W = every 4 weeks
Source: Table 11.4.1-1 in the PATHWAY CSR

Tezepelumab was well tolerated at all 3 doses and the adverse event profile was comparable between the tezepelumab and placebo groups. The proportions of subjects with at least one treatment-emergent AE were 68%, 66%, and 65%, respectively, in the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W treatment groups, compared with 65.9% in the placebo group. The proportions of subjects with at least one treatment emerged serious AE were 12.3%, 9.5%, and 13.1%, respectively, in the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W treatment groups, compared with 13.0% in the placebo group.

Refer to the clinical review and statistical review by Dr. Jennifer Lan and Ms. Susan Mayo, respectively, for more details for the observed efficacy and safety data.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

- Body weight

Based on the population PK analyses, body weight was identified as a significant covariate on the CL, Vc, Q, and Vp of tezepelumab. Increased body weight was associated with increased CL, Vc, Q, and Vp values (the estimated allometric exponents of 1.01, 0.963, 0.588, and 0.609, respectively). The effect of body weight on tezepelumab $C_{trough,ss}$ following 210 mg Q4W was

evaluated in Table 17. The Median $C_{trough,ss}$ increased 87% from body weight quantile ranged 40.2-62.6 kg to 88.8-161 kg.

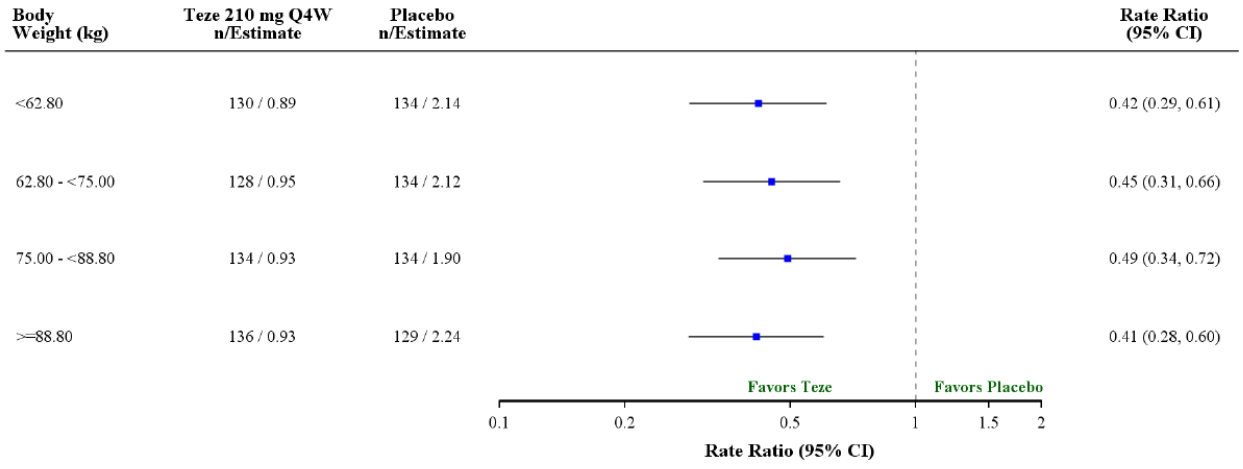
The Annualized Asthma Exacerbation Rate (AAER) ratios over 52 weeks between tezepelumab and placebo by body weight quartiles in NAVIGATOR are shown in Figure 1. The rate ratios (95% CI) of AAER over 52 weeks between the tezepelumab group and the placebo group were 0.42 (0.29, 0.61), 0.45 (0.31, 0.66), 0.49 (0.34, 0.72), and 0.41 (0.28, 0.60), respectively, for the first to the fourth body weight quartiles. The AAER rate ratios were less than 1 and the 95% CIs did not include 1 in all body weight quartiles, indicating that subjects receiving tezepelumab had lower AAER than subjects in the placebo group. The rate ratios were similar across body weight quartiles, suggesting that there was no effect of body weight on AAER reduction in tezepelumab-treated subjects.

Table 17. Summary of Observed Steady State Trough Concentrations by Body Weight Quartiles in NAVIGATOR

Body weight quartiles (kg)	Number of Subjects	Ctrough,ss (µg/mL) Median (min, max)
< 62.80 (range 40.2-62.6)	124	28.8 (10.8, 66.2)
62.80 to < 75.00 (range 62.8-74.9)	119	22.4 (6.35, 47.0)
75.00 to < 88.80 (range 75.0-88.6)	123	19.5 (4.51, 38.5)
≥ 88.80 (range 88.8-161)	128	15.4 (5.01, 33.8)

Source: Revised from Table 3 in the Exposure-Response analysis report (Module 5.3.4.2).

Figure 1. Annualized Asthma Exacerbation Rate Ratio Over 52 Weeks, Negative Binomial Model – Forest Plot by Body Weight Quartiles in NAVIGATOR



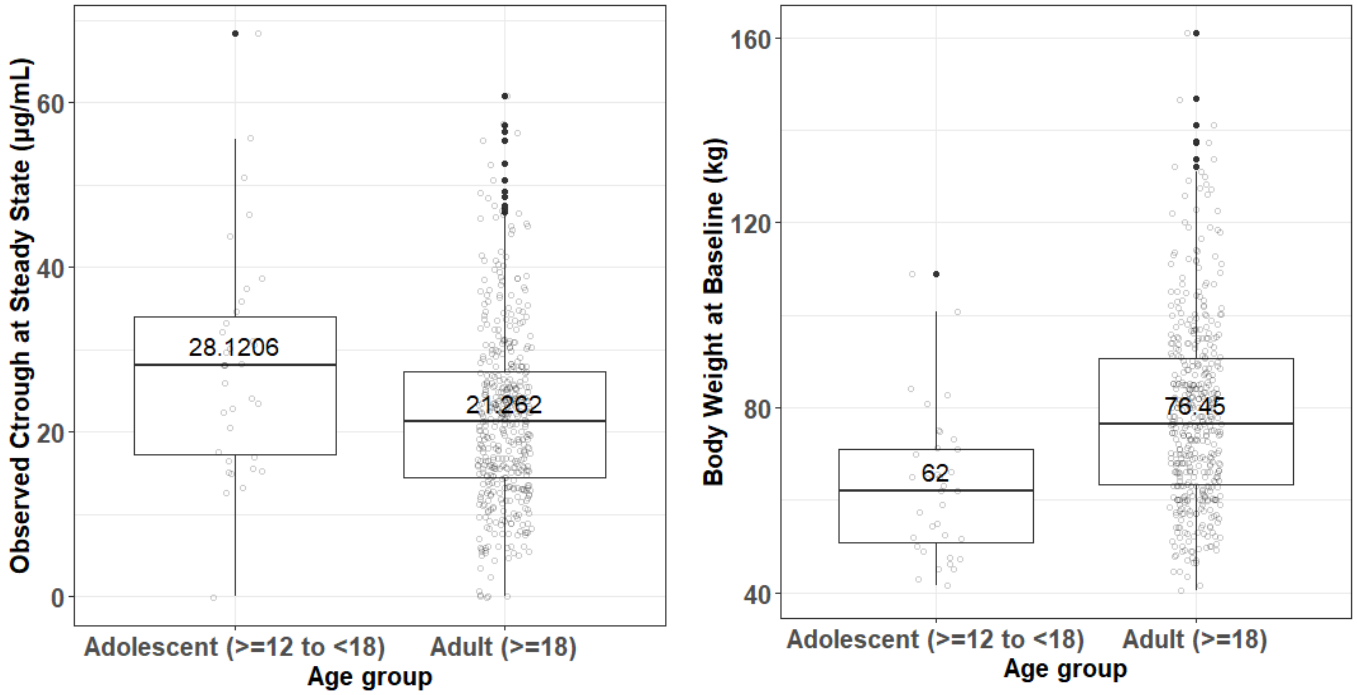
Abbreviations: CI, confidence interval; n, number of subjects in analysis; Q4W, every 4 weeks; Teze, tezepelumab.
Source: Figure 6 in the Exposure-Response analysis report in Module 5.3.4.2.

- Pediatric Patients

Forty one adolescents (12 to 17) and 487 adults (18 and above) received tezepelumab 210 mg Q4W treatment from Study NAVIGATOR. The median $C_{trough,ss}$ and body weight of the adolescents was 28.1 µg/mL and 62 kg, respectively. The median $C_{trough,ss}$ value was 32% higher than that of adults (Figure 2). This could be contributed by lower mean body weight observed in adolescent patients.

No dose adjustment is needed in adolescents due to the flat exposure-response relationship for efficacy and safety. This conclusion is also supported by the adolescent efficacy and safety findings in Study NAVIGATOR (refer to the statistical and clinical review for details in Section 8).

Figure 2. Box plot of observed Ctrough at steady state of tezepelumab (left) and body weight at baseline (right) by age group (adults and adolescents) after receiving 210 mg Q4W in Study NAVIGATOR



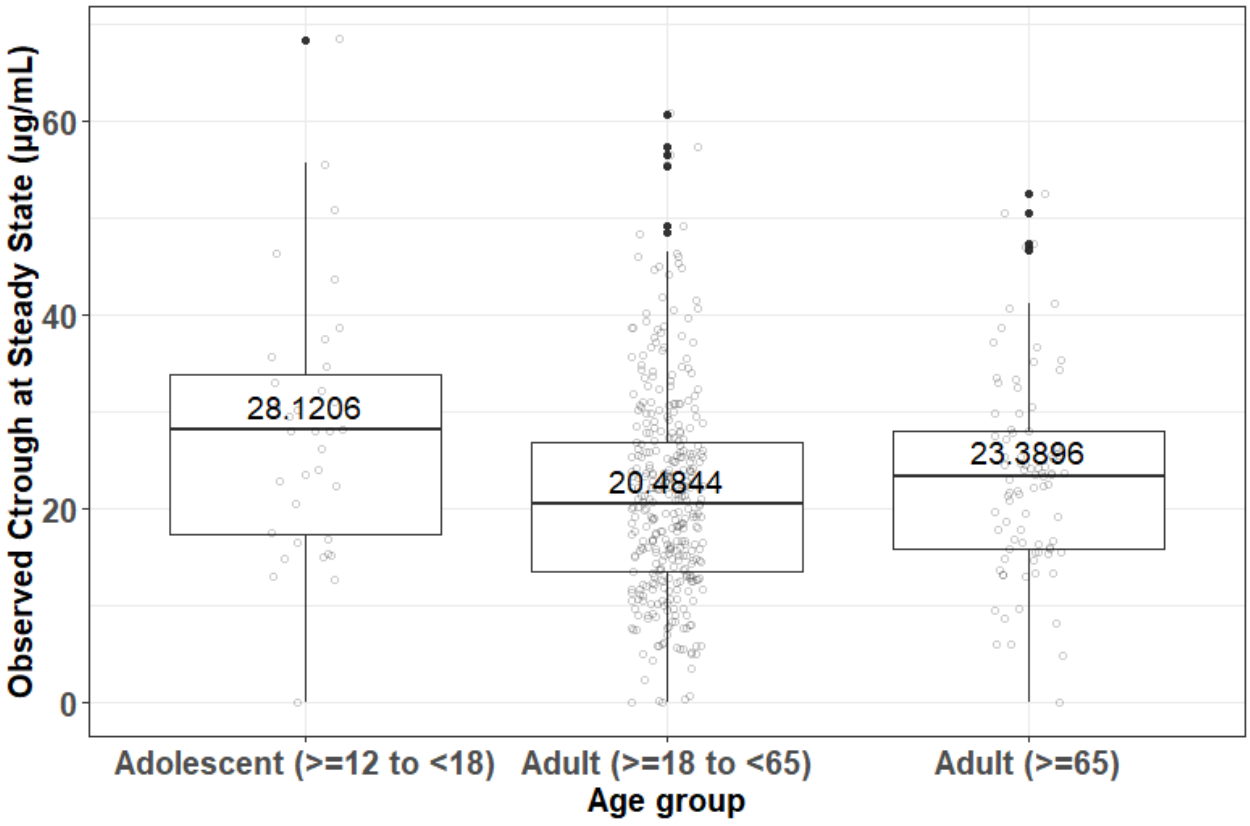
Source: Reviewer's analysis

- Elderly

Age was identified as a significant covariate on the Vc of tezepelumab in the final popPK model, where increased age was associated with a slightly increased Vc (the estimated exponent of 0.195 using power model). However, only mild influence of age was shown on tezepelumab exposure (

Figure 41 in section 19.4.1). Based on the observed C_{trough} at steady state from Study NAVIGATOR, The median C_{trough} value in adults ≥ 65 yrs was 14% higher than that of adults 18-64 yrs (Figure 3). The exposure difference is not considered clinically meaningful and no dose adjustment is recommended in senior subjects.

Figure 3. Box plot of observed Ctrough at steady state of tezepelumab by age group (adolescents, adults 18-64 and adults 65 and above) after receiving 210 mg Q4W in Study NAVIGATOR



Source: Reviewer's analysis

- Sex

Sex was not identified as a statistically significant covariate on tezepelumab PK parameters in the final popPK model.

- Race/Ethnicity

Race was identified as a statistically significant covariate on tezepelumab clearance in the population pharmacokinetic analysis, with about 10% lower systemic exposure in Asian population compared to non-Asian population. However, the effect of race/ethnicity on exposure is not considered clinically meaningful and does not require dose adjustment.

- Renal Impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on tezepelumab. The population pharmacokinetic analysis included 1008 volunteers or asthma patients (74%) with normal renal function, 320 volunteers or asthma patients (23%) with mild renal impairment and 38 asthma patients (3%) had moderate renal impairment. Tezepelumab clearance was similar in patients with mild renal impairment (estimated creatinine clearance 60 to 89 mL/min), moderate renal impairment (estimated creatinine clearance 30 to 59 mL/min) and those with normal renal function (estimated creatinine clearance ≥ 90 mL/min). Tezepelumab has not been studied in patients with severe renal impairment (estimated creatinine clearance < 30 mL/min).

- Hepatic Impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on tezepelumab. Since tezepelumab is degraded by proteolytic enzymes widely distributed in the body and not metabolized by hepatic-specific enzymes, change in hepatic function is not expected to influence tezepelumab clearance. Based on the population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.

Are there clinically relevant drug-drug interactions for tezepelumab, and what is the appropriate management strategy?

No formal drug-drug interaction studies have been conducted with tezepelumab. Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (leukotriene receptor antagonist, theophylline/aminophylline, oral and inhaled corticosteroid) had no clinically meaningful effect on tezepelumab clearance. Low potential for clinically relevant DDI involving tezepelumab, either as a victim or perpetrator, is supported by the justification below:

- Tezepelumab as a Victim

As a typical mAb, tezepelumab is not primarily cleared via hepatic pathways. Therefore, small molecule drugs that induce or inhibit the cytochrome P450 pathways are not expected to affect the PK of tezepelumab.

- Tezepelumab as a Perpetrator

Due to its large molecular size, tezepelumab is not expected to directly induce or inhibit the cytochrome P450 enzymes causing altered PK of small molecules metabolized by these enzymes.

Given that tezepelumab selectively blocks TSLP, an epithelial cell-derived cytokine and upstream regulator of the inflammatory cascade, the potential risk of cytokine-mediated TP-drug interactions as result of TSLP inhibition were evaluated. There is no information in the literature regarding the effect of TSLP on hepatic cytochrome P450 enzyme activities. Data from tezepelumab clinical studies suggest that the physiological level of TSLP in human serum is very

low. In PATHWAY, the median baseline serum TSLP level was 287.25 to 355.00 fg/mL in subjects with severe asthma. Given the low circulating levels of TSLP, an effect of TSLP on hepatic cytochrome P450 enzymes expression is not expected. Therefore, TSLP inhibition by tezepelumab is not expected to cause TP-drug interaction in vivo by altering cytochrome P450 enzymes expression.

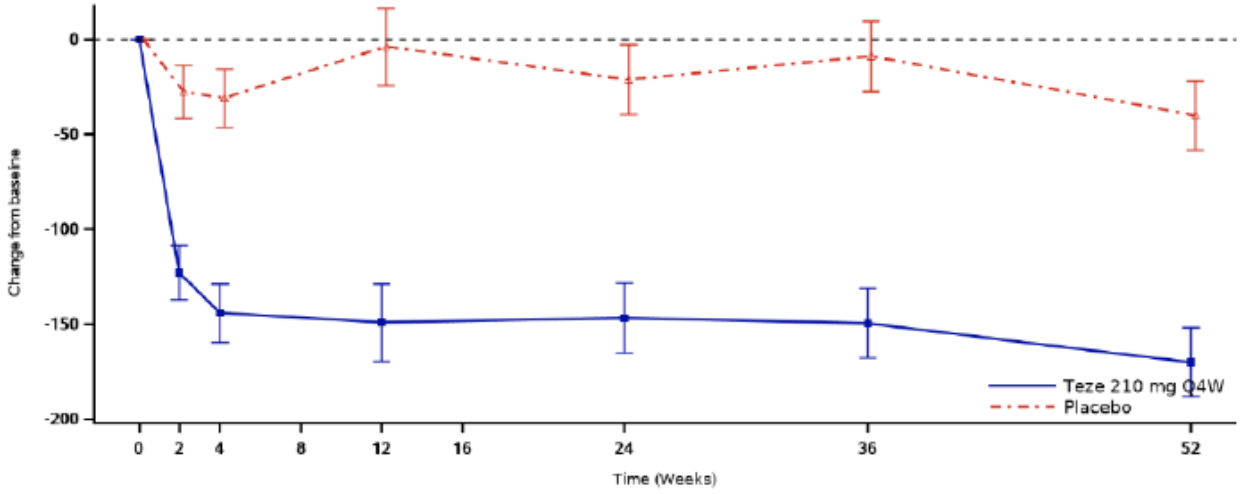
It is known that serum IL-6 level can affect hepatic cytochrome P450 enzymes expression level. The mean baseline values of ~3.5 to 3.7 pg/mL for IL-6 and ~4.4 to 4.9 mg/L for CRP were measured in study NAVIGATOR. The systemic inflammatory burden in asthma patients was lower than baseline values reported for patients with rheumatoid arthritis (~50 pg/mL for IL-6 and ~30 mg/L for CRP). And tezepelumab had limited effect on IL-6 and CRP levels (change from baseline is about 10% of the baseline value for both serum IL-6 and CRP). Thus treatment with tezepelumab is unlikely to cause clinically relevant TP-drug interaction in patients with asthma by modulating downstream pro-inflammatory cytokines that are known to affect P450 enzymes.

What is the PD characteristics of tezepelumab in the targeted population?

Blood/serum inflammatory biomarkers and cytokines

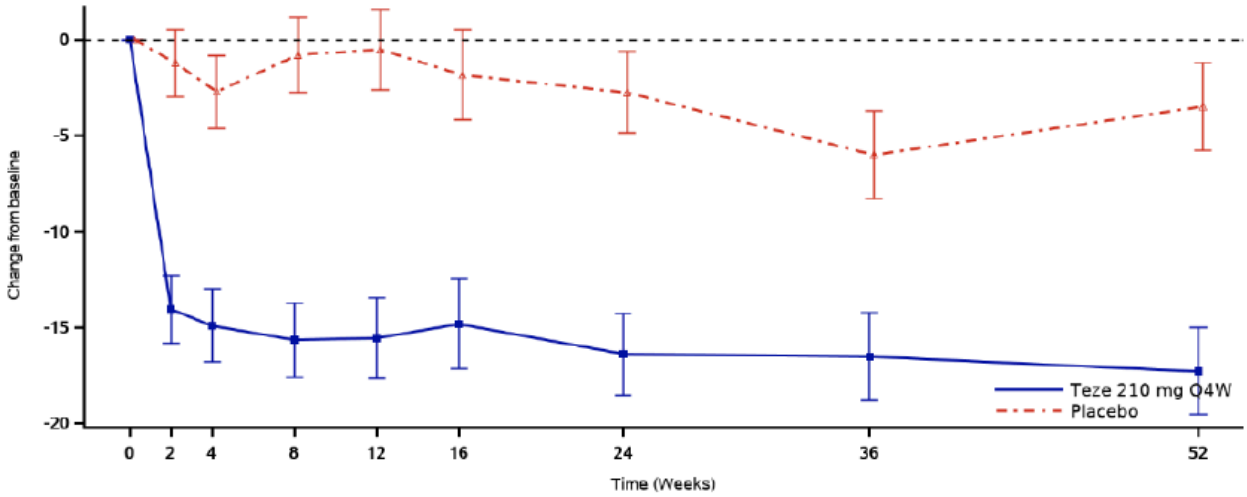
In NAVIGATOR, administration of tezepelumab 210 mg subcutaneously every 4 weeks (n=528) reduced inflammatory biomarkers and cytokines from baseline compared with placebo (n=531) with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5 concentration, and serum IL-13 concentration (Figure 4-Figure 7). tezepelumab caused a slow but progressive reduction in serum total IgE concentration throughout 52 weeks of treatment (Figure 8). Similar effects were seen in PATHWAY.

Figure 4. Adjusted Arithmatic Mean (95% CI) Change from Baseline in Blood Eosinophils Counts (cells/µL) over Time (Full Analysis Set) – NAVIGATOR



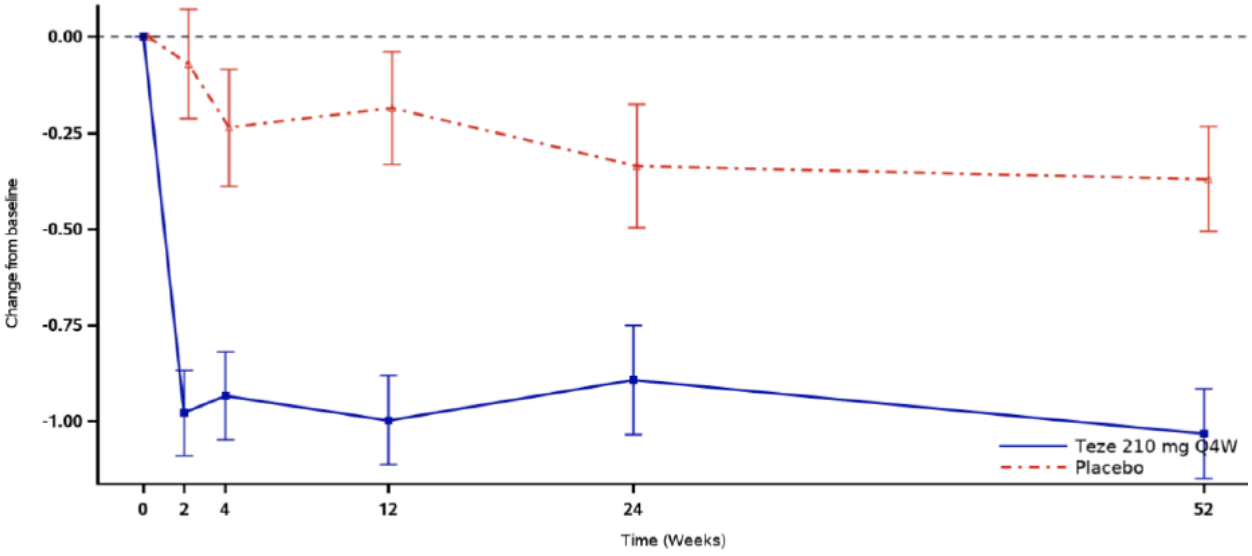
Baseline mean blood eosinophil counts (cells/µL): 326.7 for tezepelumab, 353.4 for placebo
Error bars represent 95% confidence interval. Baseline is defined as the last non-missing measurement recorded on or prior to randomization.
The model with unstructured covariance structure is: change from baseline in biomarker = treatment group + region + age + baseline biomarker + visit + treatment * visit.
CI, Confidence interval; pbo, Placebo; Q4W, Every 4 weeks; Teze, Tezepelumab 210 mg Q4W.
Source: Figure 13 in Summary of Clinical Pharmacology Studies (Module 2.7.2).

Figure 5. Adjusted Arithmatic Mean (95% CI) Change from Baseline in FeNO (ppb) over Time (Full Analysis Set) – NAVIGATOR



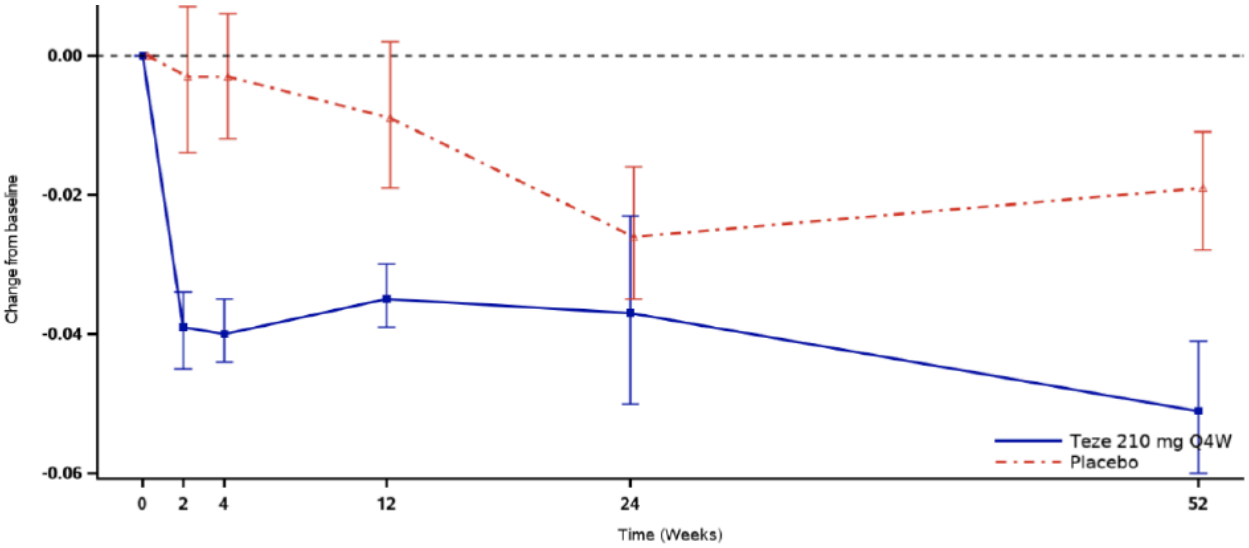
Baseline mean FeNO levels (ppb): 41.4 for tezepelumab, 46.3 for placebo
Error bars represent 95% CI. Baseline is defined as the last non-missing measurement recorded on or prior to randomization.
The model with unstructured covariance structure is: change from baseline in biomarker = treatment group + region + age +baseline biomarker + visit + treatment * visit.
CI, Confidence interval; FeNO, Fractional exhaled nitric oxide; pbo, Placebo; Q4W, Every 4 weeks; Teze, Tezepelumab 210 mg Q4W.
Source: Figure 15 in Summary of Clinical Pharmacology Studies (Module 2.7.2).

Figure 6. Mean (SE) Change from Baseline in Serum IL-5 (pg/mL) Over Time (Full Analysis Set) – NAVIGATOR



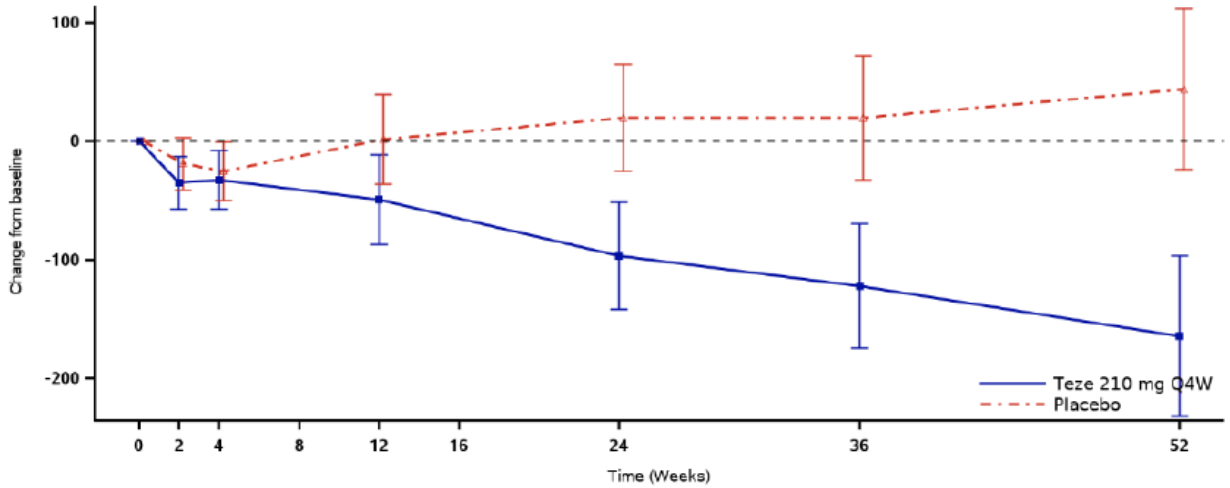
Baseline mean serum IL-5 levels (pg/mL): 1.616 for tezepelumab, 1.791 for placebo
Mean +/- 1 SE are presented.
Week 36 was not presented due to the low number (< 10 per treatment group) of subjects assessed at this time point.
pbo, Placebo; Q4W, Every 4 weeks; SE, Standard error; Teze, Tezepelumab.
Source: Figure 19 in Summary of Clinical Pharmacology Studies (Module 2.7.2).

Figure 7. Mean (SE) Change from Baseline in Serum IL-13 (pg/mL) over Time (Full Analysis Set) – NAVIGATOR



Baseline mean serum IL-13 levels (pg/mL): 0.088 for tezepelumab, 0.094 for placebo
Mean +/- 1 SE are presented.
Week 36 is not presented due to the low number (< 10 per treatment group) of subjects assessed at this time point.
pbo, Placebo; Q4W, Every 4 weeks; SE, Standard error; Teze, Tezepelumab.
Source: Figure 15 in Summary of Clinical Pharmacology Studies (Module 2.7.2).

Figure 8. Adjusted Mean (95% CI) Change from Baseline in Total Serum IgE (IU/mL) over Time (Full Analysis Set) – NAVIGATOR



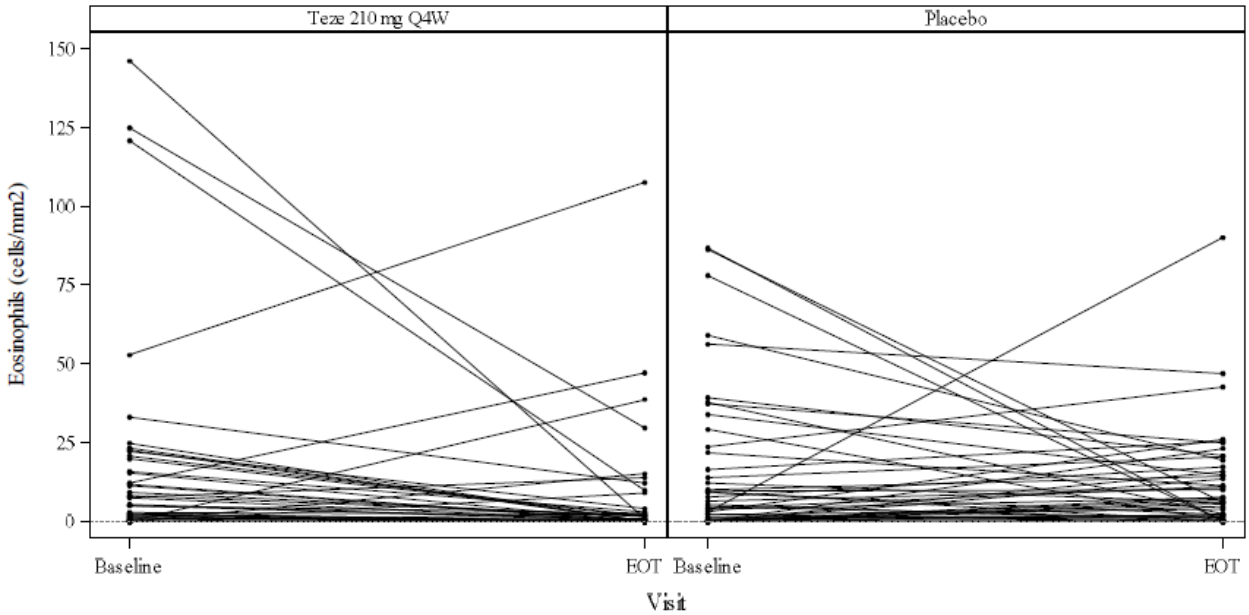
Baseline mean total serum IgE levels (IU/mL): 515.68 for tezepelumab, 614.05 for placebo
Error bars represent 95% CI. Baseline is defined as the last non-missing measurement recorded on or prior to randomization.
The model with unstructured covariance structure is: change from baseline in biomarker = treatment group + region + age +baseline biomarker + visit + treatment * visit.
CI, Confidence interval; FeNO, Fractional exhaled nitric oxide; pbo, Placebo; Q4W, Every 4 weeks; Teze, Tezepelumab 210 mg Q4W.
Source: Figure 17 in Summary of Clinical Pharmacology Studies (Module 2.7.2).

Airway submucosal eosinophil counts

Study CASCADE, a phase 2, randomized, double-blind, placebo-controlled, parallel-group mechanistic study, evaluated the effect of tezepelumab on airway inflammation in adults (n=116) with inadequately controlled moderate to severe asthma.

At baseline, the mean and median airway submucosal eosinophil counts in the tezepelumab group were 15.4 cells/mm^2 and 2.6 cells/mm^2 (range zero to 146 cells/mm^2), respectively, and 14.0 cells/mm^2 and 3.0 cells/mm^2 (range zero to 87 cells/mm^2), respectively, in the placebo group. The distribution of the eosinophil values at baseline and EOT is shown in Figure 9. At baseline, more than 35% of the biopsies in both treatment groups had no measurable eosinophils. At EOT, the percentage of biopsies with no measurable eosinophils had increased to more than 60% of biopsies in the tezepelumab group but had remained at around 35% of biopsies in the placebo group.

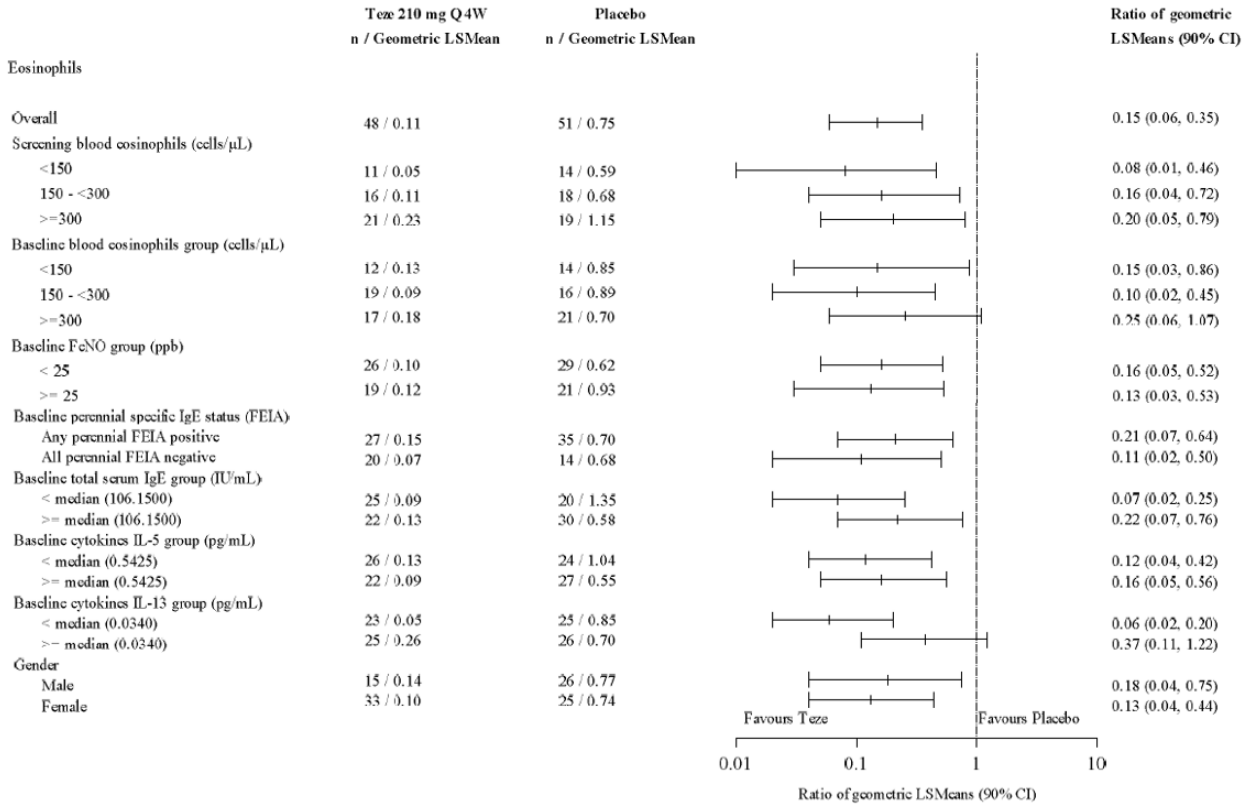
Figure 9. Airway Submucosal Eosinophils, Line Plot, Planned Treatment (Evaluable Analysis Set) – CASCADE



Baseline was the last non-missing measurement recorded on or prior to randomization. EOT, end of treatment; Q4W, every 4 weeks; Teze, tezepelumab.
Source: Figure 5 in CASCADE CSR.

Tezepelumab (210 mg SC Q4W) reduced airway submucosal eosinophil counts by 89% (end of treatment to baseline ratio 0.11 [90% CI 0.06, 0.21]) compared with a 25% reduction with placebo (0.75 [90% CI 0.41, 1.38]). Reduction trend was consistent regardless of baseline subgroup levels of blood eosinophils, FeNO, serum IL-5, serum IL-13, and allergic status (determined by a perennial aeroallergen specific IgE)(Figure 10).

Figure 10. Bronchial Submucosal Eosinophils Ratio Change from Baseline to EOT, ANCOVA Model – Forest Plot by Subgroups (Evaluable Analysis Set) – CASCADE



CI, confidence interval; EOT, end of treatment; FEIA, fluorescent enzyme immunoassay; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; IL, interleukin; LS, least squares; Q4W, every 4 weeks; Teze, tezepelumab.
Source: Figure 8 in CASCADE CSR.

What are the immunogenicity findings?

Based on the observed data in NAVIGATOR, ADA were detected at any time in 26 (4.9%) out of 527 patients who received tezepelumab during the 52-week study period. Of these 26 patients, 10 patients (1.9% of patients treated with tezepelumab) developed treatment-emergent antibodies and 1 patient (0.2% of patients treated with tezepelumab) developed neutralizing antibodies. ADA titers were generally low and often transient. Similar results were observed in SOURCE, and the overall prevalence and incidence of ADA and nAb was low (Table 18).

Table 18. Overview of Immunogenicity Results and Sampling Time Points in NAVIGATOR and SOURCE

Study identifier	Study population	Route of administration and dosage regimen	ADA sampling time points	ADA prevalence	TE-ADA	nAb prevalence
NAVIGATOR [Phase 3 confirmatory study]	Adult and adolescent subjects with severe uncontrolled asthma	210 mg Q4W SC for 52 weeks	Weeks 0, 4, 12, 24, 36, 52, 64	Tezepelumab: 4.9% (26/527) Placebo: 8.3% (44/530)	Tezepelumab: 1.9% (10/522) Placebo: 3.8% (20/523)	Tezepelumab: 0.2% (1/527) Placebo: 0.2% (1/530)
SOURCE [Phase 3 efficacy, OCS-reduction study]	Adult subjects with oral corticosteroid-dependent asthma	210 mg Q4W SC for 48 weeks	Weeks 0, 4, 12, 24, 40, 48, 60	Tezepelumab: 4.1% (3/74) Placebo: 2.6% (2/76)	Tezepelumab: 1.4% (1/73) Placebo: 0% (0/76)	Tezepelumab: 0% (0/74) Placebo: 0% (0/76)

Treatment-emergent (TE) -ADA positive: Defined as either treatment-induced ADA positive or treatment-boosted ADA positive.
Neutralizing antibody (nAb) positive: nAb positive is defined as having at least one positive nAb result at any time, including baseline and/or post-baseline.
Source: Derived from Table 5 in the Integrated Summary of Immunogenicity

The initial bioanalytical method for measuring anti-tezepelumab ADA in human serum was validated and conducted by Amgen. The method was subsequently transferred to and fully validated (b) (4) Both the Amgen method (MET-002349) and the (b) (4) method (ICDIM 271) shared similar procedures. The Amgen method was used in Study 0620, Study 0390, Study 1183, Study 0002, Japan Study 0003, and PATHWAY. The (b) (4) method was used in PATH-BRIDGE, NAVIGATOR, SOURCE, CASCADE, and PATH-HOME.

The analysis of anti-tezepelumab neutralizing antibody was validated at Amgen initially. The Amgen method was used for phase 1 and 2 clinical studies (Study 0620, Study 0390, Study 1183, Study 0002, Japan Study 0003, and PATHWAY). However, due to insufficient sensitivity and drug tolerance of the original Amgen assay, the method was later redesigned and validated (b) (4) and was used in the Phase 3 NAVIGATOR and SOURCE studies. The (b) (4) method was an MSD-based ECL immunoassay, which detected anti-tezepelumab nAb by neutralization of tezepelumab binding to its target, TSLP. In this assay, ruthenylated tezepelumab was bound to biotin-TSLP coated on the streptavidin MSD plate. If nAb was present in the sample, it would bind ruthenylated tezepelumab and inhibit biotin-TSLP/ruthenylated tezepelumab interaction. Since the Amgen assay for the determination of neutralizing antibody was insensitive as stated by the applicant, only the immunogenicity results for NAVIGATOR and SOURCE using the (b) (4) assay were included in the label.

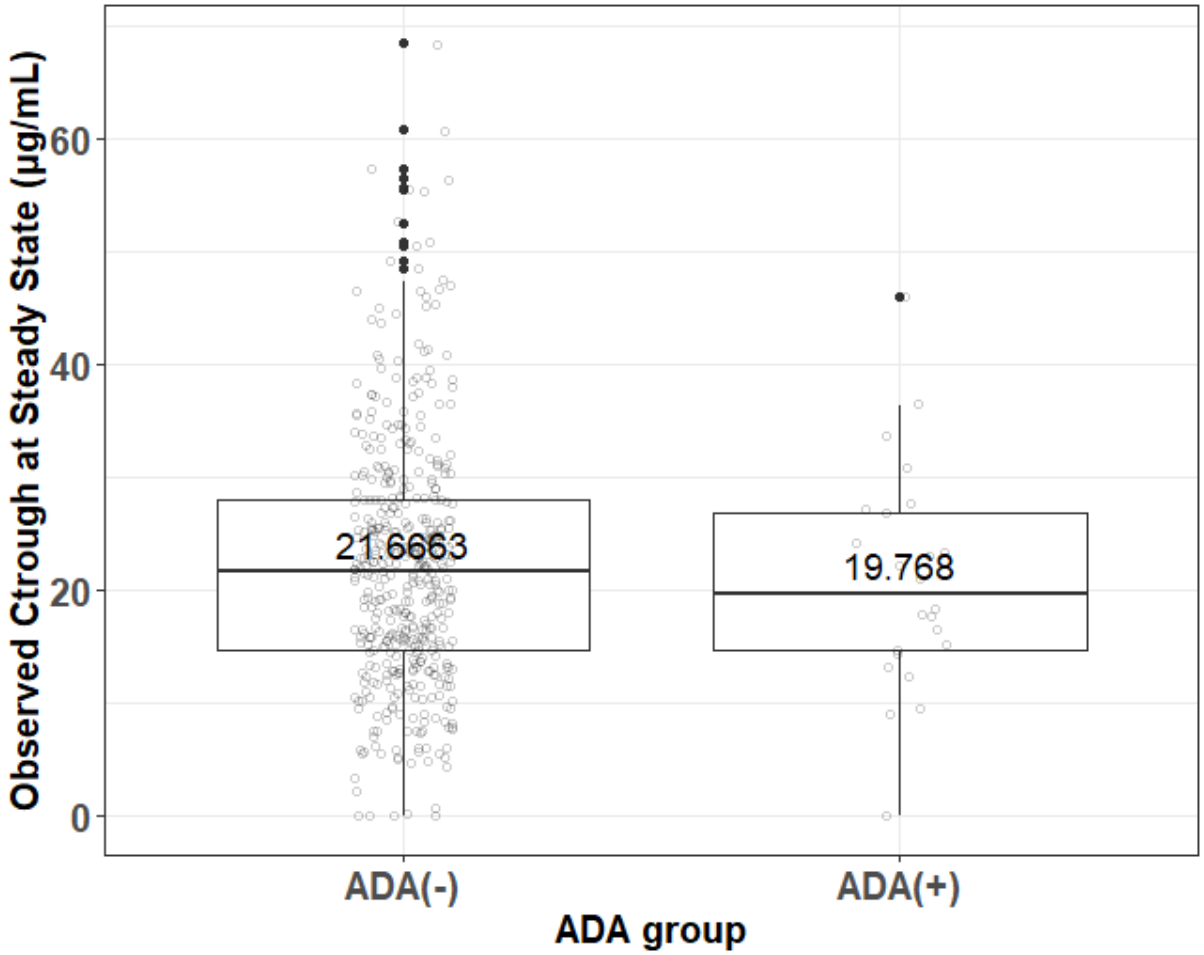
Does the immunogenicity affect the PK, PD, efficacy and/or safety of the therapeutic protein?

There was no apparent effect of ADA on the pharmacokinetics, pharmacodynamics (blood eosinophil counts, FeNO levels, and total serum IgE levels), efficacy (AAER and FEV1), or safety of tezepelumab.

- Pharmacokinetics: The effect of immunogenicity on tezepelumab PK was evaluated in the population PK analysis using pooled PK data from 8 clinical studies: Phase 3 NAVIGATOR, Phase 2b PATHWAY, and 6 supportive Phase 1 studies (Studies 0620 [Part A], 0390, 1183, 0002, 0003, and PATH-BRIDGE). ADA result (considered as positive if positive in at least one time point) was not a statistically significant covariate on any PK parameters.

  Based on the observed data In NAVIGATOR, 4.9% (26/527) of subjects treated with tezepelumab tested positive for ADA at any time. There is a slightly decrease (9%) of median C_{trough} at steady state in ADA positive patients compared to ADA-negative patients following 210 mg Q4W treatment (Figure 11). This exposure difference is not considered clinically meaningful.

Figure 11. Box plot of observed C_{trough} at steady state of tezepelumab by ADA group after receiving 210 mg Q4W in NAVIGATOR

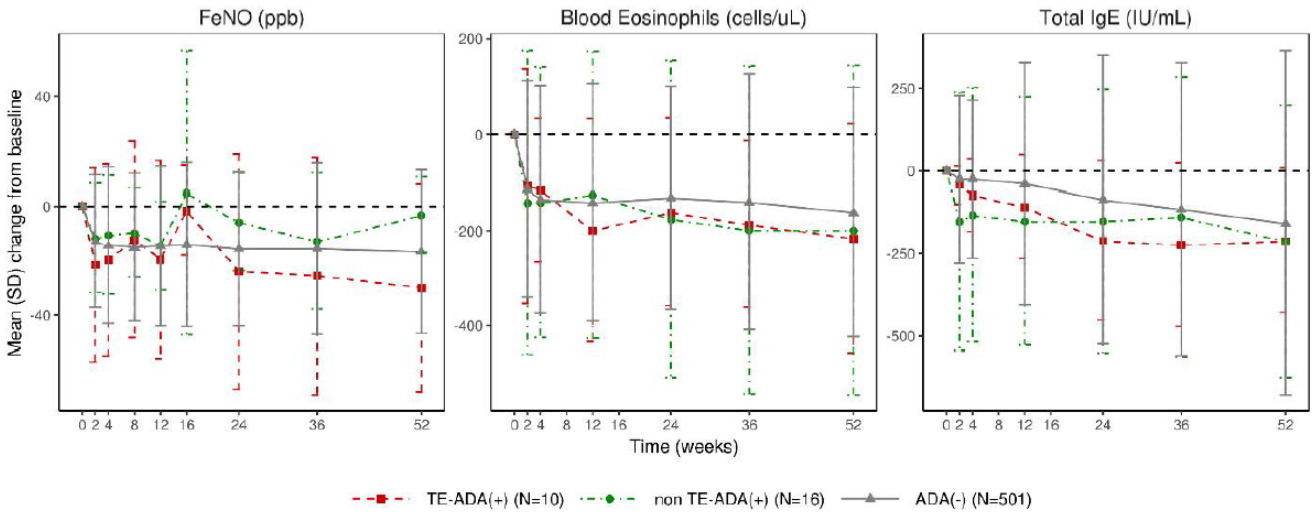


Source: Reviewer's analysis

- Pharmacodynamics: The effect of ADA on PD effects of tezepelumab was evaluated in NAVIGATOR. No clearly different trends of mean changes from baseline in FeNO, peripheral blood eosinophils cell counts, and serum total IgE levels could be observed in subjects with

TE-ADA or non-TE-ADA when compared with those in ADA-negative subjects treated with tezepelumab (Figure 12). The numbers of subjects in the ADA-positive categories were very small compared with the number of ADA-negative subjects.

Figure 12. Mean (SD) Change from Baseline in Pharmacodynamic Biomarkers in Tezepelumab-treated Subjects by ADA Category in NAVIGATOR



Error bars represent mean +/- standard deviation
ADA, Anti-drug antibodies; FeNO, Fractional exhaled nitric oxide; IgE, Immunoglobulin E; N, Number of subjects; SD, Standard deviation; TE, Treatment emergent.
Source: Figure 5 in the Integrated Summary of Immunogenicity in Module 5.3.5.3

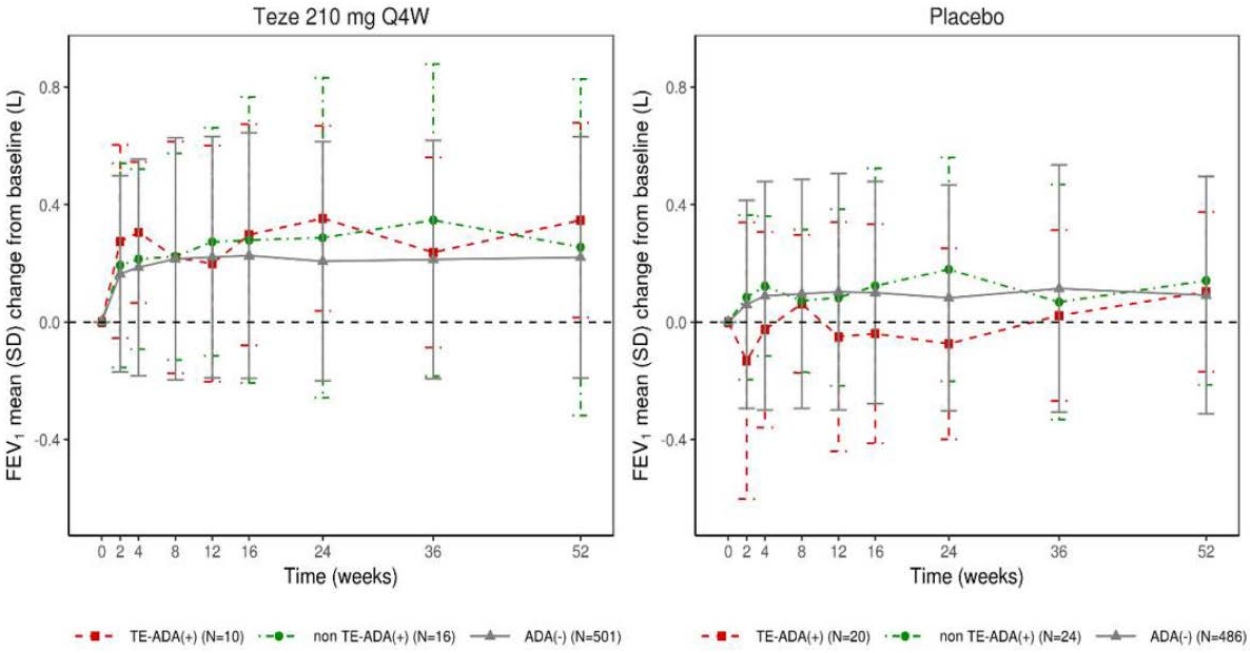
- Efficacy: The effect of ADA on the efficacy of tezepelumab on the annual asthma exacerbation rate (AAER) and FEV1 was evaluated in NAVIGATOR. The AAER was lower in the tezepelumab group compared with placebo group in all 3 ADA categories: TE-ADA positive (1.59 versus 2.35), non-TE-ADA positive (0.66 versus 1.80), and ADA negative (0.83 versus 1.79) (Table 19). In subjects with TE-ADA or non-TE-ADA who were treated with tezepelumab, mean changes from baseline in pre-bronchodilator FEV1 generally follow the similar trend compared with those in ADA-negative subjects treated with tezepelumab and placebo groups (Figure 13).

Table 19. summary of annual asthma exacerbation rate by ADA category in Study NAVIGATOR

Subset	Event	Teze 210 mg Q4W (N=528)	Placebo (N=531)
TE-ADA(+)	Number of subjects	10	20
	annual asthma exacerbation rate	1.59	2.35
non TE-ADA(+)	Number of subjects	16	24
	annual asthma exacerbation rate	0.66	1.80
ADA(-)	Number of subjects	501	486
	annual asthma exacerbation rate	0.83	1.79

Source: Derived from Table 14.3.9.7 in the NAVIGATOR **CSR**

Figure 13. Mean (SD) Change from Baseline in FEV1 by Treatment and ADA Category in Study NAVIGATOR



Error bars represent mean +/- standard deviation
ADA, Anti-drug antibodies; FEV1, Forced expiratory volume in 1 second; IgE, Immunoglobulin E; N, Number of subjects; Q4W, Every 4 weeks; SD, Standard deviation; TE, Treatment emergent; Teze, Tezepelumab.
Source: Figure 6 in the Integrated Summary of Immunogenicity in Module 5.3.5.3

- Safety: There was no apparent effect of TE-ADA-positive or non-TE-ADA-positive status on overall adverse event (AE) reporting in the NAVIGATOR study. Among antibody positive subjects (including TE-ADA and non TE-ADA), there was 2 subjects with injection site reaction (7.8%) compared with 17 (3.4%) subjects in antibody negative subjects. For hypersensitivity reactions, 2 serious AEs (SAEs) were reported in NAVIGATOR and neither of these subjects were ADA positive at any time during the study.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Two processes (Clinical (b) (4) and Clinical (b) (4)) were used to manufacture tezepelumab for testing in clinical studies. Compared to Clinical (b) (4) Clinical (b) (4) incorporated changes (b) (4) Tezepelumab manufactured by Clinical (b) (4) was used in studies conducted earlier in the clinical development program (Study 0620, Japan Study 0003, Study 0390, Study 1183, Study 0002, and PATHWAY). Tezepelumab manufactured by Clinical (b) (4) was used in later clinical studies (NAVIGATOR, SOURCE, CASCADE, and PATH-HOME, and the phase 1 PATH-BRIDGE study). Clinical (b) (4) (b) (4) has been scaled up in preparation for commercial manufacture. Changes from Clinical to the Commercial Process mainly included (b) (4)

(b) (4) The formulation is identical between Clinical (b) (4) and the commercial product (Table 20).

The Applicant provided analytical comparability data supporting the introduction of the changes throughout different phases of development (Clinical (b) (4) , Clinical (b) (4) and Commercial (b) (4)). All data were reviewed by OBP during the IND stage and found acceptable based on two review memos under IND 103031 (Reference ID: 4279347 and 4716224 in DARRTs). For details, refer to primary review by OBP reviewer Dr. Andrea Franco.

Table 20. Overview of Drug Product

	Clinical		Commercial
	(b) (4)		
Drug Substance Scale Manufacturing Site Cell Bank Concentration Storage condition			
Formulation			
Concentration			
Storage condition			
Clinical studies using drug product	Study 0620, Japan Study 0003, Study 0390, Study 1183, Study 0002, and PATHWAY	PATH-BRIDGE, NAVIGATOR, SOURCE, CASCADE, and PATH-HOME	Not applicable

a. (b) (4)
Source: Derived from Table 2 and 3 in Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1)

Has a bridge been established between different presentations?

The tezepelumab drug product manufactured by Clinical (b) (4) has been developed in 3 presentations, a vial, a pre-filled syringe (APFS), and an autoinjector (AI), each providing a 210 mg dose for subcutaneous (SC) administration. Most clinical studies tested the vial presentation, with the exception of the Phase 1 PATH-BRIDGE study (which tested the comparative bioavailability of all 3 presentations) and the Phase 3 PATH-HOME study (which tested the functionality and performance of the APFS and AI, when used at home and in the clinic). The Phase 1 PATH-BRIDGE study demonstrated bioequivalence of tezepelumab across the 3 presentations in terms of the C_{max} and AUC. However, the AI presentation was not proposed for approval in the original BLA submission.

What bioanalytical methods were used to assess tezepelumab plasma concentrations?

Bioanalytical methods for the determination of tezepelumab concentrations in human serum were summarized in Table 21. The method was originally developed and validated at Amgen (Analytical method validation report 110196 for PK method MET-001847). Subsequently, the method was transferred to and validated (b) (4) (Analytical method validation report 112687 for PK method ICD 378).

Both methods utilized an ELISA assay format to measure the concentration of tezepelumab in human serum. Calibration standards, quality controls (QCs), matrix blank nonspecific binding, and test samples were diluted 50-fold with SuperBlock® T20 and loaded onto a 96-well microplate pre-coated with anti-tezepelumab antibody, clone 1.36.1. After binding incubation, unbound material was washed away and captured tezepelumab was detected with horseradish peroxidase-conjugated anti-tezepelumab antibody, clone 55, followed by wash steps and addition of 3, 3`, 5, 5`- tetramethylbenzidine substrate solution. Colour development was stopped with phosphoric acid and the colour intensity (optical density) was measured at 450 nm and at 650 nm for correction. The optical density signal was proportional to the amount of tezepelumab bound by the capture reagent. Concentrations of tezepelumab in QC and serum samples were determined by interpolation of optical density values from the calibration curve using a 4-parameter logistic non-linear regression model with a weighting factor of 1/Y.

The assay quantification range in both validated methods was 10 to 800 ng/mL in 100% matrix. Dilution linearity was evaluated up to 1:100000 and 1:10000 dilutions at Amgen and (b) (4) respectively. The hook effect was evaluated up to 1000000 ng/mL and 2500000 ng/mL of tezepelumab concentrations at Amgen and (b) (4) respectively. Both assays demonstrated acceptable dilution linearity with no hook effect observed within the tested ranges. Incurred sample reanalysis was evaluated in Study 0620, Study 1183, NAVIGATOR, SOURCE, PATH-HOME, PATH-BRIDGE, and CASCADE. The results demonstrated acceptable reproducibility of the tezepelumab assay. There were no cross-validation studies conducted between the two bioanalytical methods.

Table 21. Methods for the Determination of Tezepelumab Serum Concentrations

Report number	Method (test site)	LLOQ ng/mL	Range ng/mL	Inter-assay % bias / %RE range [a]	Inter-assay % CV range	Intra-assay % bias / %RE range [a]	Intra-assay % CV range	Clinical studies
110196	MET-001847 (Amgen)	10	10 to 800	-4 to 3	5 to 11	-18 to 18 [b]	2 to 10 [b]	Study 0620, Study 0390
112687	ICD 378 (b) (4)	10	10 to 800	3 to 7 [c]	3 to 7 [c]	2 to 7 [c]	2 to 7 [c]	Study 1183, Study 0002, Japan Study 0003, PATHWAY, PATH-BRIDGE, PATH-HOME, NAVIGATOR, SOURCE, CASCADE

[a] % bias was measured for MET-001847 (Amgen); %RE was measured for ICD 378 (b) (4)
[b] Intra-assay accuracy and precision data for Validation Study 110196 were provided by Amgen memo BAMEM01.110196 (see Analytical method validation report 110196 for PK method MET-001847 [Amgen] in Module 5.3.1.4)
[c] Accuracy and precision results were obtained after a single outlier was removed.
% CV, percent coefficient of variation; LLOQ, lower limit of quantification; PK, Pharmacokinetics;
% RE, percent relative error.
Source: Table 4 in the Summary of Biopharmaceutic Studies and Associated Analytical Methods (Module 2.7.1)

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 22. Clinical Trials Submitted in Support of Efficacy and Safety Determinations

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Enrolled	Number of Centers and Countries
Navigator D5180C00007	Adult and adolescent subjects aged 12-80 years with severe inadequately controlled asthma	52-week, R, DB, PC	Number treated: 1059 Placebo (531) Tezepelumab 210 mg Q4W (528)	Primary: Annual asthma exacerbation rate Secondary: Change from baseline in Pre-BD FEV1, AQLQ(S)+12 total score, ACQ-6 score, and weekly mean daily Asthma Symptom Diary score	Planned: 1060 Actual: 1061 randomized, 1059 treated.	Centers: 297 Countries: 18

Pathway CD-RI-MEDI9929	Adults aged 18-75 years with severe, uncontrolled asthma.	52-week, R, DB, PC	Number treated: 550 Placebo (138) Tezepelumab (412) 70 mg SC Q4W (138) 210 mg SC Q4W (137) 280 mg SC Q2W (137)	Primary: Annualized asthma exacerbation rate measured at Week 52 Secondary: Change from baseline in Pre-BD FEV_1, and FVC	Planned: 552 Actual: 552 randomized, 550 treated.	Centers: 108 Countries: 12
SOURCE D5180C00009	Adults aged 18-80 years of age with severe, uncontrolled asthma requiring OCS	48-week, R, DB, PC	Number treated: 150 Placebo (76) Tezepelumab 210 mg Q4W (74)	Primary: Categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control. Secondary: Annualized asthma exacerbation rate	Planned: 150 Actual: 150 randomized, 150 treated	Centers: 47 Countries: 7

Source: adsl.xpt
Abbreviations: R, randomized; DB, double blind; PC.placebo controlled ACQ-6, Asthma Control Questionnaire-6; AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 years and older; BD, bronchodilator; FEV_1, forced exhalation volume in one second; FVC, forced vital capacity; N, number of subjects; Q2W, every 2 weeks; Q4W, every 4 weeks; OCS, oral corticosteroid steroids; SC, subcutaneous.

7.2. Review Strategy

The review team consisted of one primary clinical reviewer and one primary statistical reviewer. The BLA submission contained three randomized, double-blind, placebo controlled trials that were evaluated for safety and efficacy. This included a 52-week efficacy and safety trial (NAVIGATOR), a 52-week dose ranging trial (PATHWAY), and a 48-week oral corticosteroid reduction trial (SOURCE). Section 8 includes the protocol and efficacy review for each trial. Efficacy was not pooled. Summary efficacy results of PATHWAY and NAVIGATOR are briefly compared and discussed. As the SOURCE trial failed to meet its primary endpoint, the protocol and efficacy review are abbreviated.

Safety was pooled for the two 52-week pivotal trials, PATHWAY and NAVIGATOR, given the similar populations as discussed in Section 8.2. The PATHWAY trial included different dosing regimens (70 mg every 4 weeks (Q4W), 210 mg Q4W, and 280 mg every 2 weeks (Q2W)). For pooling purposes, only the to-be-marketed 210 mg Q4W dose was used in safety pooling.

Data Sources

Data sources in this electronic submission included protocols, clinical study reports, narratives, and statistical analysis systems transport datasets in ADaM format.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. NAVIGATOR Trial (D5180C00007) Design

8.1.1.1 Administrative Information

- *Study title:* A Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma
- *Study dates:* November 23, 2017 to October 29, 2020
- *Study sites:* 297 centers in 18 countries ((Argentina, Australia, Austria, Brazil, Canada, France, Germany, Israel, Japan, South Korea, Russia, Saudi Arabia, South Africa, Taiwan, Ukraine, United Kingdom, United States, and Vietnam)
- *Study report date*: February 26, 2021

8.1.1.2 Objective

- The primary objective is to assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe, uncontrolled asthma compared with placebo.

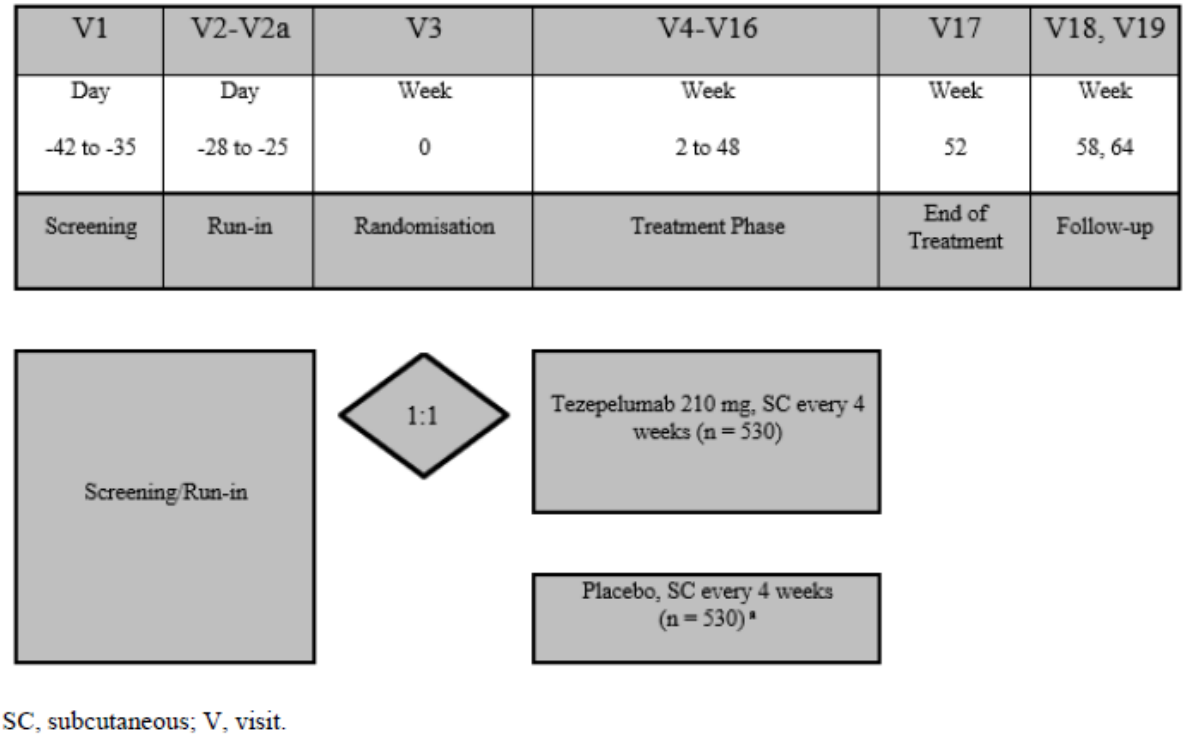
8.1.1.3 Study Design and Conduct

This was a phase 3, multicenter, global, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 210 mg of tezepelumab administered subcutaneously Q4W add-on maintenance therapy for severe, uncontrolled asthma. The trial enrolled subjects between the ages of 12 and 80 years who had documented severe, uncontrolled asthma, per GINA criteria (discussed in more detail in Section 8.1.1.5 Patient Population) for at least 12 months prior to enrollment. Subjects had to be on baseline medium or high dose inhaled

corticosteroids (ICS) and at least one additional maintenance asthma controller for at least 3 months prior to Visit 1. The trial planned for approximately 20% of the total study population to be treated with medium-dose ICS and the remaining 80% to be treated with high-dose ICS. The trial also required that 40% of the subjects in the trial had at least 3 exacerbations in the past 12 months with the remaining 60% subjects having had exactly 2 exacerbations. The trial also randomized a similar percentage of subjects with <300 eosinophils/µL and ≥300 eosinophils/µL. The Applicant expected a reasonable number of subjects would also be randomized with lower eosinophils of <150 eosinophils/µL and or higher at >450 eosinophils/ µL.

The study schematic is shown in Figure 14.

Figure 14. NAVIGATOR Study Schematic



SC, subcutaneous; V, visit.

8.1.1.4 Procedures

The study consisted of a screening/run-in period of 5 to 6 weeks, a treatment period of 52 weeks, and a post-treatment follow-up period of 12 weeks. Subjects who completed the 52-week study visit either entered a 12-week post treatment follow-up period for the assessment of safety and ADAs or enrolled in a separate extension study.

A schedule of assessments is shown in Table 23 and Table 24 below.

Table 23. NAVIGATOR Trial Screening and Run-In Schedule of Assessments

	Screening	Run-in	
Visit	**1**	**2[a]**	**2a[b]**
Day	**-42 to -35[a]**	**-28**	**-25**
Visit window	**0**	**±4[q]**	**±4[q]**
Procedures			
Informed consent	X		
Inclusion /exclusion criteria	X	X	X
Demography	X		
FENO[m]		X	X
Domiciliary FENO (only for those subjects who have opted in at consent) [n]		Completed at home on domiciliary FENO device	
Clinical Lung Function Assessments			
Spirometry (pre-BD FEV1, FVC and FEV1/FVC)[c]		X[b]	X
Reversibility (post-BD FEV1, FVC and FEV1/FVC)[d]		X[b]	X
Home peak flow monitor training and distribution		X[e]	X[e]
Check Home peak flow compliance and technique		Compliance check throughout screening period	
Home assessment every morning and evening PEF		Measurements every morning and evening	
Patient Reported Outcome assessments at Visit			
SNOT-22		X[i]	X[i]

Distribute ePRO device		X[f]	X[f]
eDiary device training		X	X
ACQ-6[g]	X		
Check compliance with PRO assessments and follow-up as needed to maintain compliance (every 7 days)		Compliance check throughout screening period	
Patient Reported Outcome assessments at home			
Daily Diary[h]		Completed twice daily at home on eDiary	
Routine safety measurements			
Complete Physical examination	X		
Vital signs	X		
Weight, Height	X		
12-lead ECG[o]	X		
Adverse events (AEs/SAEs)	X	X	X
Medical and asthma history	X		
Assessment of historical asthma exacerbations in the past 12 months	X		
Concomitant medication[j]	X	X	X

Laboratory Assessments			
Serum Chemistry	X		
Haematology (full)[p]	X		
Total immunoglobulin (IgE, IgA, IgG, IgM)[k]	X		
Pregnancy or FSH test[l]	X		
Serology (Hepatitis B, C; HIV-1; HIV-2)	X		
Urinalysis	X		

[a] Visit 2 should occur no later than 11days after Visit 1.

[b] Visit 2a is an optional visit. It can be performed if Pre-BD FEV_1 (inclusion criteria 8) and/or reversibility (inclusion criteria 9) is not met at Visit 2. If any one of these inclusion criteria is met at Visit 2, there is no need to repeat the assessment that was met at Visit 2a.

[c] Refer to section 8.1.2.1 for appropriate medication restrictions.

[d] All subjects must perform Post BD spirometry assessment at Visit 2. In the absence of historical reversibility, the subject must demonstrate reversibility at either Visit 2 or Visit 2a. Reversibility testing should be performed as per section 8.1.2.2. Refer to Footnote b for repeating the assessment if required.

[e] Home peak flow monitor training and distribution should take place only if the subject has met inclusion criteria 8 and 9. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

[f] The ePRO home device training and distribution should take place only after the inclusion criteria 8 and 9 are both met. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

[g] ACQ-6 will be done at the site during the visit on the ePRO device.

[h] Daily Diary: Asthma Symptom Diary (ASD), and items related to: Rescue medication use, Global asthma severity, Night time awakenings, Adherence to maintenance medication.

[i] Visit 2 on the handheld device should only be confirmed once both inclusion criteria 8 and inclusion criteria 9 have been met at either Visit 2 or at Visit 2a as per CSP. ePRO assessments (SNOT-22 and practice diary) need only to be collected once, either at Visit 2 or at Visit 2a if applicable. SNOT-22 questionnaire will only be triggered for subjects that have a medical history of current/ongoing nasal polyposis at Visit 2 or Visit 2a as applicable.

[j] All ICS medications in the 12 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment. To satisfy inclusion criteria #6 and #7, the history of continuous treatment with ICS plus second controller medication for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF prior to the date of randomization. All other medications taken for conditions other than asthma in the 3 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment.

[k] All total serum IgE, IgA, IgG and IgM results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

[l] FSH test done only in women < 50 years who have been amenorrheic for > 12 months to confirm postmenopausal status.

[m] FENO test needs to be completed prior to spirometry. FENO is to be completed at either Visit 2 or Visit 2a.

[n] Domiciliary FENO only for those subjects who have opted in at consent. The home FENO device will be dispensed at V2 once all spirometry criteria are met for this visit. If an optional V2a is required, then the home FENO device will be dispensed at this visit once all spirometry criteria are met.

[o] dECG to be completed prior to any blood draws.

[p] Eosinophils, basophil and monocyte counts will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

[q] If Visit 1 is conducted more than 35 days in advance of Visit 3, the Visit 2 and Visit 2a visit window is adjusted to complement the preceding visit date (Visit 1).

Table 24. NAVIGATOR Trial. Schedule of Assessments Week 0-64

	Random-ization	Treatment													EOT Period[w]	IPD[q]	FU	FU	UNS[v]
Visit	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		18	19	
Week	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52		58	64	
Day (visit window)	0	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5		±7	±7	
Procedures																			
Inclusion /exclusion criteria	X																		
Height[a]															X	X			
Weight								X							X	X			
Health care resource Utilization[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FENO at clinic[l]	X	X	X	X	X	X		X			X				X	X		X	X
Domiciliary FENO[m]	Measurements throughout treatment period																		
CGI-C			X		X			X			X				X	X			
Patient Reported Outcome Assessments at Visit[r]																			
Check compliance with PRO assessments and follow-up with subject as needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ACQ-6[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AQLQ(s) +12	X		X		X			X			X				X	X			
SGRQ[t]	X							X							X	X			
SNOT-22[d]									X						X	X			
Patient Reported Outcome Assessments at Home																			
Daily Diary[e]	Completed twice daily at home on the eDiary																		
PGI-S and PGI-C[f]	X	X	X	X	X										X	X			
EQ-5D-5L	X	Completed every 2 weeks at home on the eDiary														X			
WPAI and CIQ	X							X							X	X			
Routine safety measurements																			
Complete Physical examination	X														X	X			X
Brief physical examination			X	X	X	X	X	X	X	X	X	X	X	X			X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[g]	X							X							X	X		X	
Laboratory Assessments[h]																			

Serum Chemistry	X				X			X			X				X	X		X	X
Haematology (full)[i]	X	X	X		X			X			X				X	X		X	X
Urinalysis	X				X			X			X				X	X		X	
Urine pregnancy test, dipstick[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Serum for ADA and nAb	X		X		X			X			X				X	X		X	
Serum for PK[u]	X		X		X			X			X				X	X		X	
IgE (FEIA)	X																		
Total immunoglobulin (IgE, IgA, IgG, IgM)[k]	X	X	X		X			X			X				X	X		X	X
Serum for biomarker analysis	X	X	X		X			X			X				X	X		X	X
Blood sample for DNA (optional)[n]	X							X							X			X	
Blood samples for RNA transcriptome profiling	X	X	X		X			X							X			X	X
Flow Cytometry[s]	X							X							X				
Lung Function Assessments																			
Spirometry (pre-BD FEV1, FVC and FEV1/FVC)[o]	X	X	X	X	X	X		X			X				X	X	X	X	X
Post-BD FEV1, FVC and FEV1/FVC)	X							X							X	X			X
Home peak flow compliance and technique check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Home assessment of PEF	Measurements every morning and evening throughout treatment period																		
Study treatment administration																			
Randomization	X																		
Administration of IP[p]	X		X	X	X	X	X	X	X	X	X	X	X	X					

[a] Only to be measured for the adolescent subject.
[b] Asthma specific resource utilization (eg unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).
[c] ACQ-6 to be completed before AQLQ(s)+12.
[d] SNOT-22 questionnaire will only be completed during the treatment period for those subjects who have completed SNOT-22 at Visit 2.
[e] Daily Diary: Asthma Symptom Diary (ASD), and items related to: Rescue medication use, Global asthma severity, Night time awakenings, Adherence to maintenance medication.
[f] PGI-C will not be collected at Visit 3.
[g] ECG must be collected prior to any blood draws, spirometry, BD administration and IP administration.
[h] All blood sampling should be done prior to IP administration.
[i] Eosinophils, basophil and monocyte counts will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.
[j] For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration.
[k] All total serum IgE, IgA, IgG and IgM results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.
[l] At clinic, FENO must be performed prior to spirometry assessments. All FENO measurements will be blinded for sites and subjects throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the FENO values post randomization.
[m] Domiciliary FENO assessment must be performed after appropriate restrictions are met as per section 8.1.4.2 and prior to performing PEF assessment at home. All FENO measurements will be blinded for sites and subjects throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the FENO values post randomization.
[n] Blood sample for DNA is optional and will be collected from subjects who have consented to participate in the genetic analysis component of the study.
[o] Visit 3 spirometry must be performed on the day of randomization prior to IP administration after appropriate restriction are met as per section 8.1.2.1. For every other visit, pre-BD spirometry assessments must be performed only after appropriate restrictions are met as per section 8.1.2.1, if not this should be rescheduled to the earliest opportunity within the allowed visit window.
[p] IP should be administered after all other assessments have been completed to a scheduled visit.

[q] Refer to section 7.1.
[r] The ePRO questionnaires should be completed prior to FENO and spirometry assessments at clinic.
[s] Flow cytometry will be performed in a subset of subjects that have provided consent.
[t] SGRQ to be completed after AQLQ(s)+12
[u] Serum for PK must be collected, prior to IP administration.
[v] At unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed above is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.
[w] Subjects completing the EOT period, may be eligible to enroll in a separate extension study D5180C00018 and that these subjects will not complete the follow-up visits at Week 58 and Week 64. During the Corona Virus Disease 2019 (COVID-19) pandemic, subjects enrolling in the separate extension study D5180C00018 will continue participation in the follow-up visit(s) (Week 58, Week 64) until the on-site visit (or alternate site) for extension study randomization and IP administration can be conducted.

8.1.1.5 Patient Population

Key Inclusion Criteria

1. Physician documented asthma and on medium or high dose ICS per GINA guidelines for at least 12 months. The ICS could be contained within an ICS/(long-acting beta-agonist) LABA combination product.
2. On at least one additional maintenance asthma controller medication according to standard practice of care (i.e. LABA, leukotriene receptor antagonist (LTRA), theophylline, long-acting muscarinic antagonists (LAMA), cromones, etc). Use of additional asthma controller medications must have been documented for at least 3 months prior to Visit 1.
3. Morning pre-bronchodilator FEV1 <80% predicted normal (<90% for subjects 12 to 17 years of age) at either Visit 2/2a.
4. Documented history of at least 2 asthma exacerbation events within 12 months prior to Visit 1.
5. ACQ-6 score ≥1.5 at screening.
6. Fulfilment of at least one of the following conditions over the 7 days prior to randomization: ≥ 2 days with a daytime or night-time symptoms score ≥ 1 per ASD, Reliever short-acting β2 agonist (SABA) use on > 2 days, or ≥ 1 awakening due to asthma.

Key Exclusion Criteria

1. Current or previous smoker of ≥10 pack years.
2. Diagnosis of pulmonary disease other than asthma.
3. Acute upper or lower respiratory infections requiring antibiotics or antiviral medications within 14 days prior to Visit 1.
4. A helminth parasitic infection diagnosed within the last 6 months prior to Visit 1.
5. Treatment with any systemic immunosuppressive drugs except for OCS used in the treatment of asthma within the last 12 weeks prior to randomization.
6. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period.

8.1.1.6 Treatment

The treatments given to study participants and the formulations are found in Table 25. The presentation used in this trial was the vial presentation.

Table 25. Study Treatments

	Treatment 1	Treatment 2
Study treatment name:	Tezepelumab	Placebo
Dosage formulation:	110 mg/mL in (b) (4) L-proline, (b) (4) Polysorbate 80, pH 5.2	(b) (4) L-proline, (b) (4) polysorbate 80, pH (b) (4)
Route of administration	Subcutaneous	Subcutaneous

8.1.1.7 Study Endpoints

Primary Endpoint

1. Annualized asthma exacerbation rate (AAER)

Key Secondary Endpoints

1. Change from baseline in predose/pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV1).
2. Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score.
3. Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) Score.
4. Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) score.

Reviewer's Comment: An additional endpoint that was described in the multiplicity plan and included in the hypothesis testing in the Applicant's statistical analysis plan was: Annualized asthma exacerbation rate (AAER) in the subgroup of subjects with baseline eosinophils < 300 µL. This is the same endpoint as the primary, but a sub-population.

8.1.1.8 Efficacy Parameters

Severe exacerbation definition

Asthma exacerbation was defined as a worsening of asthma that leads to any of the following:

- Use of systemic corticosteroids for at least 3 days. A single depo-injectable dose of corticosteroids is considered equivalent to a 3-day course of systemic corticosteroids. For subjects receiving maintenance OCS, a temporary doubling of the maintenance dose for at least 3 days qualifies.
- An emergency department visit due to asthma that required systemic corticosteroids (as per above).
- An inpatient hospitalization due to asthma.

Reviewer Comments: The protocol-defined criteria for an asthma exacerbation (listed above) were used for efficacy analyses. Asthma exacerbations that did not meet criteria for a protocol-defined asthma exacerbation were included in the safety analyses as an adverse event. Asthma exacerbations that did not meet criteria as a protocol-defined asthma exacerbation were reviewed by an independent Event Adjudication Committee (EAC). If the event was confirmed by the EAC as an exacerbation event, it was included in the primary efficacy analysis.

FeNO

Airway inflammation was evaluated using a standardized single-breath FeNO[19]. Subjects were instructed to sit during FENO testing; however, if the subject was unable to sit, then standing was acceptable. The FENO testing was to be completed in the same manner (i.e., sitting or standing) at every study visit. Subjects were to inhale to total lung capacity through the NIOX MINO® Airway Inflammation Monitor and then exhale for 10 seconds at 50 mL/sec (assisted by visual and auditory cues). The value obtained was recorded and the process repeated for a total of 2 measurements. The 2 FENO values were entered into the eCRF.

Subjects were asked whether they have had a respiratory infection in the 2 weeks prior to measurement as FeNO measurements were not performed within 2 weeks of a respiratory infection. Subjects were also instructed not eat or drink 1 hour prior to FeNO assessments. FeNO was performed prior to spirometry. Subjects were instructed not to use their rescue SABA within 6 hours or inhaled bronchodilators prior to FeNO assessments.

Asthma Control Questionnaire (ACQ)-6

The ACQ is a patient-reported questionnaire assessing asthma symptoms (i.e., nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and daily rescue bronchodilator use and FEV1[20]. The ACQ-6 is a shortened version of the ACQ in that ACQ-6 omits the FEV1 component[21]. Questions are weighed equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly-controlled asthma, and a score > 1.5 indicates uncontrolled asthma[22]. Individual changes of at least 0.5 are considered to be clinically meaningful.

Asthma Quality of Life Questionnaire, Standardized (AQLQ[s])

The AQLQ(S)+12 is a 32-item questionnaire that measures the quality of life experienced by asthma patients age 12 years and older. The questionnaire consists of four separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Subjects are

[19] American Thoracic Society Documents: ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005; 171(8):912-30. Barnes NC, Kuitert LM. Risk of severe life-threatening asthma. Thorax. 1996 Nov;51(11):1073.
[20] Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999 May;115(5):1265-70.
[21] Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005 May;99(5):553-8.
[22] Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'wellcontrolled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006 Apr;100(4):616-21.

asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. Individual improvement in both the overall score and individual domain scores of 0.5 has been identified as a minimally important change, with score changes of ≥ 1.5 identified as large meaningful changes[23].

Asthma Symptom Diary

The Asthma Symptom Diary is a patient-reported questionnaire derived as the sum of the morning and evening ratings. The Diary consists of 10 items:

- Five morning items assessed nighttime symptom severity in relation to:
  - Wheezing, shortness of breath, cough, chest tightness, and the frequency of nighttime awakening
- Five evening items assessed day-time symptom severity in relation to:
  - Wheezing, shortness of breath, cough, chest tightness and activity limitation since waking

Items are scored from 0 (no symptoms) to 4 (severe symptoms). A daily ASD score is the mean of the 10 items and the mean of 7 consecutive daily scores calculated as the 7 day average score. The Applicant states that individual changes of at least 0.5 are considered clinically meaningful[24].

Reviewer Comments: (b) (4) *ASD was discussed internally and with the Division of Clinical Outcome Assessment (DCOA). Although we consider the ASD to have potential as an informative PRO, in the end, the Division determined* (b) (4) (b) (4) *a lack of adequate information supporting the interpretability and clinical meaningfulness of the ASD change scores and the small changes that were seen (see Section* 8.1.2.9 Efficacy Results – Secondary and other relevant endpoints*). The Applicant was advised to use appropriate anchor scales (i.e., easy to- interpret global scales that measure similar concepts and which have the same recall period as the target ASD endpoint) in future clinical trials to facilitate interpretation of clinically meaningful within-patient changes in ASD scores from the patient perspective. The Division also relayed* (b) (4) (b) (4) *once the above is addressed. See DCOA review for further details.*

8.1.1.9 Safety Parameters

Safety parameters included clinical labs (hematology, serum chemistry, urine analysis, hepatitis and HIV screening, and pregnancy testing), vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight), physical examination, and electrocardiograms.

[23] Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994 Jan;47(1):81-7.
[24] Globe G, Wiklund I, Mattera M, Zhang H, Revicki DA. Evaluating minimal important differences and responder definitions for the asthma symptom diary in patients with moderate to severe asthma. Journal of Patient-Reported Outcomes 2019;3(22).

8.1.1.10 Statistical Analysis Plan

Trial Analysis Populations

The full analysis set (FAS) is comprised of all subjects randomized to treatment who received at least one dose of treatment, irrespective of their protocol adherence and continued participation in the trial. Demographics, baseline characteristics and efficacy analyses were performed using all subjects in the FAS, according to the intent-to-treat (ITT) principle. Subjects were analyzed according to their randomized treatment (including in the case of any discrepancies between randomized and actual treatment).

Primary estimand

The five attributes of the primary estimand as described by the Applicant are noted here:

1. *Treatment condition of interest and alternative treatment:* 210 mg tezepelumab administered SC Q4W or matching placebo for a period of 52 weeks.
2. *Targeted population:* Adult and adolescent subjects with severe, uncontrolled asthma
3. *Variable or endpoint:* Asthma exacerbations
4. *Population-level summary:* Annual asthma exacerbation rate (AAER)
5. *Intercurrent event and data handling strategy:* Study treatment discontinuations were handled with a treatment policy strategy; data were collected and used, regardless of whether treatment discontinuation occurred.

The above estimand, therefore, describes the clinical question as follows [25]: The trial will compare 210 mg tezepelumab administered SC Q4W with matching placebo administered SC Q4W for a period of 52 weeks in adult and adolescent patients with severe, uncontrolled asthma. The primary objective was to demonstrate superiority using annual asthma exacerbation rate. The treatment effect of primary interest was to use all the subjects' data for the duration of the trial, regardless of whether treatment discontinuation occurred.

Hypothesis testing

The null (H01) and alternative hypothesis test for the primary estimand was:

H01: AAER ratio over 52 weeks

(tezepelumab/placebo) = 1 versus

H11: AAER ratio over 52 weeks

(tezepelumab/placebo) ≠ 1

The direction of superiority of tezepelumab was indicated by a rate ratio less than 1.

[25] J. Bell, A. Hamilton, O. Sailer and F. Voss, 2021. The detailed clinical objectives approach to designing clinical trials and choosing estimands. *Pharmaceutical Statistics*. 2021;1–13.

Primary analysis and its sensitivity analyses

The primary analysis of the primary efficacy endpoint, AAER over 52 weeks, quantified the effect of the initially randomized group, regardless of the treatments that subjects received or whether the subject received other controller therapy/rescue medications post randomization. This analysis used a treatment policy strategy and therefore had subjects continue to undergo study related visits for the full 52 weeks, regardless of whether they continued study treatment. Subjects were encouraged to continue their enrollment and continue data collection for the duration of the trial. Additional analyses of the primary endpoint were conducted by the Applicant, including sensitivity analyses and for the hypothetical scenario that the COVID-19 pandemic did not occur. Consequently, subjects lost to follow-up, who died or who withdrew their consent would be the only sources of missing information for the primary analysis.

Reviewer's comment: It is noted the Applicant describes the event of death as missing data, which is incorrect.[26] Death is an intercurrent event, and relevant to study outcomes. However, with only 2 deaths in this trial, death did not have appreciable influence on trial interpretation.

Missing data from early trial withdrawal was modelled based on what was observed during the trial using direct likelihood approaches, a valid approach under the assumption that data are missing at random (MAR). AAER in the tezepelumab group was compared to that seen in the placebo group using a negative binomial model.

The response variable in the model was the number of asthma exacerbations experienced by a subject over the 52-week planned treatment period (or shorter duration if not followed up for the full 52 weeks). Treatment, region, age (adolescents or adults), and history of exacerbations ($\leq$2 or >2 in previous 12 months) were included as factors in this model. The logarithm of the time at risk (in years) for exacerbation was used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occurred. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, were not included in the calculation of time at risk for exacerbation.

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, controlled multiple imputation analyses were performed, which allowed for different underlying assumptions to be used. An underlying negative binomial stochastic process was assumed for the rate of exacerbations, and post-study withdrawal counts analysis was imputed conditional upon the observed number of events prior to the withdrawal under both MAR and missing not at random (MNAR)/dropout reason-based multiple imputation (DRMI) assumptions, respectively:

[26] E9(R1) STATISTICAL PRINCIPLES FOR CLINICAL TRIALS: ADDENDUM: ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS Guidance for Industry, May 2021. https://www.fda.gov/media/148473/download

(i) MAR: Missing counts in each group were imputed assuming the estimated event rate within that treatment group.

(ii) MNAR/DRMI: Missing counts were imputed differently depending on the reason for dropout. Missing counts for subjects in the tezepelumab group who dropped out for a treatment-related reason were imputed based on the estimated event rate in the placebo group (the "copy reference" approach), whereas the remaining subjects who dropped out were imputed assuming MAR.

A second sensitivity analysis was also conducted for the primary endpoint using similar multiple imputation methodology, tipping point analysis. In this analysis, various degrees of improvement in the placebo group after withdrawal, and various degrees of worsening in the tezepelumab group after withdrawal, were simultaneously explored. Missing data were imputed for placebo subjects who withdrew from the study (irrespective of reason for discontinuing study drug) by multiplying the estimated placebo exacerbation rate by an improvement factor. Missing data were imputed for tezepelumab subjects who withdrew from the study (irrespective of reason for discontinuing investigational product (IP) or study) by multiplying the estimated tezepelumab exacerbation rate by a worsening factor. Tipping points were defined as the range of smallest values, which would result in a change of conclusion. If a tipping point was observed with analysis using 0.5 increments, smaller increments (e.g., of 0.25) were needed to be explored in the relevant range to determine the tipping point more precisely.

Secondary analyses

The key secondary efficacy analysis, H02 was on AAER in the population of subjects with baseline eosinophil counts <300/µL. This analysis was conducted as described above for AAER on the full target population.

The null (H02) and alternative hypothesis test for the primary estimand was:

H02: AAER ratio over 52 weeks (tezepelumab/placebo) in

subjects with baseline eosinophils < 300/µL = 1

versus

H12: AAER ratio over 52 weeks (tezepelumab/placebo)

subjects with baseline eosinophils < 300/µL ≠ 1

Reviewer comment: The Applicant describes H02 as part of the primary analysis. The primary statistical reviewer does not agree that H02 is part of the primary analysis, because the primary estimand and estimator are used for regulatory decision-making. Therefore, this is denoted as the first secondary estimand and first secondary analysis.

The remaining secondary endpoints were conducted in the full target population mean change from baseline at Week 52. The hypothesis tests are:

H03: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) = 0

versus

H13: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) ≠ 0

H04a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) ≠ 0

H04b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) ≠ 0

H05: Difference in mean change from baseline in weekly mean ASD score at 52 weeks (tezepelumab minus placebo) = 0

versus

H15: Difference in mean change from baseline in weekly mean ASD score at 52 weeks (tezepelumab minus placebo) ≠ 0

The five attributes of the main estimand for the key secondary endpoints as described by the Applicant are noted here:

1. *Treatment condition of interest and alternative treatment:* 210 mg tezepelumab administered SC Q4W or matching placebo for a period of 52 weeks.
2. *Targeted population:* Adult and adolescent subjects with severe, uncontrolled asthma
3. *Variable or endpoint:* FEV1, AQLQ(S) +12 and ACQ-6, and weekly mean ASD score
4. *Population-level summary:* Mean change from baseline at Week 52
   Intercurrent event and data handling strategy: Study treatment discontinuations were handled with a treatment policy strategy; data were collected and used, regardless of whether treatment discontinuation occurred.

These analyses were conducted based on the effect of the initially randomized treatment, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications prior to Week 52. These analyses used a treatment policy strategy, where subjects were encouraged to continue to undergo applicable study-related visits/procedures for the full 52-week period, even after premature study treatment withdrawal. Sources of missing data (subjects lost to follow-up, who died, who withdrew their consent, and who chose not to continue their follow-up post-study drug withdrawal) were the only sources of missing information for these. Missing data from study discontinuation was modelled based on what was observed during the study using direct likelihood approaches, under the assumption that data are missing at random (MAR).

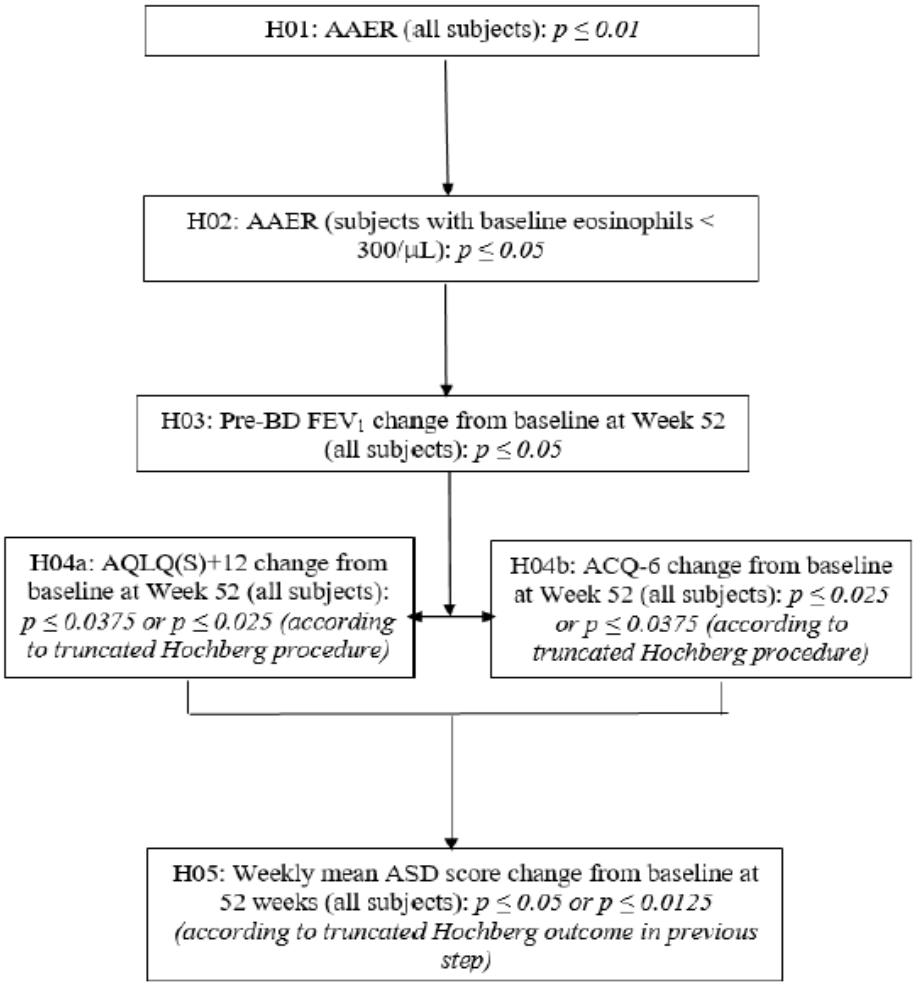
Change from baseline for these key secondary endpoints was performed using a mixed model for repeated measures (MMRM). This model was used to perform the statistical tests of the null hypotheses noted above and to estimate the treatment effect at Week 52 and its 95% CI for each endpoint. Treatment, visit, region, age (adolescents or adults) and treatment by visit interaction were included as factors in these analyses. Baseline of the corresponding endpoint was also included in the model as a continuous linear covariate. Unstructured covariance was assumed to model the relationship between pairs of response variables taken at different visits on the same subject. For the ASD endpoint, each of the 52 weeks used for weekly mean calculation replaced visit in the above model specification.

Reviewer comment: We noted in the Applicant's main analysis for these secondary endpoints: change from baseline to Week 52 for pre-BD FEV1, AQLQ(S)+12 Total Score, ACQ-6 Score, and weekly mean ASD score that anywhere from 43 to 176 subjects were excluded in a given treatment arm. The Applicant clarified in their response to our September 17, 2021 information request that

> *"The main analyses for the secondary endpoints provided in the NAVIGATOR CSR and submission documents do use the ITT analyses; all subjects in the Full Analyses Set were included in the model. AstraZeneca recognizes that for the Week 52 timepoint, the outputs provide the n for the number of subjects with observed data at this timepoint, rather than the number of subjects contributing to the analyses. AstraZeneca believes this has caused the misunderstanding as the footnotes of the forest plots are not explicit."*

Multiplicity control

Figure 15. Multiplicity Testing



Source: NAVIGATOR CSR, Figure 2

The overall Type I error rate was strongly controlled at the 0.05 level across the primary and key secondary endpoints. The primary endpoint, AAER, (in all subjects) was tested at the 0.01 level to further ensure statistically persuasive evidence. Observed p ≤ 0.01 of the primary analysis in all subjects was considered successful. In order to assess the primary objective of effect across the pre-specified subgroup, subjects with baseline eosinophils < 300 cells/µL were added into the multiple testing procedure (MTP) following direction from the Agency (See Figure 15).

Sensitivity analyses for key secondary endpoints

Sensitivity analyses of the repeated measures analyses were performed for all four of the continuous key secondary endpoints using controlled sequential multiple imputation methods based on pattern mixture models. The multiple imputations were done in two steps:

(i) The non-monotone (intermediate) missing values were imputed first, assuming MAR (the Markov chain Monte Carlo method was used to partially impute the data using SAS PROC MI).

(ii) Then, the remaining monotone missing values at each visit were imputed using the sequential regression method. At each iteration, missing values were imputed sequentially, one time point at a time.

Different assumptions were made to impute the monotone missing data:

(i) MAR: Missing data in each group were imputed assuming the distribution within that treatment group.

(ii) MNAR/DRMI: Missing data were imputed differently depending on the reason for study withdrawal. Missing data for subjects who dropped out for a treatment-related reason were imputed assuming the subject's whole distribution, both pre-withdrawal and post-withdrawal, is the same as the placebo group (the "copy reference" approach), whereas the remaining subjects were imputed assuming MAR.

Subjects with missing baseline data were excluded from these analyses. All decisions about how individual subject data would be imputed in the DRMI analyses were documented prior to primary database lock (DBL).

Tipping Point Analysis

A tipping point analysis was performed for each of the four key secondary endpoints using similar multiple imputation methodology. In this analysis, various degrees of improvement in the placebo group after withdrawal, and various degrees of worsening in the tezepelumab group after withdrawal, were simultaneously explored. Placebo subjects who withdrew from the study (irrespective of reason for discontinuing study treatment) had their first imputed value adjusted by an improvement factor. This resulted in a one-time shift towards a better value in the outcomes of placebo subjects who withdrew from the study after a given visit. Tezepelumab subjects who withdrew from the study (irrespective of reason for discontinuing study treatment) had their first imputed value adjusted by a worsening factor. This resulted in a one-time shift towards a worse value in the outcomes of tezepelumab subjects who withdrew from the study after a given visit. Tipping points were defined as the range of smallest values that would result in a change of conclusion. If a tipping point was observed with analysis using increments of 1, smaller increments (e.g., of 0.5) were explored in the relevant range to determine the tipping point more precisely.

Subgroup analyses

Biomarkers of interest: Descriptive summaries of the AAER by treatment group were pre-specified for each of the following categorical variables and summarized using the FAS population:

(i) Baseline eosinophils group: <300/µL, ≥300/µL
(ii) Baseline eosinophils group: <150/µL, 150-<300/µL, 300-<450/µL, ≥450/µL
(iii) Baseline eosinophils group: <150/µL, ≥150/µL
(iv) Baseline clinic visit FeNO group: <25ppb, ≥25ppb
(v) Baseline clinic visit FeNO group: <25ppb, 25-<50ppb, ≥50ppb
(vi) Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial *FEIA negative, Unknown perennial FEIA*

A similar negative binomial model was fit for the primary analysis for each of the above subgroup variables, with additional factors for the subgroup variable and the treatment by subgroup interaction. This model was used to estimate the treatment effect and its 95% CI within each of the subgroup categories.

Based on the statistical reviewer's preliminary analysis with this model, both eosinophils and FeNO met the criteria of significant interaction term, but IgE did not. To further understand the affect of eosinophil and FeNO biomarkers, we requested that the Applicant:

a. Conduct an interaction analysis that includes both continuous eosinophil-by-treatment and continuous FeNO-by-treatment interactions (along with main effects for FeNO, eosinophil, and treatment) to explore whether there is evidence that higher FeNO levels are independently predictive of greater treatment effects among subjects with similar eosinophil levels.

b. Perform these models on the primary efficacy endpoint (annualized asthma exacerbation rate (AAER; negative binomial regression)) and the key secondary endpoint, pre-dose/pre-BD FEV1 (MMRM using the complete ITT data with a contrast to calculate a treatment policy strategy estimator for the landmark timepoint).

Further we requested the Applicant use the primary statistical model for the subgroups below to compare various FeNO subgroups with various baseline eosinophil subgroups

Reviewer Comment: FeNO is a tool used by practitioners to assess airway inflammation and can be correlated with eosinophil level[27]. Eosinophils, FeNO, and total IgE were three markers of interest to further understand the efficacy of tezepelumab. Previous biologics approved for moderate to severe and severe asthma were found to be only efficacious in either eosinophilic asthma or allergic asthma in which subjects had positive perennial allergy specific IgE levels. As the mechanism of tezepelumab is upstream to previous known targets, it was important to assess the efficacy in across eosinophil and perennial IgE subgroups.

8.1.1.11 Protocol Amendments

[27] Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR; American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011 Sep 1;184(5):602-15. doi: 10.1164/rccm.9120-11ST. PMID: 21885636; PMCID: PMC4408724.

There were five protocol amendments submitted. The first four amendments submitted were clarifications to various aspects of the procedures and did not impact the design of the trial significantly. The last amendment submitted (Version 5.0 on May 14, 2020) was done in response due to the COVID-19 pandemic. Protocol changes such as allowing home administration by a qualified health care professional and remote visits were made to reduce the risk of subjects and site staff to COVID-19. The above changes did not impact the results of the trial.

8.1.2. NAVIGATOR Trial Results

8.1.2.1 Compliance with Good Clinical Practices

As with the NAVIGATOR trial, PATHWAY was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Additional details for compliance are the same as NAVIGATOR (See Section 8.1.2.1 Compliance with Good Clinical Practices).

8.1.2.2 Financial Disclosure

The NAVIGATOR trial was conducted by AstraZeneca and Amgen. In early January 2018 it was discovered that the financial disclosure information was collected related to only Amgen. On January 30, 2018, updated financial disclosure forms which listed both AstraZeneca and Amgen were distributed for signature. Financial disclosure information related to AstraZeneca was collected from 1443/1448 (>99%) of the clinical investigators. Financial disclosure information related to Amgen was collected from 1434/1448 (99%) of the clinical investigators. Of these, four investigators had disclosable financial interest to declare in either company, in which they randomized (b) (6) of the 1061 ((b) (6)%) subjects of the trial. AstraZeneca was unable to collect financial disclosure information related to Amgen for 14/1448 (1%) of the investigators. Five investigators (< 1%) did not sign financial disclosure information. The same due diligence process was applied to those with missing information. See Appendix 16.1 for completed financial disclosure form.

8.1.2.3 Data Quality and Integrity

Per the Applicant, quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures.

AstraZeneca's quality assurance and quality control procedures provide reassurance that the clinical study program was carried out in accordance with GCP guidelines. AstraZeneca participates in a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented AstraZeneca policies

and procedures are directed towards all aspects of the clinical study process and its associated documentation.

For sites with restricted access for Applicant monitoring or because of travel restrictions due to the COVID-19 pandemic, some on-site monitoring visits did not take place after the start of the COVID-19 pandemic, including some final on-site monitoring visits prior to DBL. As a result, for the impacted sites, no source data verification and source data review were completed for data points generated whilst COVID-19 restrictions were in place, including any previous data backlog, if applicable. The data that were not verified or source data not reviewed prior to DBL have been documented. The risk assessment of the impact to data integrity was conducted and documented prior to DBL.

Where possible, remote monitoring activities took place (i.e., audio and video contact) in place of on-site monitoring visits. If remote access to the source documents was allowed according to local or site processes, source data review was performed. The COVID-19 pandemic was judged to not meaningfully impact the overall quality of the study, including the conduct of the study and the data quality.

Reviewer comment: In general, the submitted efficacy data were acceptable in terms of quality and integrity. The quality and integrity of the programming code supplied in the application was not sufficient, as it was missing a key parameter (EXP, or exponential) to reproduce the planned primary result from the SAP. The primary statistical reviewer was able to reproduce the primary and secondary efficacy endpoints analyses, after an information request response from the Applicant regarding the specific code used to produce the primary efficacy results was provided from one of the code examples provided.

8.1.2.4 Subject Disposition

The subject disposition for NAVIGATOR Trial can be found in Table 26. The proportion of subjects discontinuing investigational product was lower in the tezepelumab group (7%) compared with placebo group (11%). There were more subjects who discontinued due to adverse events in the placebo group (3%) compared to tezepelumab group (1%).

Table 26. NAVIGATOR Trial Subject Disposition in Randomized Subjects

Disposition Outcome	Tezepelumab 210 mg Q4W N=528 n (%)	Placebo N=531 n (%)
Subjects randomized	528	531
Safety population	528	531
Discontinued study	15 (3)	22 (4)
Death	0 (0)	2 (<1)
Lost to follow-up	5 (1)	2 (<1)

Disposition Outcome	Tezepelumab 210 mg Q4W N=528 n (%)	Placebo N=531 n (%)
Other	2 (<1)	3 (1)
Withdrawal by subject	8 (2)	15 (3)
Discontinued treatment	36 (7)	57 (11)
Adverse event	7 (1)	14 (3)
Development of study-specific withdrawal criteria	4 (<1)	5 (1)
Lost to follow-up	5 (1)	0 (0)
Other	4 (1)	11 (2)
Protocol deviation	2 (<1)	1 (<1)
Withdrawal by subject	14 (3)	26 (5)

Source: ds.xpt, adsl.xpt; Software: R
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable; Q4W, every 4 weeks.

8.1.2.5 Protocol Violations/Deviations

Overall, 195 subjects (18% of subjects) had at least one important protocol deviation with 15% in the tezepelumab arm and 22% in the placebo arm. None of the deviations were considered to impact the quality of the study or overall interpretation of the results.

Due to COVID-19, a subset (7%) of the subjects experienced at least one study disruption, which included missed or altered study visits and measurements. Three subjects missed two study medication administrations; FEV1 and FeNO was not measured in a subset of subjects due to the potential of virus spread. Additional assessments such as laboratory and physical exams were missed or administered outside the protocol study window due to the pandemic.

8.1.2.6 Subject Demographics

The demographics are summarized in Table 27. The population was overall evenly randomized between treatment arms. The population enrolled a higher proportion of females (approximately 64% vs 37%) and white subjects (62%). The mean age in both treatment groups was approximately 49 years old. Eight percent of the enrolled population consisted of the adolescent age group.

Table 27. NAVIGATOR Trial Baseline Demographic Characteristics in Randomized Population

	Tezepelumab 210 mg Q4W N=528	Placebo N=531	Total N= 1059
Sex, (n%)			
Female	335 (63)	337 (64)	672 (63)
Male	193 (37)	194 (37)	387 (37
Age, years			
Mean (SD)	50 (16)	49 (16)	49 (16)
Median (min, max)	53 (12, 80)	52 (12, 80)	52 (12,80)
Age group, years, (n%)			
Adolescent (≥12 to <18)	41 (8)	41 (8)	82 (8)
Adult (≥18 to <65)	391 (74)	416 (78)	807 (76)
Adult (≥65)	96 (18)	74 (14)	170 (16)
Ethnicity, (n%)			
Hispanic or Latino	83 (16)	81 (15)	164 (15)
Not Hispanic or Latino	445 (84)	450 (85)	895 (85)
Race, (n%)			
Asian	146 (28)	149 (28)	295 (28)
Black or African American	30 (6)	31 (6)	61 (6)
Other	20 (4)	24 (5)	44 (4)
White	332 (63)	327 (62)	659 (62)

	Tezepelumab 210 mg Q4W N=528	Placebo N=531	Total N= 1059
Country of participation, (n%)			
Argentina	40 (7)	41 (8)	81 (8)
Australia	8 (2)	11 (2)	19 (2)
Austria	2 (<1)	6 (1)	8 (1)
Bulgaria	0 (0)	0 (0)	0 (0)
Brazil	47 (9)	46 (9)	93 (9)
Canada	19 (4)	17 (3)	36 (3)
Czech Republic	0 (0)	0 (0)	0 (0)
Germany	56 (11)	47 (9)	103 (10)
France	20 (4)	21 (4)	41 (4)
Hungary	0 (0)	0 (0)	0 (0)
Israel	25 (5)	22 (4)	47 (4)
Japan	58 (11)	39 (7)	97 (9)
Korea	54 (10)	72 (14)	126 (12)
Lithuania	0 (0)	0 (0)	0 (0)
Latvia	0 (0)	0 (0)	0 (0)
Russia	25 (5)	26 (5)	51 (5)
Saudi Arabia	5 (1)	2 (<1)	7 (<1)
Serbia	0 (0)	0 (0)	0 (0)
Slovakia	0 (0)	0 (0)	0 (0)
Taiwan	5 (1)	4 (1)	9 (1)
Ukraine	13 (3)	13 (2)	26 (2)
United States	92 (17)	94 (18)	186 (18)
Vietnam	8 (2)	12 (2)	20 (2)
South Africa	51 (10)	58 (11)	109 (10)

Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, every 4 weeks; SD, standard deviation.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline clinical characteristics can be found in Table 28. The baseline clinical characteristics were approximately the same in each treatment group. The overall population had an elevated baseline eosinophil level (327 cells/uL in tezepelumab arm and 353 cells/uL in the placebo arm). However, there was an even distribution of subjects enrolled with a varying eosinophil level with approximately 26% of the population with eosinophils <150 cells/uL. Similarly, subjects with a range of baseline FeNO levels were enrolled with approximately 40% of the population with a <25 ppb baseline FeNO level. Approximately 9% of the population enrolled required baseline oral corticosteroid use and 75% were on high-dose ICS.

Table 28. NAVIGATOR Trial Baseline Clinical Characteristics in Randomized Population

Characteristic	Tezepelumab 210 mg Q4W N=528 n (%)	Placebo N=531 n (%)	Total N = 1059 n(%)
Baseline Eosinophils, cells/uL			
Mean (SD)	327 (293)	353 (488)	340 (403)
Median (min, max)	250 (0, 3650)	250 (0, 8170)	250 (0, 8170)
Pooled Baseline Eosinophils, (n%)			
<150	138 (26)	138 (26)	276 (26)
150 - <300	171 (32)	171 (32)	342 (32)
300 - <450	99 (19)	95 (18)	194 (18)
≥450	120 (23)	127 (24)	247 (23)
Baseline FeNO, ppb			
Mean (SD)	41.4 (36)	46.3 (45)	44 (41)
Median (min, max)	31 (5, 235)	30 (5, 265)	30 (5, 265)
Pooled Baseline FeNO, (n%)			
<25	213 (40)	220 (41)	433 (41)
≥25 - <50	158 (30)	151 (28)	309 (29)
≥50	151 (29)	156 (29)	307 (29)
Missing	6 (1)	4 (1)	10 (1)
Baseline IgE, mg/L			
Mean (SD)	516 (960)	614 (1160)	565 (1066)
Median (min, max)	195 (2, 12823)	197 (2, 9741)	196 (2, 12823)

Characteristic	Tezepelumab 210 mg Q4W N=528 n (%)	Placebo N=531 n (%)	Total N = 1059 n(%)
Baseline IgE Status, (n%)			
All perennial FEIA negative	184 (35)	177 (33)	361 (34)
Any perennial FEIA positive	339 (64)	341 (64)	680 (64)
Unknown perennial FEIA	5 (1)	13 (2)	18 (2)
Smoking Status, (n%)			
Former	99 (19)	110 (21)	209 (20)
Never	429 (81)	421 (79)	850 (80)
Smoker, Pack Years			
Mean (SD)	4.3 (3)	5.2 (3)	4.8 (3)
Median (min, max)	5 (0, 9)	5 (0, 9)	5 (0, 9)
Baseline ICS Level, (n%)			
High	397 (75)	398 (75)	795 (75)
Low	0 (0)	1 (<1)	1 (<1)
Medium	131 (25)	132 (25)	263 (25)
Baseline OCS Level, (n%)			
Absent	479 (91)	480 (90)	959 (91)
Present	49 (9)	51 (10)	100 (9)
Years Since First Diagnosis			
Mean (SD)	22 (17)	22 (16)	22 (16.5)
Median (min, max)	18 (1, 69)	19 (1, 65)	18 (1, 69)
Exacerbations in Previous 12 months			
Mean (SD)	3 (1)	3 (1)	3 (1)
Median (min, max)	2 (2, 15)	2 (1, 11)	2 (1, 15)
Atopic Dermatitis			
No	459 (87)	473 (89)	932 (88)
Yes	69 (13)	58 (11)	127 (12)
Nasal Polyps within last 2 years			
No	438 (83)	456 (86)	894 (84)
Yes	90 (17)	75 (14)	165 (16)
FEV1, L			
Mean (SD)	1.8 (0.7)	1.9 (0.7)	1.9 (0.7)
Median (min, max)	1.7 (0.4, 4.8)	1.7 (0.4, 4.8)	1.7 (0.4, 4.8)
Percent Predicted FEV1, %			
Mean (SD)	63 (18)	63 (18)	63 (18)
Median (min, max)	63 (18, 106)	64 (15, 127)	63 (15, 127)
FEV1 Reversibility, L			
Mean (SD)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)

Characteristic	Tezepelumab 210 mg Q4W N=528 n (%)	Placebo N=531 n (%)	Total N = 1059 n(%)
Median (min, max)	0.2 (-0.4, 1.6)	0.2 (-0.3, 1.2)	0.2 (-0.4, 1.6)
ACQ-6 Score			
Mean (SD)	3 (1)	3 (1)	3 (1)
Median (min, max)	3 (2, 5)	3 (2, 6)	3 (2,6)

Source: adsl.xpt, adre.xpt, adqsacq.xpt; Software: R
Abbreviations: ACQ, Asthma control questionnaire; FEV1, Forced Expiratory Volume in 1 second; ICS, Inhaled corticosteroids; N, number of subjects in treatment group; n, number of subjects with given characteristic; OCS, Oral corticosteroids; SD, standard deviation; IgE, Immunoglobulin E; FEIA, fluorescent enzyme immunoassay

Reviewer comment: During the development of tezepelumab, the Applicant developed inclusion criteria to enroll severe asthmatics (i.e. on medium to high dose ICS/LABA and an additional asthma controller) who were uncontrolled on their current asthma regimen (≥ 2 exacerbations within the past year, ACQ-6 ≥1.5, and symptoms and/or rescue medication use within the 1 week prior to randomization) in NAVIGATOR and PATHWAY trials. (b) (4) *GINA guidelines[28] define severe asthma as asthma that is uncontrolled despite high-dose ICS/LABA or that requires high dose ICS/LABA to remain controlled. For subjects to be classified as moderate severity, the subjects would need to be well controlled on low or medium dose ICS/LABA. Per the NHLBI guidelines[29], classifying severity relies on assessing subjects who are well controlled by lowest level of treatment required to maintain control. Severe asthma is defined as subjects that are controlled on high-dose ICS/LABA +/- oral corticosteroids. Based on the population enrolled, all subjects were uncontrolled on medium to high-dose ICS/LABA and would be classified as severe asthma per GINA and NHLBI criteria.*

The Division further reviewed the enrolled population baseline characteristics and compared them to the populations of other asthma biologic trials. Tezepelumab's population was similar to those of the anti-IL5 products (indicated for severe asthmatics), given that those enrolled had 2 or more asthma exacerbations in the last 12 months. Furthermore, approximately 9% of the tezepelumab population was on baseline OCS which is in line with the anti IL5 biologics. Based on the enrolled population and guideline definitions for moderate and severe asthma, the enrolled population reflects a severe asthma population and the indication should reflect the studied population. As such, (b) (4)

[28] Global Initiative for Asthma (GINA), 2020, Global Strategy for Asthma Management and Prevention, accessed July 16, 2021: http://www.ginasthma.org/.
[29] National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute (NHLBI), 2007, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, NIH publication no. 07-4051.

(b) (4) *the indication will be for treatment of severe asthma.*

8.1.2.7 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance
Compliance to the IP was high and balanced across treatment group (99% in both tezepelumab and placebo groups). Eighty-three percent and 76% subjects received all planned doses in the tezepelumab and placebo groups. This was similar in the adolescent population as well. The COVID-19 pandemic effected conduct of the trial for 27 (3%) of the subjects. The Applicant relayed the data impact from these effects were minimal.

Treatment compliance to background medication was monitored via an eDiary and overall was similar between the tezepelumab group and the placebo group (80% and 78%).

Concomitant Medications
The proportion of subjects taking concomitant medications was similar across treatment groups for both allowed and prohibited medications. All of the subjects took at least one concomitant medication (either allows or prohibited) that was required to be stopped prior to treatment. A total of 27 (3%) subjects took at least one prohibited concomitant medication that was stopped prior to treatment. In the majority of cases, these medications were taken to manage asthma exacerbations prior to the first dose of IP. The most common concomitant medications were systemic corticosteroids, other systemic drugs for obstructive airway disease, and adrenergics in combination with corticosteroids.

During treatment, the most common concomitant medication for conditions other than asthma were: adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics (97%), selective beta2- adrenoreceptor agonists (89%), systemic glucocorticoids (55%), leukotriene receptor antagonists (41%), corticosteroids (38%), anilides (28%), and anticholinergics (3%). The use of systemic glucocorticoids was higher in the placebo group (49% in the tezepelumab group versus 62% in the placebo group).

8.1.2.8 Efficacy Results- Primary Endpoint

Primary Endpoint: Annualized Asthma Exacerbation Rate
The primary endpoint of AAER over 52 weeks showed that tezepelumab treatment resulted in a reduction in AAER by 56% compared with placebo in the overall population (RR 0.44 [95% CI 0.37, 0.53]; p <0.001; Table 29). Multiple imputation methods exploring the effect of missing data on the reliability of the results did not impact any conclusions from the primary analyses.

Table 29. Efficacy results for annualized asthma exacerbation rate over 52 Weeks (Full Analysis Set Population and subjects with baseline eosinophils < 300 cells/µL population)

Variable	Teze 210 mg N, Crude rate	Placebo N, Crude rate	Rate Ratio	Confidence Interval
AAER over 52 weeks using primary analysis[1]	528,0.84[2]	531,1.91[2]	0.44	95%:(0.37, 0.53)[2] 99% (0.34, 0.57)
AAER over 52 weeks in subjects with baseline eosinophils < 300 cells/µL[3]	309,0.91[2]	309,1.57[2]	0.59	95% (0.46, 0.75)
AAER over 52 weeks using multiple imputation assuming MAR[4]	528, NR	531, NR	0.44	95%: (0.37, 0.53)
AAER over 52 weeks using dropout reason-based multiple imputation[5]	528, NR	531, NR	0.45	95%: (0.37, 0.54)

Abbreviations: AAER, annual asthma exacerbation rate; MAR, missing at random: NR, no rate provided
[1] Source: NAVIGATOR CSR, Table 14.2.2.7. The overdispersion parameter is estimated to be 1.41. FAS population.
[2] Confirmed by statistical reviewer (t_eff_val.sas, t_eff_valbyeos300.sas)
[3] Source: statistical reviewer (t_eff_valby_eos300.sas), which is nearly identical to NAVIGATOR CSR, Table 14.2.2.12 results. Subjects with baseline eosinophils < 300 cells/µL population.
[4] Source: NAVIGATOR CSR, Table 14.2.2.9. Number of events (total time at risk) is the average number of events over 100 imputations. FAS population
[5] Source: NAVIGATOR CSR, Table 14.2.2.10. Number of events (total time at risk) is the average number of events over 100 imputations. FAS population
Rate ratio and 95% CI are based on the model: a negative binomial regression analysis with treatment, region, age group, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable. Annual exacerbation rates displayed are estimated marginal rates from the model. Note that the model for the eosinophil subgroup included the treatment by subgroup interaction term.
Crude rate: Number of exacerbation events divided by Total time at-risk (years)
Note: Model-based rate ratios and CIs are combined using Rubin's rule over multiply imputed analyses, here 100 analyses results. Because the rate ratios and CIs from the multiple imputation analyses are very close to those from the primary analysis, crude rates, if similarly combined, would be very close to those from the primary analysis.

Annualized Rate of Exacerbations Associated with Emergency Room (ER) Visits or Hospitalizations

Tezepelumab reduced the rate of asthma exacerbations requiring hospitalizations or ER visits compared to placebo over 52 weeks by 79% (AAER: 0.06 vs 0.22, AAER ratio 0.21 [95% CI 0.12, 0.37], Table 30). Tezepelumab treatment reduced the 52 week rate of asthma exacerbations

requiring hospitalization compared with placebo by 85% (AAER ratio 0.15 [95% CI 0.07, 0.33]).

Table 30. Annual exacerbations over 52 weeks associated with hospitalization or ER visit and hospitalization alone (Full Analysis Set Population)

Variable	Teze 210 mg N, Crude rate	Placebo N, Crude rate	Rate Ratio	95% Confidence Interval
AAER over 52 weeks associated with hospitalization or ER visit[1]	528, 0.06	531, 0.22	0.21	0.12, 0.37
AAER over 52 weeks associated with hospitalization[2]	528, 0.03	531, 0.15	0.15	0.07, 0.33

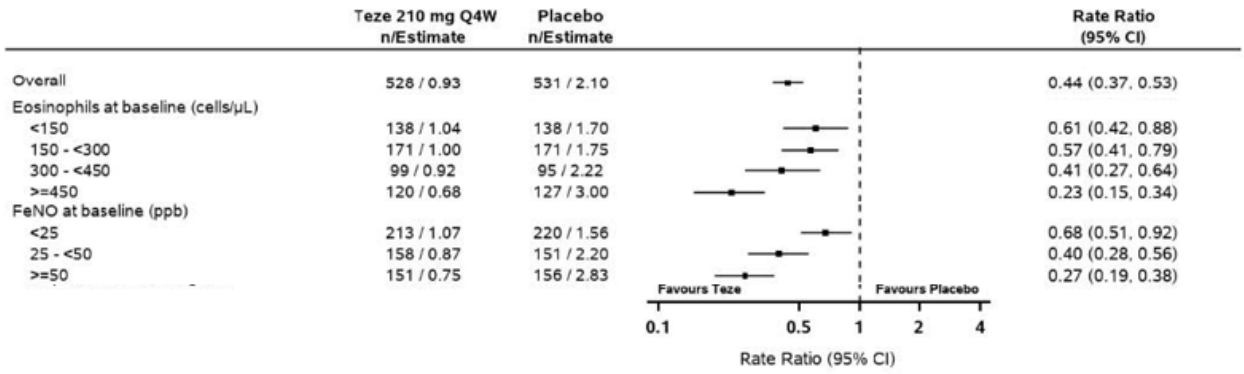
Abbreviations: AAER, annual asthma exacerbation rate; ER, emergency room
[1]Source: NAVIGATOR CSR, Table 14.2.2.15, confirmed by statistical reviewer
[2]Source: NAVIGATOR CSR, Table 14.2.2.16, confirmed by statistical reviewer.
Rate ratio and 95% CI are based on the model: a negative binomial regression analysis with treatment, region, age group, history of exacerbations as covariates. The logarithm of the time at risk is used as an offset variable.
Crude rate: Number of exacerbation events divided by Total time at-risk (years)

AAER and baseline biomarkers

Subjects receiving tezepelumab experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils and FeNO; however efficacy did improve with increasing baseline blood eosinophils and baseline FeNO (Figure 16). Based on the multiplicity controlled subgroup analysis of the primary endpoint, there was a reduction in AAER by 41% for tezepelumab compared with placebo in subjects with baseline blood eosinophils <300 cells/µL (rate ratio 0.59 [95% CI 0.46, 0.75]; P<0.001).

In all four pre-specified baseline eosinophil categories (<150, 150-<300, 300-<450, ≥450 cells/µL), AAER was reduced (by 39%, 43%, 59% and 77%, respectively) in tezepelumab compared to placebo and all four confidence intervals did not include 1, the point of no difference (See Figure 16). Similarly with the three baseline FeNO categories (<25, 25-<50, ≥50 ppb), AAER was reduced (by 32%, 60% and 73%, respectively) in tezepelumab compared to placebo and all three confidence intervals did not include 1. The magnitude of benefit increased with increasing levels of eosinophils and FeNO.

Figure 16 Forest plot by biomarker subgroups for annual asthma exacerbation rate ratio over 52 weeks (Full Analysis Set Population)



Abbreviations: CI, confidence interval, FeNO = fractional exhaled nitric oxide
Source: Modified from NAVIGATOR CSR Figure 4, confirmed by statistical reviewer
Rate ratio is displayed on the log scale. Dotted line represents no treatment difference.
Rate ratio and 95% CI are based on the model, including subgroups, is a negative binomial regression analysis with treatment, region, age, history of exacerbations, subgroup (if not already included), and treatment * subgroup as covariates.
Time at risk is used as an offset variable in the model to adjust for subjects' having different exposure times during which the events occur.

Reviewer's comment: In the biomarker analysis conducted by the primary statistical reviewer, which includes interaction of baseline biomarker by treatment interaction, the interaction term for baseline eosinophil counts with treatment and the interaction term for baseline FeNO with treatment are both statistically significant, demonstrating that the biomarker itself has a significant effect. Therefore, we requested and received additional analyses from the Applicant to further demonstrate the biomarker effects of baseline eosinophils and FeNO.

Exploratory continuous analyses (Table 31) and categorical analyses (Table 32) were conducted by the Applicant based on a request from the Agency to further investigate the predictive nature of baseline eosinophils and FeNO in the primary endpoint. Five models were analyzed for baseline eosinophils and FeNO as continuous variables and a similar 5 models were analyzed as categorical variables with the categories, Eosinophil subgroups [<150 or >=150 cells/µL] and FeNO subgroups [<25 or >=25 ppb]. Models A and B investigated the addition to the primary efficacy model of baseline eosinophils or FeNO and its interaction with treatment. Models C and D were similar to A and B, except that the other biomarker was also added to the model. Model E was similar to Models C and D, except that both eosinophil and FeNO interaction terms with treatment group were included. Model E explored the greatest extent of independence between the two biomarkers: significance of both interaction terms in Model E indicates independent predictability of baseline eosinophils and baseline FeNO biomarkers. Note that significance level for interaction terms is considered at p-values less than 0.15. The results for the continuous variable analysis were significant for all 5 models (Table 31) and were also significant for all 5 of the categorical analysis models, with the exception of Model E for eosinophils (Table 32). However, since independent predictability of FeNO in addition to

eosinophils is of main interest from Model E analysis, FeNO interaction with treatment is focused among the two interaction terms in the model. As a result, the biomarker analyses appear to support biomarker predictability of both eosinophils and FeNO and independent predictability of FeNO in addition to eosinophils.

Table 31 NAVIGATOR Summary of Continuous Biomarker Variables for Annual Asthma Exacerbation Rate Ratios over 52 Weeks and Interaction Tests Assessed under Different Models (Full Analysis Set Population)

	Placebo vs Tezepelumab		Interaction p-value	
	Rate Ratio (95% CI)	p-value	Eosinophil * Treatment	FeNO * Treatment
CSR Model	0.441 (0.365, 0.533)	<0.001		
Model A	0.444 (0.368, 0.536)	<0.001	0.003	
Model B	0.438 (0.362, 0.529)	<0.001		<0.001
Model C	0.442 (0.365, 0.534)	<0.001	0.004	
Model D	0.439 (0.363, 0.531)	<0.001		<0.001
Model E	0.439 (0.364, 0.531)	<0.001	0.080	0.003

Abbreviations: CI, confidence interval, CSR, clinical study report, FeNO = fractional exhaled nitric oxide

Source: Applicant's response to 09/17/2021 IR, Table 1, **c**onfirmed by statistical reviewer

Model A: AAER = Trt + history of exacerbations + Region + Age group + log(Eos at BL) + log(Eos at BL)*Trt
Model B: AAER = Trt + history of exacerbations + Region + Age group + log(FeNO at BL) + log(FeNO at BL)*Trt
Model C: AAER = Trt + history of exacerbations + Region + Age group + log(Eos at BL) + log(FeNO at BL) + log(Eos at BL)*Trt
Model D: AAER = Trt + history of exacerbations + Region + Age group + log(Eos at BL) + log(FeNO at BL) + log(FeNO at BL)*Trt
Model E: AAER = Trt + history of exacerbations + Region + Age group + log(Eos at BL) + log(FeNO at BL) + log(Eos at BL)*Trt + log(FeNO at BL)*Trt

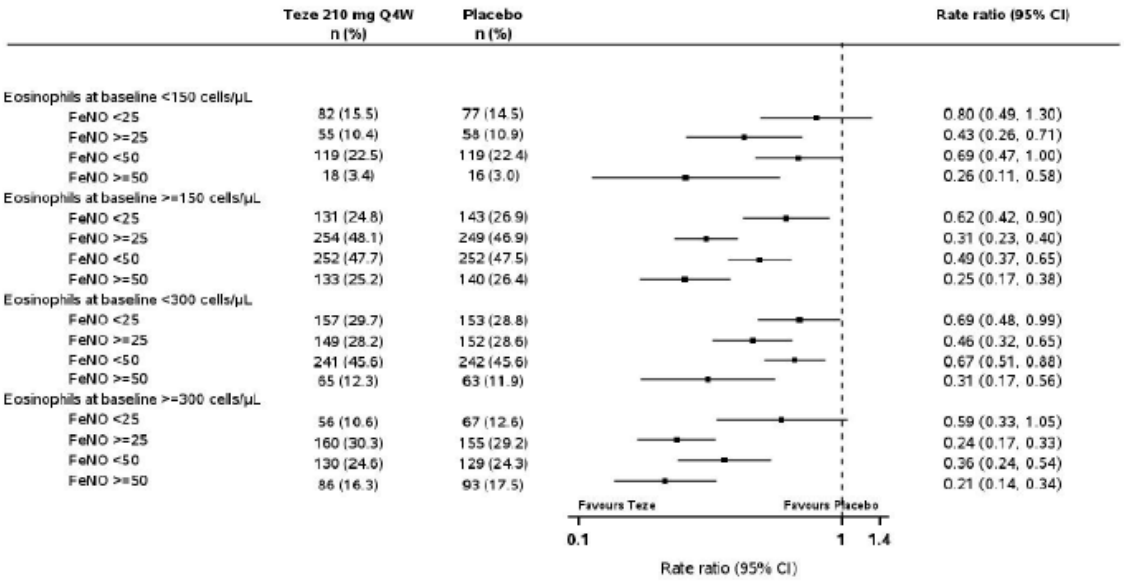
Table 32 NAVIGATOR Summary of Binary Biomarker Factors for Annual Asthma Exacerbation Rate Ratios over 52 Weeks and Interaction Tests Assessed under Different Models (Full Analysis Set Population)

	Placebo vs Tezepelumab		Interaction p-value	
	Rate Ratio (95% CI)	p-value	Eos * Treatment	FeNO * Treatment
CSR Model	0.441 (0.365, 0.533)	<0.001		
Model A	0.442 (0.366, 0.533)	<0.001	0.046	
Model B	0.441 (0.365, 0.532)	<0.001		<0.001
Model C	0.440 (0.364, 0.533)	<0.001	0.049	
Model D	0.441 (0.366, 0.533)	<0.001		<0.001
Model E	0.441 (0.365, 0.532)	<0.001	0.198	<0.001

Abbreviations: CI, confidence interval, FeNO = fractional exhaled nitric oxide, CSR, clinical study report
Source: Applicant's response to 09/17/2021 IR, Table 3, confirmed by statistical reviewer
Model A: AAER = Trt + history of exacerbations + Region + Age group + Eos subgroup [<150 or >=150] +Eos subgroup [<150 or >=150]*Trt
Model B: AAER = Trt + history of exacerbations + Region + Age group + FeNO subgroup [<25 or >=25] + FeNO subgroup [<25 or >=25]*Trt
Model C: AAER = Trt + history of exacerbations + Region + Age group + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + Eos subgroup [<150 or >=150]*Trt
Model D: AAER = Trt + history of exacerbations + Region + Age group + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + FeNO subgroup [<25 or >=25]*Trt
Model E: AAER = Trt + history of exacerbations + Region + Age group + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + FeNO subgroup [<25 or >=25]*Trt + Eos subgroup [<150 or >=150]*Trt

Further, the confidence intervals and point estimates for eosinophil categories, <150 and ≥150 cells/µL and <300 and ≥300 cells/µL and FeNO categories, < 25 and ≥ 25ppb and < 50 and ≥ 50 ppb, were estimated using the primary analysis model (Figure 17). Confidence intervals for 3 of the four lowest categories for both biomarkers included or very nearly included the no difference value of 1. All other biomarker categories had confidence intervals that favored tezepelumab (with the exception of eosinophils < 150 cells/µL and FeNO < 50ppb), a further indication of the predictability of both biomarkers with AAER in this population.

Figure 17 Annualized asthma exacerbation rate ratio over 52 weeks – Forest plot of FeNO subgroups within eosinophil subgroups (Full Analysis Set Population)



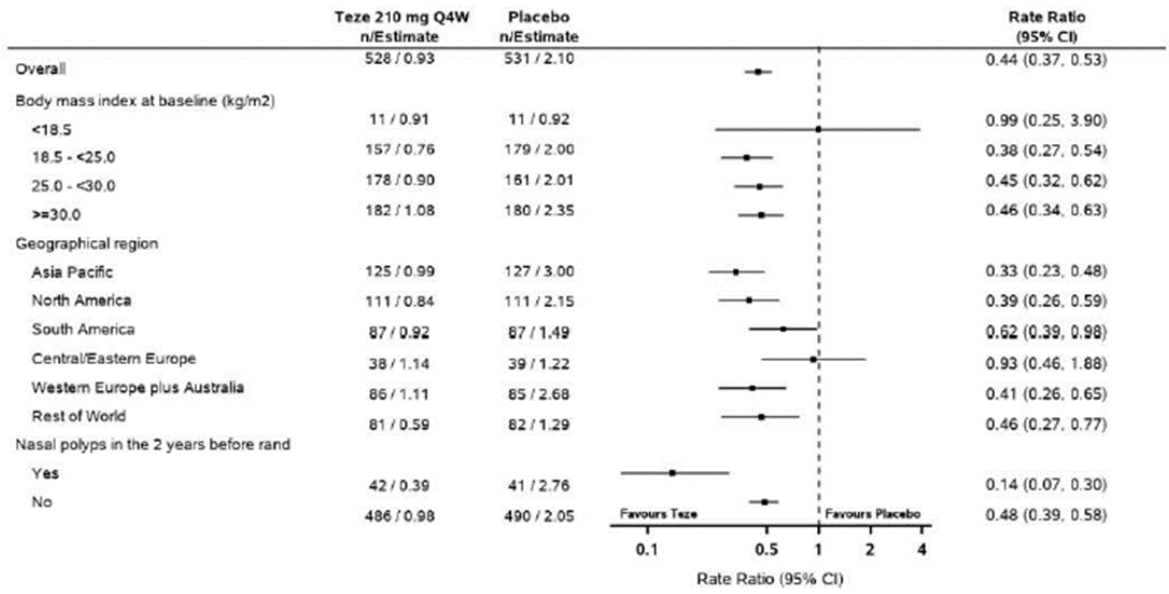
Abbreviations: CI, confidence interval, FeNO = fractional exhaled nitric oxide
Source: Applicant's response to 09/17/2021 IR, Figure 1
Rate ratio and 95% CI are based on the model for each subgroup is a negative binomial regression analysis with treatment, region, age, and history of exacerbations as covariates. Time at risk is used as an offset variable in the model to adjust for different exposure times.

Primary endpoint and baseline characteristics

Tezepelumab treatment resulted in clinically and statistically meaningful reductions in AAER for many subgroups (Figure 18, Figure 19): baseline ICS dose, all age groups except adolescents, both genders, race (except for Black or other race), exacerbation history, OCS use (only if absent), BMI in groups ≥ 18.5, geographic region excluding Central/Eastern Europe, and presence or absence of nasal polyps in the 2 years before randomization. For those subgroups that were not different from placebo, each had small numbers of subjects so the CIs not excluding 1.0 may be due to low power rather than lack of efficacy.

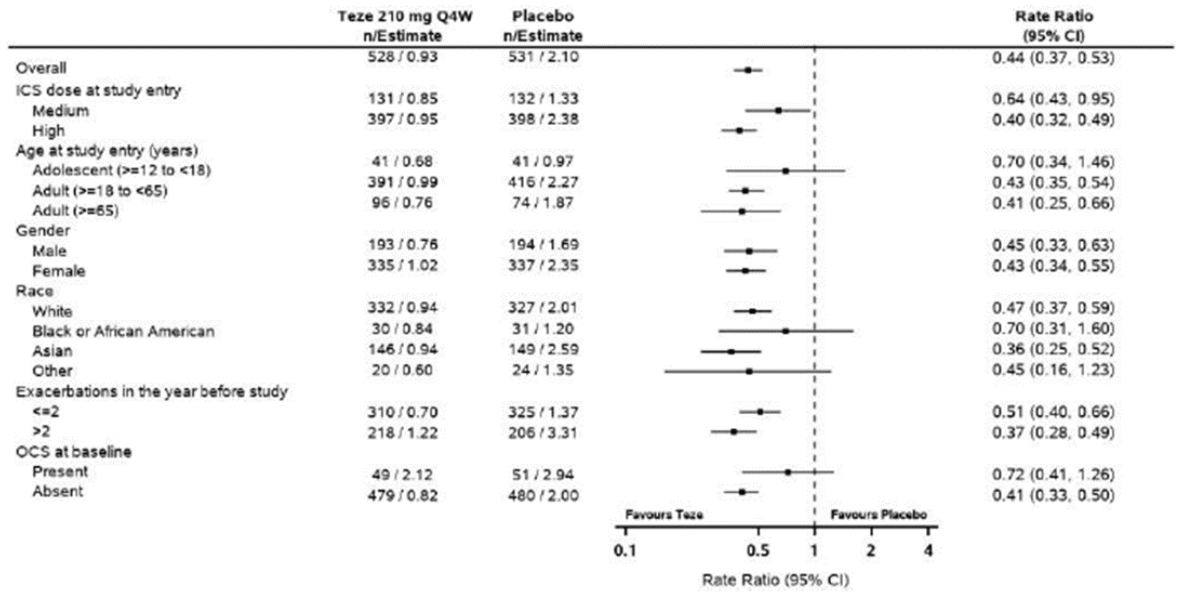
While the confidence interval for the adolescent subgroup was wider than for the other age categories and did not exclude no difference, it had the smallest number of subjects of these three age categories and the point estimate favored tezepelumab.

Figure 18. Annualized asthma exacerbation rate ratio over 52 weeks, by baseline characteristics, Part A (Full Analysis Set Population)



Abbreviations: CI, confidence interval, Q4W, every 4 weeks
Source: NAVIGATOR CSR, Figure 6
Rate ratio and 95% CI are based on the model for each subgroup is a negative binomial regression analysis with treatment, region, age history of exacerbations, subgroup (if not already included) and treatment*subgroup as covariates. Time at risk is used as an offset variable in the model to adjust for different exposure times.

Figure 19. Annualized asthma exacerbation rate ratio over 52 weeks, by baseline characteristics, Part B (Full Analysis Set Population)



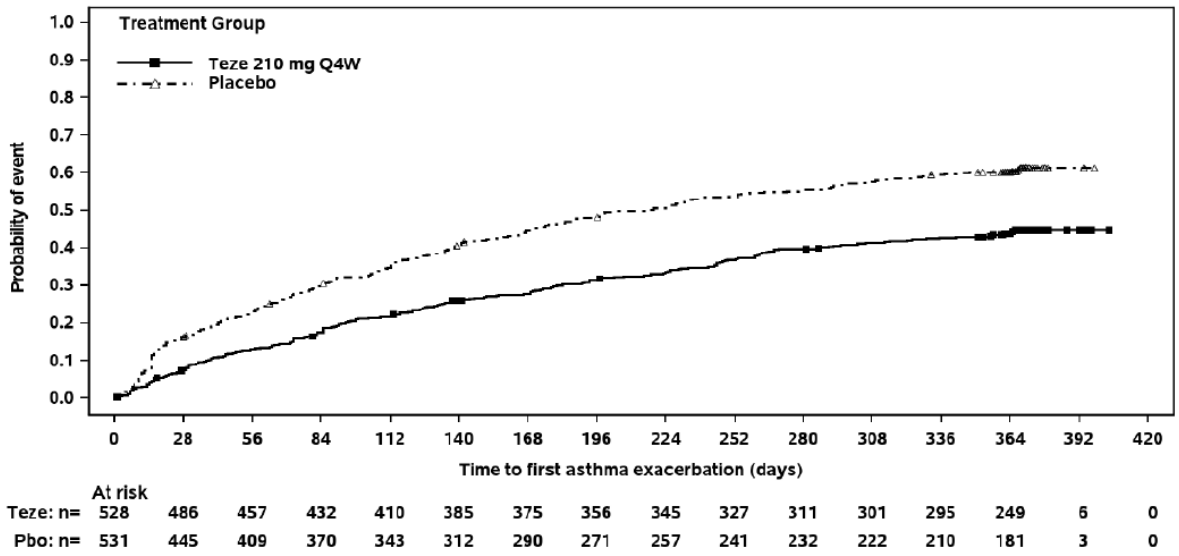
Abbreviations: CI, confidence interval, Q4W, every 4 weeks
Source: NAVIGATOR CSR, Figure 6
Rate ratio and 95% CI are based on the model for each subgroup is a negative binomial regression analysis with treatment, region, age history of exacerbations, subgroup (if not already included) and treatment*subgroup as covariates. Time at risk is used as an offset variable in the model to adjust for different exposure times.

8.1.2.9 Efficacy Results – Secondary and other relevant endpoints

Time to first exacerbation

The time to first exacerbation was longer in the tezepelumab group compared to placebo in the overall population (HR 0.59 [95% CI 0.50, 0.70] Figure 20) and in subjects with eosinophils levels <300 cells/ul (HR 0.68 [95% CI 0.55, 0.95]).

Figure 20 Time to first asthma exacerbation, Kaplan-Meier Plot (Full Analysis Set Population)



Abbreviations: Q4W, every 4 weeks
Source: NAVIGATOR CSR, Figure 7, confirmed by statistical reviewer

Proportion of Subjects Experiencing No Asthma Exacerbations Over 52 weeks
The proportion of subjects who experienced no asthma exacerbations was higher the tezepelumab group (54%) compared to the placebo group (39%) in the overall population (OR 1.93 [95% CI 1.51, 2.47] Table 33). Similar results were seen in subjects with eosinophils <300 cells/uL.

Table 33 Proportion of subjects with no exacerbations during the treatment period (Full Analysis Set Population)

Proportion of subjects with no exacerbations during the treatment period	**Tezepelumab 210 mg N (%)**	**Placebo N (%)**	**Odds Ratio (95% CI)**
Overall	286 (54%)	205 (39%)	1.93 (1.51, 2.47)
Subjects with baseline <300 cells/µL	167 (54%)	127 (41%)	1.69 (1.23, 2.34)
Subjects with baseline ≥300 cells/µL	119 (54%)	78 (35%)	2.33 (1.58, 3.44)

Abbreviations: CI, confidence interval, n, number of subjects contributing to the analysis at that time point, Q4W, every 4 weeks
Source: NAVIGATOR CSR, Figure 9

The estimate of the odds ratio is obtained using a logistic regression model with treatment, region, age, history of exacerbations, subgroup (if already not included), and treatment * subgroup as covariates.

FEV1 (L)

Subjects who received tezepelumab had an increase from baseline in pre-BD FEV1 compared to placebo at 52 weeks (0.23 L vs 0.10 L, difference 0.13 L [95% CI 0.08, 0.18; p <0.001; Table 34). This effect was seen at the first post baseline assessment at 2 weeks and was maintained for over 52 weeks (Figure 21).

Table 34 Mean change from baseline in FEV1 (L) and subject reported outcomes at Week 52 (Full Analysis Set Population)

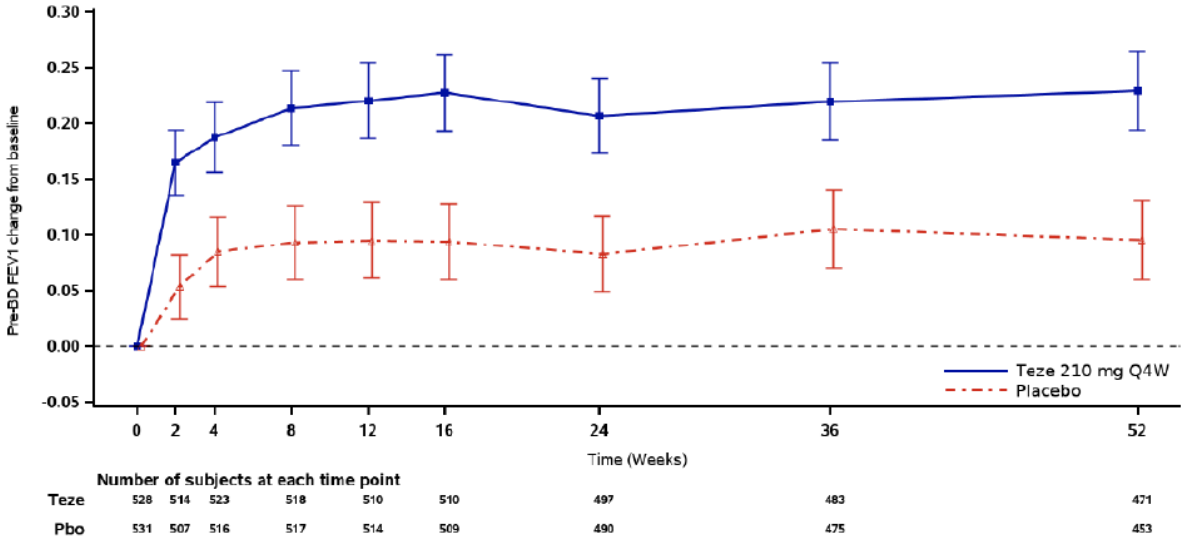
Variable	Tezepelumab 210 mg N	Placebo N	LS Mean Difference	95% Confidence Interval
FEV1 (L)	527	531	0.13	0.08, 0.18
AQLQ(S) +12	525	526	0.33	0.20, 0.47
ACQ-6	527	531	-0.33	-0.46, -0.20
Asthma Symptom Diary	525	531	-0.11	-0.19, -0.04

Abbreviations: FEV1, forced expiratory volume in 1 second; AQLQ(S) + 12, Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; ACQ-6, Asthma Control Questionnaire-6; LS, least square

Source: NAVIGATOR CSR, Table 23 and Response to 15 October 2021 Information Request , Table 1, confirmed by statistical reviewer.

Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a mixed model repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + age + baseline FEV1 + visit + treatment * visit. This analysis includes the full ITT population and a contrast for the week 52 landmark timepoint.

Figure 21 Adjusted means and 95% CIs over time for FEV1 (L) change from baseline (Full Analysis Set Population)

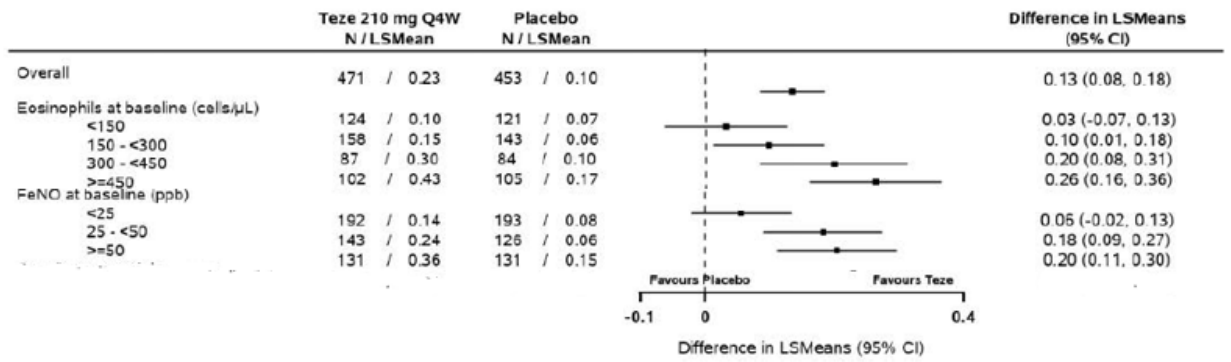


Abbreviations: FEV1, forced expiratory volume in 1 second; CI, confidence interval
Source: NAVIGATOR CSR, Figure 10, confirmed by statistical reviewer
Estimate of the mean change from baseline at each week in tezepelumab is compared with placebo using a mixed model repeated measures analysis. Estimates are least squares means. The model with unstructured covariance structure is: Change from baseline in FEV1 = treatment group + region + age + baseline FEV1 + visit + treatment * visit.

FEV1 and baseline biomarkers

Subjects receiving tezepelumab experienced improvement in FEV1 at Week 52 compared to those receiving placebo; however for the lowest baseline eosinophil (< 150 cells/uL) and FeNO level (< 25 ppb; Figure 22) the 95% confidence interval included 0, an indicator of no difference between treatment groups. Change from baseline in FEV1 at Week 52 did increase with increasing baseline eosinophil categories, and baseline FeNO categories.

Figure 22 Forest plot by biomarker subgroups for FEV1 change from baseline over 52 weeks (Full Analysis Set Population)



Abbreviations: FEV1, forced expiratory volume in 1 second; CI, confidence interval, Q4W, every 4 weeks; LSMean, least square mean; FeNO = fractional exhaled nitric oxide
Source: Modified from NAVIGATOR CSR Figure 11, confirmed by statistical reviewer
Model, including subgroups: Change from baseline in FEV_1 = Treatment group + region + age + baseline FEV_1 + visit + subgroup + treatment * visit + treatment * subgroup + visit * subgroup + treatment * visit * subgroup.

Reviewer comment: Despite the lack of significant different in the lowest subgroups for baseline eosinophils and FeNO for change from baseline in FEV1 at Week 52 as AAER was significantly reduced in these subgroups, the data supports an indication of severe asthma without limiting to subjects with an eosinophilic phenotype.

Exploratory continuous analyses (Table 35) and categorical analyses (Table 36) for FEV1 behaved similarly to the analysis described above for AAER.

Table 35 Summary of Continuous Biomarker Variables for FEV1 change from baseline over 52 weeks and interaction tests assessed under different models (Full Analysis Set Population)

	Placebo vs Tezepelumab			Interaction p-value	
	LSMean	95% CI	p-value	Eosinophil * Treatment	FeNO * Treatment
CSR Model	0.134	(0.084, 0.184)	<0.001		
Model A	0.136	(0.087, 0.185)	<0.001	0.015	
Model B	0.139	(0.089, 0.189)	<0.001		0.038
Model C	0.140	(0.091, 0.189)	<0.001	0.020	
Model D	0.140	(0.090, 0.189)	<0.001		0.041
Model E	0.140	(0.091, 0.189)	<0.001	0.072	0.159

Abbreviations: LSMean, least square mean; FeNO = fractional exhaled nitric oxide

Source: Applicant's response to 09/17/2021 IR, Table 3
Model A: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + log(Eos at BL) + log(Eos at BL)*Trt
Model B: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + log(FeNO at BL) + log(FeNO at BL)*Trt

Model C: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + log(Eos at BL) + log(FeNO at BL) + log(Eos at BL)*Trt
Model D: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + log(Eos at BL) + log(FeNO at BL) + log(FeNO at BL)*Trt
Model E: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + log(Eos at BL) + log(FeNO at BL) + log(Eos at BL)*Trt + log(FeNO at BL)*Trt

Table 36 Summary of Binary Biomarker Factors for FEV1 change from baseline over 52 weeks and interaction tests assessed under different models (Full Analysis Set Population)

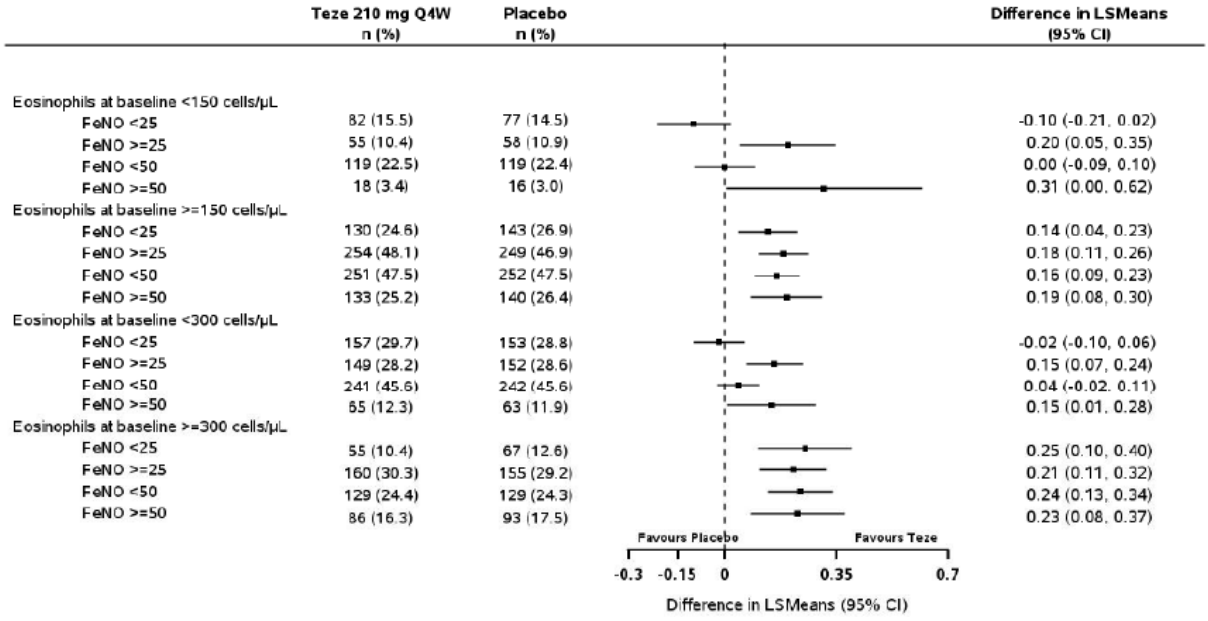
	Placebo vs Tezepelumab			Interaction p-value	
	LSMea	95% CI	p-value	Eosinophil * Treatment	FeNO * Treatment
CSR Model	0.134	(0.084, 0.184)	<0.001		
Model A	0.134	(0.085, 0.184)	<0.001	0.003	
Model B	0.135	(0.085, 0.185)	<0.001		0.045
Model C	0.136	(0.086, 0.186)	<0.001	0.004	
Model D	0.136	(0.086, 0.186)	<0.001		0.054
Model E	0.136	(0.086, 0.186)	<0.001	0.012	0.169

Abbreviations: LSMean, least square mean; FeNO = fractional exhaled nitric oxide

Source: Applicant's response to 09/17/2021 IR, Table 7
Model A: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + Eos subgroup [<150 or >=150] +Eos subgroup [<150 or >=150]*Trt
Model B: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + FeNO subgroup [<25 or >=25] + FeNO subgroup [<25 or >=25]*Trt
Model C: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + Eos subgroup [<150 or >=150]*Trt
Model D: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + FeNO subgroup [<25 or >=25]*Trt
Model E: Change from baseline in FEV1 = Trt +FEV1 BL + Region + Age group + Visit + Visit*Trt + Eos subgroup [<150 or >=150] + FeNO subgroup [<25 or >=25] + Eos subgroup [<150 or >=150]*Trt + FeNO subgroup [<25 or >=25]*Trt

Further, the confidence intervals and point estimates for eosinophil categories, <150 and ≥150 cells/µL and <300 and ≥300 cells/µL and FeNO categories, < 25 and ≥ 25ppb and < 50 and ≥ 50ppb were estimated using the main analysis model for FEV1 (Figure 23). Confidence intervals for FeNO at the higher eosinophil categories did not include the no difference value of 0, indicating the predictive characteristic of FeNO at all categories in the two higher eosinophil categories. However, the two lower eosinophil categories, especially the < 150 cells/µL category, was not predictive of change from baseline in FEV1 at Week 52 in this population.

Figure 23 FEV1 change from baseline at Week 52 – Forest plot of FeNO subgroups within eosinophil subgroups (Full Analysis Set Population)



Abbreviations: Q4W, every 4 weeks; LSMean, least square mean; CI, confidence interval
Source: Applicant's response to 09/17/2021 IR, Figure 3
Model for each subgroup is change from baseline in FEV1 = treatment group + region + age + visit + treatment * visit.

AQLQ(S) +12

Tezepelumab demonstrated improvements from baseline in AQLQ(S)+12 when compared to placebo (1.48 vs 1.14) with the mean difference of 0.33 ([95% CI 0.20, 0.47]; p <0.001). Improvement was seen as early as 4 weeks after administration and maintained to 52 weeks.

In the responder analysis, a greater proportion of subjects in the tezepelumab group achieved clinically meaningful improvements in the AQLQ(S)+12 score (at least 0.5 units increase from baseline) compared with placebo at Week 52 (tezepelumab 78% vs placebo 72%, OR: 1.36 [95% CI 1.02, 1.82]). These results were confirmed by the statistical reviewer.

ACQ-6

Tezepelumab treatment resulted in improvement from baseline when compared to placebo at 52 weeks (-1.53 vs. -1.20 in the tezepelumab vs placebo groups, difference -0.33 [95% CI -0.46, -0.20]; p <0.001). This was seen by 2 weeks and maintained to 52 weeks.

In the responder analysis, a greater proportion of subjects in the tezepelumab group achieved clinically meaningful improvements in the ACQ-6 score (at least 0.5 units reduction from

baseline in the ACQ-6 score) compared with placebo at Week 52 (tezepelumab 86% vs placebo 77%, OR: 1.99 [95% CI 1.43, 2.76]). These results were confirmed by the statistical reviewer.

Asthma Symptom Diary
Those treated with tezepelumab had improvements from baseline compared to placebo in weekly mean total ASD scores at Week 52 (LSMean tezepelumab -0.70 vs. placebo -0.59, difference of -0.11 [95% CI -0.19, -0.04]; p= 0.04). Onset of improvement was seen as early as week one and continued through Week 52.

8.1.2.10 Durability of Response

The Applicant is currently conducting a phase 3 long-term extension study for eligible subjects previously randomized in one of the predecessor phase 3 asthma studies NAVIGATOR and SOURCE. The results of this trial are not available at the time of this application.

8.1.2.11 Summary of NAVIGATOR Effectiveness

The primary endpoint of reduced AAER for tezepelumab vs placebo over 52 weeks was met. Efficacy was also demonstrated for subjects who had asthma exacerbations that required emergency room visits or hospitalizations. Subgroup analysis demonstrated efficacy based on the primary endpoint across baseline eosinophil and FeNO subgroups. Efficacy also increased based on baseline blood eosinophil count and baseline FeNO. The primary endpoint results are supported by the key secondary endpoints of increased pre-BD FEV1 at Week 52 and PROs such as ACQ-6, AQLQ(+12) and ASD. Partial extrapolation of efficacy was used to support the adolescent subgroup given the same pathophysiology of the disease as adults. Although the adolescent subgroup was not powered to demonstrate statistical significance for the primary endpoint, numerical and clinically meaningful reductions in asthma exacerbations along with improvement in lung function compared to placebo were demonstrated.

8.1.3. PATHWAY Trial (CD-RI-MEDI9299-1146) Design

8.1.3.1 Administrative Information :

- *Study title:* A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma.
- *Study dates*: December 19, 2013 to March 1, 2017
- *Study sites*: 108 study centers (98 study centers randomized subjects) in 12 countries (USA, Slovakia, Bulgaria, Czech Republic, Hungary, Israel, Japan, Latvia, Lithuania, Serbia, South Africa, and Ukraine).
- *Study report date:* April 5, 2018

8.1.3.2 Objectives

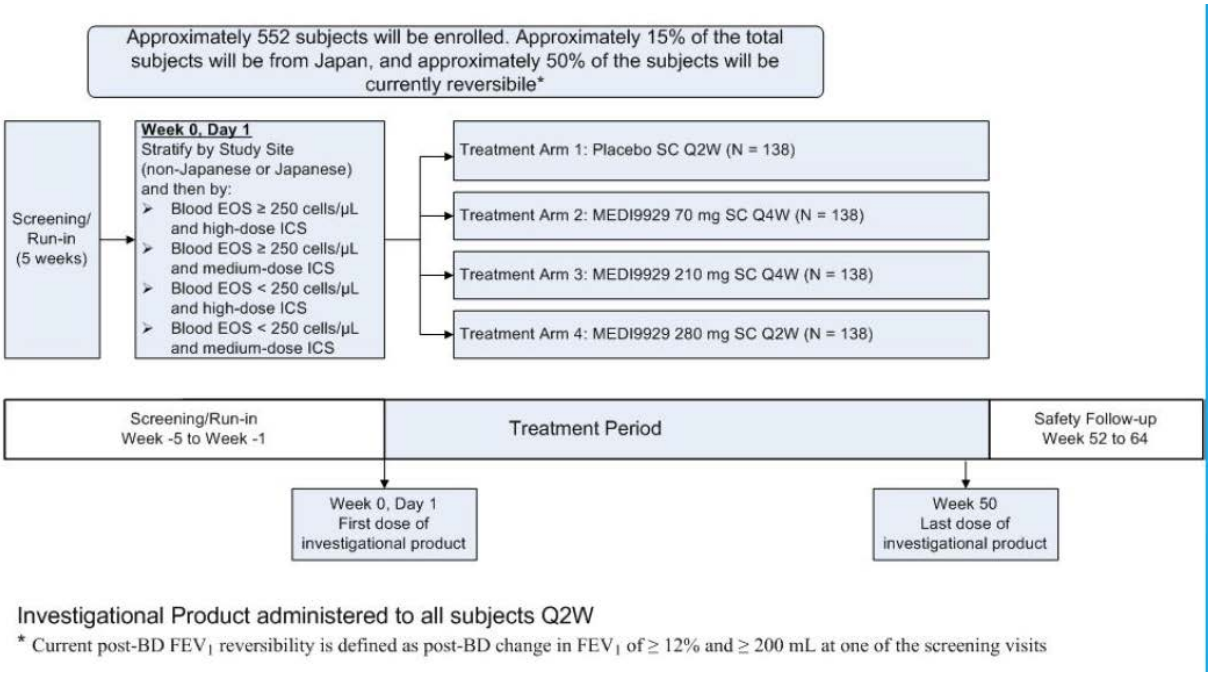
Primary Objective: To evaluate the effect of 3 dose levels of tezepelumab on asthma exacerbations in adult subjects with inadequately controlled, severe asthma.

8.1.3.3 Study Design and Conduct

This was a phase 2, multicenter, dose ranging, double-blind, randomized, parallel arm, placebo controlled trial to evaluate the effect of 3 doses of tezepelumab (280 mg Q2W, 210 mg Q4W, or 70 mg Q4W) on AAER in adults with inadequately controlled severe asthma. Prior to randomization, subjects were stratified by study site (Japanese and non-Japanese), then blood eosinophil count (≥ or < 250 cells/µL), and by inhaled corticosteroid dose level (medium or high). At least 50% of the total subjects were planned to be enrolled in the high blood eosinophil stratum (≥ 250 cells/µL), and at least 40% of the subjects in each blood eosinophil stratum were receiving high-dose ICS. Once the required number of subjects had been enrolled into a stratum, any subjects already in screening/run-in were enrolled into that stratum if eligible.

The study schematic is shown in Figure 24.

Figure 24. PATHWAY Trial Schematic



8.1.3.4 Procedures

The trial consisted of three phases: screening (1 to 5 weeks), randomized treatment (52 weeks) with a 12 week post treatment follow up period.

A schedule of assessments is provided in Table 37, Table 38, and Table 39.

Table 37. PATHWAY Trial: Schedule of Screening Procedures

Study Week	-5	-4	-1
Procedure/Visit Window	+2 D	±2 D	±2 D [a]
Written informed consent/consent for DNA/assignment of SID number	X		
ePRO device training [b]	X	X	
Complete ACQ-6 at site in ePRO device	X	X	X
Home peak flow monitor training and distribution		X	
Distribute ePRO device		X	
Check compliance with PRO assessments			X
Check compliance and technique with home peak flow meter			X
Medical and asthma history	X		
Concomitant medications	X	X	X
Assessment of AEs/SAEs	X	X	X
Assessment of asthma exacerbations	X	X	X
Physical examination, height and weight	X		
Vital signs	X	X	X
ECG [c]	X		
Chest x-ray (if required) [d]	X		
Serum chemistry	X		X
Hematology	X		X
CBC with differentials at local laboratory [e]	X		X

Total serum IgE			X
Urinalysis	X		X
Pregnancy test, serum (females only [f])	X		
Hepatitis B, C; HIV-1, HIV-2	X		
QFT-G test	X		
FeNO	X	X	X
Spirometry (pre-BD)	X	X	X
Spirometry (post-BD)	X	X	X
Verify eligibility criteria	X	X	X

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); AE = adverse event; CBC = complete blood count; BD = bronchodilator; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; ePRO = electronic patient-reported outcome; FeNO = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HIV = human immunodeficiency virus; IgE = immunoglobulin E; PRO = patient reported outcome; QFT-G = QuantiFERON®-tuberculosis Gold; SAE = serious adverse event; SID = subject identification; TB = tuberculosis; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

[a] There must have been a minimum of 5 days between Visit 3 and Visit 4.

[b] The PRO assessments included Asthma Daily Diary, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules were programmed into the ePRO device. Subjects were triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly).

[c] The ECG was to be completed in triplicate until site was notified by sponsor that ECG sub-study was complete.

[d] The chest x-ray may have been done at another visit during the screening/run-in period if necessary, as long as results had been reviewed prior to randomization.

[e] The CBC samples were analyzed as quickly as possible, preferably within 12 hours of sample collection.

[f] The serum pregnancy test was required of all females in the study regardless of childbearing potential.

Table 38. PATHWAY Trial: Schedule of Procedures Treatment Period Week 0 to Week 24

Study Period	Treatment Period												
Visit Number	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Week	0 (Day 1)	2	4	6	8	10	12	14	16	18	20	22	24
Procedure/Visit Window	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D
Verify eligibility criteria	X												
Check compliance with PRO assessments [a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Check compliance and technique with home peak flow meter	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO assessments at site	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X
HRU	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, including weight	X												
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [c]	X						X				X		
Serum chemistry	X		X				X				X		
Hematology	X		X				X				X		
Urinalysis	X		X				X				X		
Urine pregnancy test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	X
QFT-G test [d]							X						
IgE FEIA	X												
Total serum IgE	X		X				X				X		
Serum for PK	X		X				X				X		
Serum for ADA	X		X				X				X		
Serum for biomarker analysis	X		X				X				X		
Whole blood for flow cytometry (selected sites)	X						X						
Blood sample for DNA (optional)	X												
FeNO	X		X		X		X				X		
Spirometry (pre-BD)	X		X		X		X				X		
Spirometry (post-BD)	X												
Randomize	X												
Investigational product administration [e]	X	X	X	X	X	X	X	X	X	X	X	X	X

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1; ADA = anti-drug antibody(ies); AE = adverse event; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); BD = bronchodilator; D = Day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; FEIA = fluorescence enzyme immunoassay; FeNO = fraction of exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; HRU = healthcare resource utilization; IgE = immunoglobulin E; PK = pharmacokinetic(s); PRO = patient reported outcome; QFT-G = QuantiFERON®-tuberculosis Gold; SAE = serious adverse event; WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

[a] The PRO assessments included Asthma Daily Diary, home peak flow, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules were programmed into the ePRO device. Subjects were triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly).

[b] Vital signs were done prior to investigational product administration, 60 and 120 minutes (± 5 minutes) after the first 2 doses of investigational product were administered, and 60 minutes (± 5 minutes) after the third and subsequent doses of investigational product were administered. If the subject was not stable, vital signs were monitored at least hourly until the subject was discharged from the study center.

[c] The ECG was completed in triplicate until site notified by sponsor that the ECG sub-study was complete.

Table 39. PATHWAY Trial: Schedule of Treatment Period Procedures Week 26 to 52

Study Period	Treatment Period													
Visit Number	17	18	19	20	21	22	23	24	25	26	27	28	29	EDV30
Study Week	26	28	30	32	34	36	38	40	42	44	46	48	50	52
Procedure/Visit Window	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D	± 3 D
Check compliance with PRO assessments [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Check compliance and technique with home peak flow meter	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs and SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRU	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, including weight		X												X
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [c]		X						X						X
Serum chemistry		X						X						X
Hematology		X						X						X
Urinalysis		X						X						X
Urine pregnancy test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QFT-G test [d]		X						X						X
Total serum IgE		X						X						X
Serum for PK		X						X						X
Serum for ADA		X						X						X
Serum for biomarker analysis		X						X						X
Whole blood for flow cytometry (selected sites)		X												X
FeNO		X						X						X
Spirometry (pre-BD)		X						X						X
Spirometry (post-BD)		X												X
Investigational product administration [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	

ACQ -6 = Asthma Control Questionnaire, omitting FEV_1 ADA = anti-drug antibody(ies); AE = adverse event; AQLQ(S)+12 = Asthma Quality of Life Questionnaire (Standardised); BD = bronchodilator; D = day; ECG = electrocardiogram; EDV = early discontinuation visit; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life - 5 Dimensions 5 Level Version; FeNO = fraction of exhaled nitric oxide; HRU = healthcare resource utilization; IgE = immunoglobulin E; PK = pharmacokinetic(s); PRO = patient reported outcome; QFT-G = QuantiFERON®-tuberculosis Gold; SAE = serious adverse event WPAI+CIQ = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions.

[a] The PRO assessments included Asthma Daily Diary, home peak flow, ACQ-6, AQLQ(S)+12, EQ-5D-5L, WPAI+CIQ. The assessment schedules were programmed into the ePRO device. Subjects were triggered to complete the appropriate questionnaires/assessments at the appropriate intervals (eg, daily, weekly, biweekly).

[b] Vital signs were done prior to investigational product administration, 60 and 120 minutes (± 5 minutes) after the first 2 doses of investigational product were administered, and 60 minutes (± 5 minutes) after the sixth and subsequent doses of investigational product were administered. If the subject was not stable, vital signs were monitored at least hourly until the subject was discharged from the study center.

[c] The ECG was completed in triplicate until site notified by sponsor that ECG sub-study was complete.

[d] Only subjects with an indeterminate QFT-G result at screening.

[e] There must have been ≥ 7 days between doses.

8.1.3.5 Subject Population

Key Inclusion Criteria

1. Adults age 18 through 75 years old
2. Documented physician diagnosed asthma for at least 12 months with a post-bronchodilator reversibility of FEV1 12% and ≥ 200 mL during screening.
3. On medium or high dose ICS plus LABA for at least 6 months prior to Visit 1 and the dose of ICS must have been stable for at least 15 days prior to Visit 1.
4. If on an asthma controller medication in addition to ICS plus LABA, the dose of the other controller medications (leukotriene receptor inhibitors, theophylline, secondary ICS, LAMA, cormones, or maintenance oral steroid) must have been stable for at least 15 days prior to Visit 1.
5. Have a morning pre-BD FEV1 value of ≥ 40% and ≤ 80%, predicted at 2 Screening Visits
6. Subjects must have had an ACQ-6 score of ≥1.5 twice during screening.
7. At Visit 4 (Week 0, Day 1), subjects must have had at least one of the following over the previous 7 days from the ePRO device: > 2 days with a daytime or nighttime symptoms score ≥ 1 (Asthma Daily Diary); or ≥ 1 awakening due to asthma requiring rescue medication use; or Rescue/reliever short-acting β2 agonist (SABA) use > 2 days.
8. Must have had a documented history of at least 2 asthma exacerbation events OR at least 1 severe asthma exacerbation resulting in hospitalization (for at least 24 hours) within the 12 months prior to Visit 1.

Key Exclusion Criteria

1. Current or previous smoker of ≥10 pack years
2. Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation and panic attacks, or other mimics of asthma.
3. Acute upper or lower respiratory infections requiring antibiotics or antiviral medications within 15 days prior to Visit 1.
4. A helminth parasitic infection diagnosed within 24 weeks of Visit 1.
5. History of anaphylaxis to any biologic therapy.
6. Systemic corticosteroid burst including taper withing 15 days prior to Visit 1.
7. Receipt of any live or attenuated vaccines within 15 days prior to Visit 1.

8.1.3.6 Treatment

Approximately 552 subjects were planned to be randomized in a 1:1:1:1 ratio to receive one of 3 dose levels of tezepelumab or placebo for 52 weeks. The 3 dose levels included 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W. All subjects received 3 injections (2 × 1.5 mL and 1 × 1.0 mL) Q2W in order to maintain the blinding of the different doses. The doses will be drawn from vials.

The investigational product formulation can be found in Table 40.

Table 40. Formulation of the Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
MEDI9929 (AMG 157)	Amgen	(b) (4) mg/mL MEDI9929 formulated with (b) (4) (w/v) polysorbate (b) (4)
Placebo	Amgen	Placebo contains the same excipients, in the same concentration only lacking

(w/v) = weight by volume

Excipients include (b) (4) and polysorbate (b) (4) Investigational product will be supplied to the site in open-label kits with 10 vials of either MEDI9929 or placebo. Each kit has a unique number that is printed on all labels within the kit (i.e., the outer carton label and the label of each container within the carton).

8.1.3.7 Study Endpoints

Primary Endpoint
The annualized asthma exacerbation rate measured at Week 52.

Secondary Endpoints

1. Reduction in AAER, change from baseline in FEV1, and change from baseline in overall symptom score will be evaluated at Week 52 in the following pre-specified subpopulations of asthma: 1) eosinophilic and noneosinophilic; 2) Th2 high/low 3) FENO high/low; 4) periostin high/low; 5) current post-BD FEV1 reversibility; and 6) allergic and non-allergic.

2. Change from baseline in lung function as measured by pre-BD and post-BD FEV1 and forced vital capacity (FVC) at Week 52 in the overall population.

3. Change from baseline in asthma symptoms (daytime and nighttime symptom frequency and severity, activity avoidance and limitation, asthma-related stress and fatigue as well as rescue asthma medication use) as measured by the Asthma Daily Diary, and other measures of asthma control as measured by the ACQ-6 at Week 52 in the overall population.

4. Annualized rate of hospitalizations due to asthma (i.e., severe asthma exacerbations), time to first asthma exacerbation/severe asthma exacerbation, and proportion of subjects with one or more asthma exacerbations/severe asthma exacerbations at Week 52.

5. A dose- and exposure-response analysis will be done at Week 52 on reduction in AER, change from baseline in FEV1, and change from baseline in overall symptom score to determine the optimal dose and regimen of tezepelumab.

6. Change from baseline in AQLQ[S])+12 and European Quality of Life - 5 Dimensions 5 Level Version (EQ-5D-5L) at Week 52.

7. Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), vital signs, laboratory assessments, and electrocardiogram (ECG) during the study (Week 0 [Day 1] to Week 64).

8. Tezepelumab PK and anti-drug antibodies (ADA) during the study (Week 0 [Day 1] to Week 64).

8.1.3.8 Efficacy Parameters

The Efficacy Parameters were the same as the NAVIGATOR Trial, except Asthma Symptom Diary was not assessed in this trial. See Section 8.1.1.8 Efficacy Parameters.

8.1.3.9 Safety Parameters

The Safety Parameters were the same as NAVIGATOR Trial. See 8.1.1.9 Safety Parameters.

8.1.3.10 Statistical Analysis Plan

The analysis populations are defined in Table 41. The primary analysis was conducted base on the ITT population.

Table 41. PATHWAY Trial Analysis Populations

Population	Description
ITT population	Subjects who were randomized and received any investigational product were included in the ITT population, and subjects were analyzed according to their randomized treatment group. This was the primary efficacy population.
As-treated population	Subjects who received any investigational product were included in the as-treated population and subjects were analyzed according to the treatment they actually received.
Per-protocol population	Subjects who did not have significant protocol violations and received at least 80% of the intended doses of investigational product were included in the per-protocol population, and subjects were analyzed according to the treatment they actually received.
PK population	Subjects who received any investigational product and had a sufficient number of serum concentration measurements for computing PK parameters were included in the PK population, and subjects will be analyzed according to the treatment they actually received.

ITT = intent-to-treat; PK = pharmacokinetic(s).

A subgroup analysis was also planned to explore the treatment effect in pre-specified populations of asthma on the primary efficacy variable and secondary endpoints, change from baseline in FEV1 and overall symptom score at Week 52 (gender, race, maintenance OCS use, FeNO levels, primary asthma exacerbations, and geographical region).

Primary estimand

The five attributes of the primary estimand as described by the Applicant are noted here:

1. *Treatment condition of interest and alternative treatment:* Three dose arms (70 mg Q4W, 210 mg Q4W, and 280 mg Q2W) tezepelumab administered or matching placebo administered SC for a period of 52 weeks. Note: for purposes of substantial evidence of effectiveness for this application, the 210 mg dose is the focus of this estimand.
2. *Targeted population:* Adult subjects with severe, uncontrolled asthma
3. *Variable or endpoint:* Asthma exacerbations
4. *Population-level summary:* Annual asthma exacerbation rate (AAER)
5. *Intercurrent event and data handling strategy:* Study treatment discontinuations were handled with a treatment policy strategy; data were collected and used, regardless of whether treatment discontinuation occurred.

It follows that the clinical question this estimand describes is: The trial will compare 280 mg Q2W, then 210 mg Q4W, and then 70 mg Q4W of tezepelumab with matching placebo administered SC for a period of 52 weeks in adult and adolescent subjects with severe, uncontrolled asthma. The primary objective was to demonstrate superiority using annual asthma exacerbation rate in these doses. The treatment effect of primary interest was to use all the subjects' data for the duration of the trial, regardless of whether treatment discontinuation occurred.

Hypothesis testing

The null (H01) and alternate hypothesis test for the primary estimand was:

H01: AAER ratio over 52 weeks (tezepelumab/placebo) = 1

versus

H11: AAER ratio over 52 weeks (tezepelumab/placebo) ≠ 1

The direction of superiority of tezepelumab was indicated by a rate ratio less than 1. The primary endpoint was tested using a stepdown method for 3 hypotheses (from the high dose [280 mg Q2W] to the medium dose [210 mg Q4W] to the low dose [70 mg Q4W] when compared with placebo) to maintain the overall Type-I error rate at 0.1 (two sided).

Reviewer comment: The Applicant's planned significance level of 10% indicates this phase 2 study was not planned as an adequate and well-controlled trial to support substantial evidence of effectiveness, but planned to inform their phase 3 program. However, given the robust

efficacy noted in Section 8.1.4.8 Efficacy Results – Primary Endpoint this trial was considered adequate to demonstrate substantial evidence of effectiveness.

Primary analysis and its sensitivity analyses

The primary endpoint analysis was conducted using a negative binomial regression model with treatment group, baseline blood eosinophils count (≥ or < 250 cells/µL), and baseline ICS dose level (medium or high) as covariates. The response variable in the model was the number of asthma exacerbations experienced by a subject over the 52-week study period. The follow-up time was adjusted by the offset option in the model to adjust for subjects having different exposure times during which the events occurred as the logarithm of number of days in the study.

Exacerbation rates, 90% and 95% CIs of exacerbation rates, estimated treatment effects (i.e., the rate ratios of each tezepelumab group versus placebo), corresponding 90% and 95% CIs of the rate ratios, and 2-sided p-values for the rate ratios were provided based on a negative binomial regression model.

As a sensitivity analysis, the AAER was assessed by a Poisson regression model to assess the robustness with regard to the distributional assumptions. In the Poisson regression model, the correction for potential over-dispersion was made by the Pearson chi-square method. The same covariates used for the negative binomial regression model were considered.

Multiplicity control

The primary endpoint was tested using a stepdown method for 3 hypotheses (from the high dose (280 mg) to the medium dose (210 mg) to the low dose (70 mg) when compared with placebo) to maintain the overall Type I error rate at 0.1 (two sided). No planned multiplicity adjustments were applied for secondary endpoints or subgroups.

Reviewer comment: The lack of planned multiplicity adjustments for secondary endpoints is not indicative of a robust statistical plan for demonstrating substantial evidence of effectiveness.

Secondary analyses

Secondary endpoints were conducted in the full target population for the mean change from baseline at Week 52.

The five attributes of the main estimand for these key secondary endpoints as described by the Applicant are noted here:

1. *Treatment condition of interest and alternative treatment:* 210 mg tezepelumab administered SC Q4W or matching placebo for a period of 52 weeks.
2. *Targeted population:* Adult subjects with severe, uncontrolled asthma
3. *Variable or endpoint:* For purposes of this review, the endpoints used in NAVIGATOR are noted here. Note that several other endpoints for lung function, ACQ-6, and asthma daily diary score were also explored in this study. Pre-BD FEV1, ACQ-6, weekly mean

ASD score, and AQLQ(S) +12 are the endpoints from PATHWAY that support this application.

4. *Population-level summary:* Mean change from baseline at Week 52
5. *Intercurrent event and data handling strategy:* Study treatment discontinuations were handled with a treatment policy strategy; data were collected and used, regardless of whether treatment discontinuation occurred.

These analyses were conducted based on the effect of the initially randomized treatment, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications prior to Week 52. Missing data from study discontinuation was modelled based on what was observed during the study using direct likelihood approaches, under the assumption that data were missing at random (MAR).

Change from baseline for these key secondary endpoints was performed using a mixed model for repeated measures (MMRM) model. This model was used to estimate the treatment effect at Week 52 and its 95% CI.

- Treatment, visit, treatment-by-visit interaction, baseline blood eosinophil count (≥ or < 250 cells/µL), baseline ICS dose level (medium or high), age, gender, race, and respective baseline measure as fixed effects were used for change from baseline in pre-BD FEV1 (L) were included as factors in the FEV1 analysis.
- Treatment, visit, treatment-by-visit interaction, baseline blood eosinophil count (≥ or < 250 cells/µL), baseline ICS dose level (medium or high), and baseline mean ACQ-6 score were included as factors in the ACQ-6, asthma daily diary (mean symptom scores, activity limitation, rescue medication, nights without nocturnal awakening and nights without asthma-related nocturnal awakening), and AQLQ(S)+12 analyses.

<u>Post-hoc analyses</u>

Some of the analyses were *post hoc*, conducted to be more consistent with the methodology and subgroups used in the NAVIGATOR study:

- The Intent-to-Treat analysis set remained the same between *a priori* and *post hoc* analyses
- Subgroup analyses were added:
  - Baseline blood eosinophil subgroups were added (in addition to the a priori subgroups of <300/µL and ≥300/µL): <150/µL, ≥150/µL, 150 – <300/µL, 300 – <450/µL, and ≥450/µL
  - Baseline fractional exhaled nitric oxide (FeNO) groups: <25ppb, ≥25ppb, 25 – <50ppb, and ≥50ppb
  - Age: Adults (>65) , Adults (≥18 – <65)
  - Race: White, Black or African American, Asian, and Other
  - Body Mass Index: <18.5 kg/m2, 18.5 – <25.0 kg/m2, 25.0 – <30.0 kg/m2, ≥30.0 kg/m2
  - History of nasal polyps: yes and no

- Baseline perennial specified IgE status: Any perennial FEIA positive, all perennial FEIA negative, and unknown status

- Analysis of proportion of subjects with no exacerbations was added using a logistic regression model with factors for treatment, baseline local blood eosinophil count, and baseline inhaled corticosteroids (ICS) dose level
  - A similar logistic regression model will be fitted for the subgroup based on baseline eosinophils (<300/µL, ≥300/µL), as above, with an additional factor for the subgroup and the treatment by subgroup interaction. This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories.
- The same generalized linear mixed model as described in the PATHWAY *a priori* SAP was fitted for the change from baseline in FEV_1, ACQ-6, and AQLQ(S)+12 for each visit using the ITT analysis set for each new subgroup specified above, i.e., treatment group, visit, treatment-by-visit interaction, baseline local blood eosinophil count, baseline ICS dose, and respective baseline values were included as fixed effects in the model. Age, gender, and race were added to the model for FEV_1
- Responder analyses were conducted for ACQ-6 Responder and AQLQ(S)+12 responder (Yes or No). Responders/non-responders were analyzed using a generalized linear model for repeated measures, using a logit link function. The response variable in the model was the binary responder status at each scheduled post-randomization visit up to and including Week 52, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, baseline local blood eosinophil count, baseline ICS dose level, visit, and treatment by visit interaction will be included as factors in this model. Baseline of the corresponding endpoint was included in the model as a continuous linear covariate.

Note that asthma exacerbation rate analyses for the above noted subgroups used the negative binomial model that was described *a priori* in the PATHWAY SAP.

Reviewer comment: In order to further understand the effect of biomarkers, we requested additional information from the Applicant as outlined in the Navigator SAP Subgroup analyses.

8.1.3.11 Protocol Amendments

One protocol amendment was made on October 15, 2014. The amendment was to clarify various aspects of the procedures and did not impact the design of the trial significantly.

8.1.4. PATHWAY Trial Results

8.1.4.1 Compliance with Good Clinical Practices

The study was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of

investigational products and data protection. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

The Applicant certified that all clinical investigations in this BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the United States were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in GCP.

8.1.4.2 Financial Disclosure

MedImmune was the initial company who conducted the PATHWAY trial. MedImmune was subsequently acquired by AstraZeneca. MedImmune collected financial information from all clinical investigators prior to the trial. Towards the end of the trial, it was discovered that neither AstraZeneca nor Amgen were mentioned in the disclosure documents. In April 2018, efforts were made to collect financial disclosure information regarding AstraZeneca and Amgen from the sites that had not yet been closed out. AstraZeneca attempted to collect all remaining missing financial disclosure documentation prior to BLA submission. Financial disclosure information related to MedImmune was collected from 401/401 (100%) of the investigators. Financial disclosure information related to AstraZeneca was collected from 339/401 (85%) of investigators. These investigators enrolled 69% of the subjects randomized in trial. One of the 401 investigators declared financial interest in AstraZeneca which representing (b) (6) of subjects randomized into the trial. Financial disclosure information related to Amgen was collected from 290/401 (72%) of investigators who participated in PATHWAY, representing 55% of those randomized in the trial. No investigators declared financial interest in Amgen. AstraZeneca has opened a quality investigation and is working on preventative action plan to address this issue. A total of 111 due diligence forms were submitted for the 111 investigators that either did not provide financial disclosures for Amgen, Astra Zeneca, or both.

Thirty two investigators with missing information did not randomize any subjects in the PATHWAY trial. The Applicant relayed that as these investigators were not directly involved in the treatment and evaluation of research subjects and therefore could not impact the trial, the Sponsor did not make significant attempts to obtain missing information. For those remaining investigators who were directly involved, the Applicant attempted multiple attempts to contact via contact information and contact information found on the internet. At least three attempts to contact each clinical investigator were made by two different methods over multiple business days. AstraZeneca further reviewed financial disclosure information from other AstraZeneca clinical trials during the same timeframe as PATHWAY and found 24 of the missing investigators financial disclosure related to AstraZeneca. None of the 24 investigators disclosed any financial interest in or payments from AstraZeneca. See Appendix 16.1 for completed financial disclosure form.

Amgen also reviewed financial disclosure information from other Amgen clinical trials during similar timeframes as PATHWAY and found 11 of the missing investigators had no financial interest in or payments from Amgen. AstraZeneca and Amgen confirmed none of the

investigators in PATHWAY were employees or contractors of either company during the conduct of the trial or up to one year after study completion.

Reviewer comment: Although the number of investigators with missing financial disclosure information for the other two parties involved are higher than expected (15% related to AstraZeneca and 28% for Amgen), the Applicant provide due diligence forms for all investigators with any missing financial disclosure information outlining the efforts made to acquire the missing financial disclosure information. The Applicant also provided supplementary information from other trials conducted by the AstraZeneca. Since financial disclosures were provided for 100% of the investigators related to the study Sponsor (MedImmune) and due diligence forms were submitted for all investigators with any missing financial disclosures, per 21 CFR 54.4, this is acceptable.

8.1.4.3 Data Quality and Integrity

See Section 4.1 for summary of data quality and integrity review.

The Applicant relayed that anomalous data at site 2000179 was identified. During the Applicant-led investigation, the Applicant believed the site did not comply with principles of Good Clinical Practice. This was primarily based on PK samples suggesting that subjects allocated to tezepelumab did not receive tezepelumab and exploratory DNA samples indicated that blood samples marked as different subjects may have been from the same individual. An Applicant-initiated site audit was inconclusive. Due to this finding, all data for the 34 randomized subjects from the site were excluded. Specific protocol deviations of the site could not be identified. The exclusion of the data did not change any conclusion per the Applicant.

Reviewer Comment: The Division reviewed the justification provided by the Applicant in the December 7, 2021 Information Request response. The Division agreed that site 2000179 appeared to have not complied with Good Clinical Practice and this supported excluding the 34 randomized subjects from the efficacy and safety analyses. For completeness, the Applicant provided an efficacy and safety analyses including the 34 subjects. Review of the data from site 200179 does not change any efficacy or safety conclusions.

8.1.4.4 Subject Disposition

Subject disposition is summarized in Table 42. Disposition for the PATHWAY trial showed a higher number of subjects in the tezepelumab arm who discontinued the trial (11% tezepelumab vs 6% placebo). The most frequent reason for not completing the trial was “other” and withdrawal of consent. “Other” reasons for not completing the trial included missed dose, subject’s decision, failure to meet eligibility criteria, lack of available investigational product, Applicant decision, pregnancy, and use of prohibited medication. Only a few subjects across treatment groups discontinued due to adverse events.

Table 42. PATHWAY Trial Subject Disposition

Disposition Outcome	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Placebo N=138 n (%)
Subjects randomized	138	137	137	138
Safety population	138	137	137	138
Discontinued study	11 (8)	15 (11)	22 (16)	8 (6)
Death	1 (1)	0	0	0
Lost to follow-up	0	1 (1)	2 (1)	0
Other	6 (4)	7 (5)	10 (7)	4 (3)
Withdrawal by subject	4 (3)	7 (5)	10 (7)	4 (3)
Discontinued treatment	9 (7)	16 (12)	20 (15)	9 (7)
Adverse event	0	2 (3)	3 (2)	1 (1)
Development of study-specific withdrawal criteria	0	0	0	0
Lost to follow-up	0	1 (1)	2 (1)	0
Other[a]	6 (4)	6 (4)	7 (5)	3 (2)
Protocol deviation	0	0	0	0
Withdrawal by subject	3 (2)	7 (5)	8 (6)	5 (4)

Source: ds.xpt, adsl.xpt; Software: R
[a] Other reasons included subject's decision, AE, failure to meet eligibility criteria, visit out of window, sponsor decision, lack of available investigational product, pregnancy, use of prohibited medication, and missed dose.
Abbreviations: n, number of subjects in specified population or group; N, number of subjects in treatment arm; NA, not applicable; Q4W, every 4 weeks

8.1.4.5 Protocol Violations/Deviations

The majority of the protocol deviations were related to criteria for visit schedules, study procedures, inclusion/exclusion, laboratory assessment, TESAE criteria, randomization, and investigational product compliance.

8.1.4.6 Subject Demographics

The demographics are summarized in Table 43. The subjects enrolled had similar baseline demographics across treatment groups. As similar with the NAVIGATOR trial, a majority enrolled were female (66%). The mean age enrolled was 52 years as no adolescents were enrolled in this trial. The majority of the trial participants were white (92%).

Table 43. PATHWAY Trial Baseline Demographic Characteristics in Randomized Population

Characteristic	Tezepelumab 70 mg Q4W N=138	Tezepelumab 210 mg Q4W N=137	Tezepelumab 280 mg Q2W N=137	Total Tezepelumab N=412	Placebo N=138	Total N=550
Sex, (n%)						
Female	89 (65)	87 (64)	91 (66)	267 (65)	94 (68)	361 (66)
Male	49 (36)	50 (37)	46 (34)	145 (35)	44 (32)	189 (34)
Age, years						
Mean (SD)	50.8 (12)	52.7 (13)	50 (12)	51 (12)	52 (12)	52 (12)
Median (min, max)	52 (20, 74)	55 (21, 75)	52 (21, 72)	53 (20, 75)	54 (20, 74)	53 (20, 75)
Age group, years, (n%)						
Adult (≥18 to <65)	117 (85)	114 (83)	122 (89)	353 (86)	118 (86)	471 (86)
Adult (≥65)	21 (15)	23 (17)	15 (11)	59 (14)	20 (15)	79 (14)
Ethnicity, (n%)						
Hispanic or Latino	0 (0)	1 (1)	2 (2)	3 (1)	1 (1)	4 (1)
Not Hispanic or Latino	138 (100)	136 (99)	135 (99)	409 (99)	137 (99)	546 (99)
Race, (n%)						
Asian	3 (2)	5 (4)	5 (4)	13 (3)	6 (4)	19 (4)
Black or African American	4 (3)	3 (2)	6 (4)	13 (3)	6 (4)	19 (4)
Other	0 (0)	1 (1)	4 (3)	5 (1)	3 (2)	8 (2)
White	131 (95)	128 (93)	122 (89)	381 (93)	123 (89)	504 (92)

Characteristic	Tezepelumab 70 mg Q4W N=138	Tezepelumab 210 mg Q4W N=137	Tezepelumab 280 mg Q2W N=137	Total Tezepelumab N=412	Placebo N=138	Total N=550
Country of participation, (n%)						
Bulgaria	14 (10)	14 (10)	11 (8)	39 (10)	18 (13)	57 (10)
Czech Republic	11 (8)	16 (12)	8 (6)	35 (9)	9 (7)	44 (8)
Hungary	20 (15)	27 (20)	26 (19)	73 (18)	22 (16)	95 (17)
Israel	7 (5)	8 (6)	8 (6)	23 (6)	6 (4)	29 (5)
Japan	3 (2)	5 (4)	5 (4)	13 (3)	6 (4)	19 (4)
Lithuania	4 (3)	0 (0)	6 (4)	10 (2)	3 (2)	13 (2)
LVA	11 (8)	7 (5)	9 (7)	27 (7)	9 (7)	36 (7)
Serbia	0 (0)	2 (2)	0 (0)	2 (1)	2 (1)	4 (1)
Slovakia	22 (16)	14 (10)	20 (15)	56 (14)	19 (14)	75 (14)
Ukraine	37 (27)	34 (25)	32 (23)	103 (25)	32 (23)	135 (25)
United States	8 (6)	10 (7)	9 (7)	27 (7)	9 (7)	36 (7)
South Africa	1 (1)	0 (0)	3 (2)	4 (1)	3 (2)	7 (1)

Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; Q4W, every 4 weeks; SD, standard deviation

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The clinical baseline characteristics for subjects in the PATHWAY trial can be found in Table 44.

Table 44. PATHWAY Trial Baseline Clinical Characteristics in Randomized Population

Characteristic	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)	Total N= 550 n (%)
Baseline Eosinophils, cells/uL						
Mean (SD)	352 (288)	365 (351)	385 (433)	367 (361)	380 (328)	383 (369)
Median (min, max)	280 (10, 1600)	280 (0, 3180)	260 (0, 3990)	280 (0, 3990)	275 (0, 1870)	300 (0, 3990)
Pooled Baseline Eosinophils, (n%)						
<150	36 (26)	28 (20)	34 (25)	98 (24)	33 (24)	131 (24)
150 - <300	35 (25)	42 (31)	39 (29)	116 (28)	40 (29)	156 (28)
300 - <450	33 (24)	28 (20)	26 (19)	87 (21)	21 (15)	108 (20)
≥450	34 (25)	39 (29)	38 (28)	111 (27)	44 (32)	155 (28)
Baseline FeNO, ppb						
Mean (SD)	36 (48)	32 (30)	33 (34)	34 (38)	37.8 (40)	35 (39)
Median (min, max)	23 (3, 349)	22 (4, 153)	21 (2, 218)	22 (2, 349)	22 (4, 276)	22 (2, 349)
Pooled Baseline FeNO, (n%)						
<25	74 (54)	78 (57)	75 (55)	227 (55)	74 (54)	301 (55)
≥25 - <50	43 (31)	33 (24)	33 (24)	109 (27)	30 (22)	139 (25)
≥50	20 (15)	24 (18)	25 (18)	69 (17)	33 (24)	102 (19)
Missing	1 (1)	2 (3)	4 (3)	7 (2)	1 (1)	8 (1)
Baseline IgE, mg/L						
Mean (SD)	323 (891)	484 (1403)	358 (595)	388 (1018)	475 (1272)	410 (1087)
Median (min, max)	112 (2, 7423)	135 (2, 11430)	149 (2, 3814)	130 (2, 11430)	148(6, 11860)	134 (2, 11860)

Characteristic	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)	Total N= 550 n (%)
Baseline IgE Status, (n%)						
All perennial FEIA negative	77 (56)	64 (47)	74 (54)	215 (52)	74 (54)	289 (53)
Any perennial FEIA positive	56 (41)	67 (49)	55 (40)	178 (43)	60 (44)	238 (43)
Unknown perennial FEIA	3 (2)	3 (2)	3 (2)	9 (2)	2 (1)	11 (2)
Missing	2 (1)	3 (2)	5 (4)	10 (2)	2 (1)	12 (2)
Smoking Status, (n%)						
Former	25 (18)	34 (25)	28 (20)	87 (21)	16 (12)	103 (19)
Never	113 (82)	103 (75)	109 (80)	325 (79)	122 (88)	447 (81)
Smoking History, Pack Years						
Mean (SD)	4 (3)	5 (2)	4 (3)	5 (3)	4 (2)	5 (3)
Median (min, max)	4 (0, 10)	5 (0, 10)	5 (0, 9)	5 (0, 10)	4 (0, 9)	5 (0. 10)
Baseline ICS Level, (n%)						
High	71 (51)	67 (49)	66 (48)	204 (50)	65 (47)	269 (49)
Low	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Medium	67 (49)	70 (51)	71 (52)	208 (51)	73 (53)	281 (51)
Baseline OCS Level, (n%)						
Absent	123 (89)	128 (93)	124 (91)	375 (91)	124 (90)	499 (91)
Present	15 (11)	9 (7)	13 (1)	37 (9)	14 (10)	51 (9)
Years Since First Diagnosis						
Mean (SD)	16 (11)	18 (13)	18 (12)	17 (12)	16 (12)	17 (12)
Median (min, max)	14 (1, 53)	15 (1, 57)	14 (1, 50)	15 (1, 57)	14 (1, 63)	15 (1, 63)
Exacerbations in Previous 12 months						

Characteristic	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)	Total N= 550 n (%)
Mean (SD)	3 (1)	2 (1)	2 (1)	2 (1)	3 (1)	2 (1)
Median (min, max)	2 (1, 10)	2 (1, 10)	2 (1, 12)	2 (1, 12)	2 (1, 10)	2 (1, 12)
Atopic Dermatitis						
NA	1 (1)	1 (1)	4 (3)	6 (2)	3 (2)	9 (2)
No	126 (91)	119 (87)	123 (90)	368 (89)	124 (90)	492 (90)
Yes	11 (8)	17 (12)	10 (7)	38 (9)	11 (8)	49 (9)
Nasal Polyps within last 2 years						
NA	1 (1)	2 (2)	4 (3)	7 (2)	3 (2)	10 (2)
No	118 (86)	112 (82)	111 (81)	341 (83)	117 (85)	458 (83)
Yes	19 (14)	23 (17)	22 (16)	64 (16)	18 (13)	82 (15)
FEV1, L						
Mean (SD)	1.9 (0.7)	1.8 (0.6)	1.8 (0.6)	1.9 (0.6)	1.8 (0.6)	1.9 (0.6)
Median (min, max)	1.8(0.7, 4.1)	1.8 (0.7, 3.9)	1.8 (0.6, 3.4)	1.8 (0.6, 4.1)	1.7 (0.7, 3.2)	1.8 (0.6, 4.1)
Percent Predicted FEV1, %						
Mean (SD)	61 (14)	59 (13)	59 (12)	59 (13)	60 (14)	60 (13)
Median (min, max)	61 (28, 93)	59 (33, 91)	60 (24, 84)	60 (24, 93)	59 (30, 100)	60 (24, 100)
ACQ-6 Score						
Mean (SD)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)
Median (min, max)	3 (1, 5)	3 (0, 5)	3 (1, 5)	3 (0, 5)	3 (0, 5)	3 (0, 5)
AQLQ(S)+12 Score						
Mean (SD)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)	4 (1)
Median (min, max)	4 (2, 6)	4 (2, 7)	4 (2, 7)	4 (2, 7)	4 (2, 6)	4 (2, 7)

Source: adsl.xpt, adre.xpt, adqsacq.xpt; Software: R
Abbreviations: ACQ, Asthma control questionnaire; FEV1, Forced Expiratory Volume in 1 second; ICS, Inhaled corticosteroids; N, number of subjects in treatment group; n, number of subjects with given characteristic; OCS, Oral corticosteroids; SD, standard deviation

8.1.4.7 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The proportion of subjects who took concomitant medications was low and similar between tezepelumab and placebo groups

8.1.4.8 Efficacy Results – Primary Endpoint

The primary endpoint was the AAER measured at Week 52 (Table 45). Statistically significant decreases in AAER of 62%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab treatment groups, respectively, when compared with placebo in the ITT population ($p<0.001$) at Week 52 was demonstrated.

Table 45 PATHWAY Summary of asthma annual exacerbation rate through Week 52 (ITT Population)

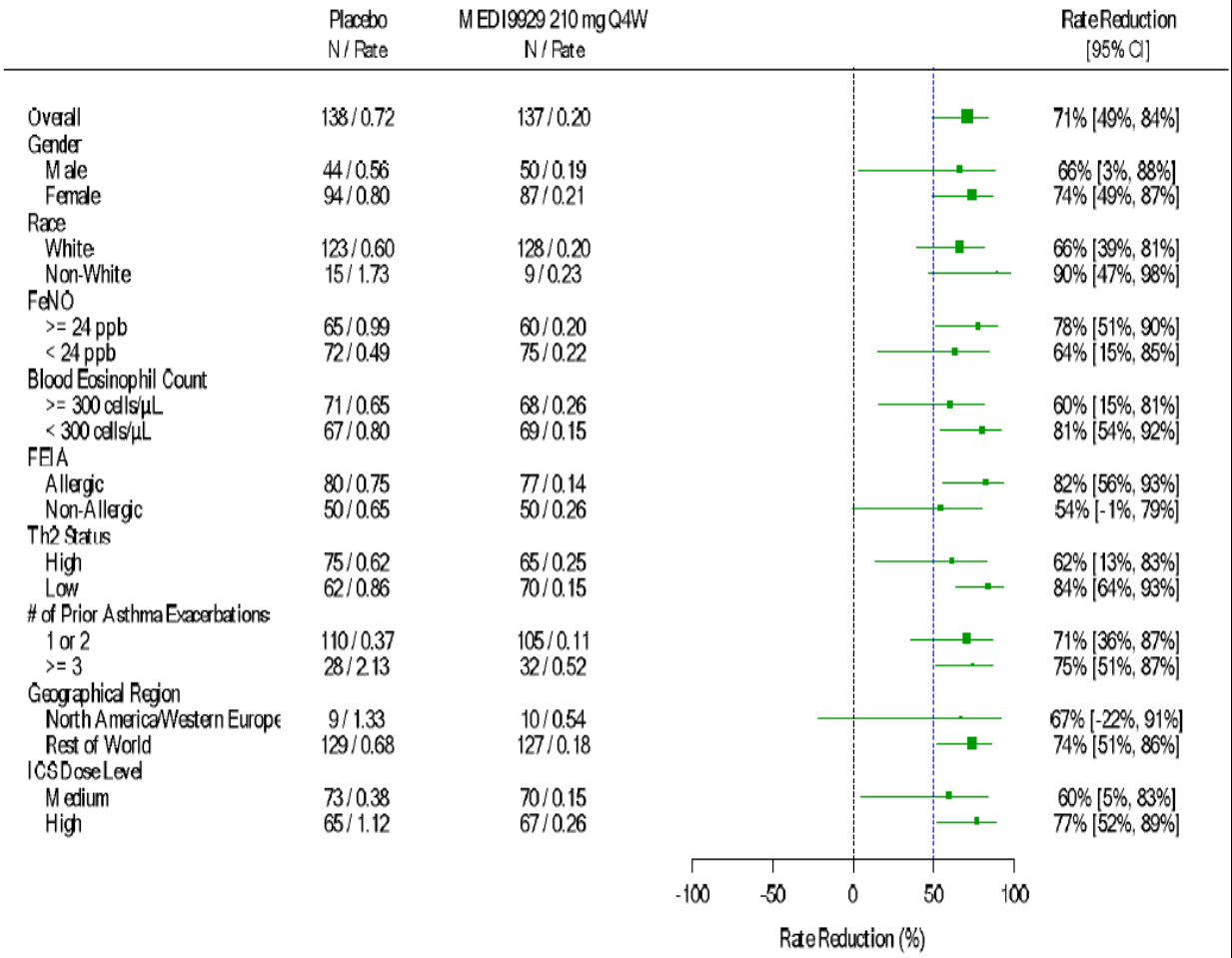
Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Rate (95% CI)	0.72 (0.59, 0.88)	0.27 (0.19, 0.38)	0.20 (0.13, 0.30)	0.23 (0.16, 0.34)
Rate ratio (95% CI)	---	0.38 (0.23, 0.63)	0.29 (0.16, 0.51)	0.34 (0.20, 0.58)
p-value	---	< 0.001	< 0.001	< 0.001

Abbreviations: Q2W = every two weeks; Q4W = every four weeks; CI = confidence interval
Source: PATHWAY CSR, Table 14.2_1.1.1, confirmed by statistical reviewer, prime_eff.sas
Rate ratio and 95% CI for rate ratio are estimated from the negative binomial regression with treatment group, baseline blood eosinophil count (>= or < 250 cells/uL), and baseline ICS dose level (medium or high) as covariates. P-value is from the negative binomial regression based on pairwise comparison against placebo group.

Due to a concern about data from one of the investigational sites, Dr. Melnyk's site (2000366), a subsequent analysis was conducted with this site removed from the primary analysis. This site contributed 22 subjects to the trial, with a total of 10 subjects removed from the primary efficacy analysis: 6 subjects from the tezepelumab 210 mg arm and 4 subjects from the placebo arm. There was no appreciable difference in results when the data from Dr. Melynk's site was removed, leading to the conclusion that the contribution of this site's data on primary efficacy did not have an appreciable influence on the trial results.

This improvement was also seen irrespective of gender, race, FeNO level, baseline eosinophil level, number of prior exacerbations, or baseline ICS dose level (Figure 25).

Figure 25 Forest plot by subgroups for annual asthma exacerbation rate reduction over 52 weeks (ITT Population, 210 mg tezepelumab and placebo arms only)



Abbreviations: MEDI19929 = tezepelumab; FEIA = fluorescent enzyme immunoassay, Th2 Status = T helper 2 cells pathway; High = IgE >100 IU/mL and blood eosinophils ≥ 140 cells/µL; Low = IgE ≤ 100 IU/mL OR blood eosinophil count ICS = inhaled corticosteroids; FeNO = fractional exhaled nitric oxide
Source: Figure 11.4.1.1-3
Rate ratio, and 95% CI for rate ratio were estimated from negative binomial regression with treatment group, and the stratification factors-baseline blood eosinophil count (≥ or < 250 cells/µL) and baseline ICS dose level (medium or high) as the covariates. Rate reduction (%) relative to placebo was calculated as 100*(1-rate ratio).

As with NAVIGATOR, the effect of tezepelumab on the AAER compared to placebo was significant across baseline levels of blood eosinophils and FeNO. This improvement was also seen irrespective of gender, race, number of prior exacerbations or baseline dose level (Figure 25).

In both baseline eosinophil categories (<300, ≥300 cells/µL), AAER was reduced (by 81% and 60%, respectively) in the tezepelumab group compared to placebo and both confidence intervals did not include 0, the point of no difference. Similarly, with the two baseline FeNO categories (<24, ≥24 ppb), AAER was reduced (by 64% and 78%, respectively) in tezepelumab

compared to placebo and both confidence intervals did not include 0. The magnitude of benefit increased with increasing levels of FeNO and decreased with increasing levels of eosinophils.

Reviewer comments: Although the subgroup analysis showed efficacy in both eosinophil subgroups, the degree of change from baseline in AAER was unexpectedly different than what was seen in the NAVIGATOR population. In PATHWAY, greater AAER reduction were seen in subjects with lower eosinophils (<300 cells/uL) compared to the higher eosinophil (> 300 cells/uL) whereas in NAVIGATOR the inverse was demonstrated. The PATHWAY AAER results across eosinophil and FeNO subgroups were also incongruent which is also unexpected as eosinophils and FeNO tend to track together. Overall, conclusions based on subgroups are limited due to the sample size, and the sample size for PATHWAY For the 210 mg Q2W group was smaller than NAVIGATOR which further limits interpretation of these subgroup results.

Exploratory continuous analyses and categorical analyses were conducted by the Applicant based on a request from the Agency to further investigate the predictive nature of baseline eosinophils and FeNO in the primary endpoint, similar to what was conducted for the NAVIGATOR study. The results for the continuous and categorical variable analyses were not significant for any of the 5 models possibly due to low power for interaction tests with small sample size.

Exacerbations requiring ER or hospitalization
Reductions of 75%, 85%, and 69% were observed with 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups, respectively, compared with placebo at Week 52 with the greatest reduction observed with the 210 mg Q4W dose through Week 52 (Table 46).

For hospitalizations only, reductions of 74%, 86%, and 74% were observed with 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups, respectively, compared with placebo at Week 52 with the greatest reduction observed with the 210 mg Q4W dose through Week 52 (Table 46).

Table 46 PATHWAY Summary of asthma annual exacerbation rate for those events requiring hospitalization and ER visits through Week 52 (ITT Population)

Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Asthma annual exacerbation rate leading to hospitalization or ER visit requiring SCS[1]				
Rate (95% CI)	0.18 (0.12, 0.27)	0.04 (0.02, 0.10)	0.03 (0.01, 0.08)	0.05 (0.02, 0.10)
Rate ratio (95% CI)		0.25 (0.08, 0.77)	0.15 (0.04, 0.58)	0.31 (0.10, 0.96)

p-value		0.015	0.005	0.042
Asthma annual exacerbation rate leading to hospitalization[2]				
Rate (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)
Rate ratio (95% CI)		0.26 (0.07, 0.97)	0.14 (0.06,1.10)	0.26 (0.06,1.10)
p-value		0.045	0.017	0.067

Abbreviations:Q4W, every 4 weeks; Q2W, every 2 weeks; CI, confidence interval

[1]Source: PATHWAY CSR, Table A.1.2.1 Note: this was a post-hoc analysis conducted to supplement the NAVIGATOR analysis, confirmed by statistical reviewer

[2]Source: PATHWAY CSR, Table 14.2_1.1.2, confirmed by statistical reviewer

Rate ratio and 95% CI for rate ratio are estimated from the negative binomial regression with treatment group, baseline local blood eosinophil count (>= or <250 cells/µL), and baseline ICS dose level (medium or high) as covariates. p-value is from the negative binomial regression based on pairwise comparison against the placebo group.

8.1.4.9 Efficacy Results – Secondary and other relevant endpoints

FEV1

Increases in pre-bronchodilator FEV1 at Week 52 were seen in all 3 tezepelumab dose groups when compared to placebo ($p<0.05$, Table 47) and with small increases with increasing dose. Increases from baseline in pre-BD FEV1 were observed as early as Week 4 in all three treatment groups when compared to placebo and generally maintained over time for the duration of the trial (Figure 26).

Table 47 PATHWAY change from baseline in FEV1 at Week 52 (ITT Population)

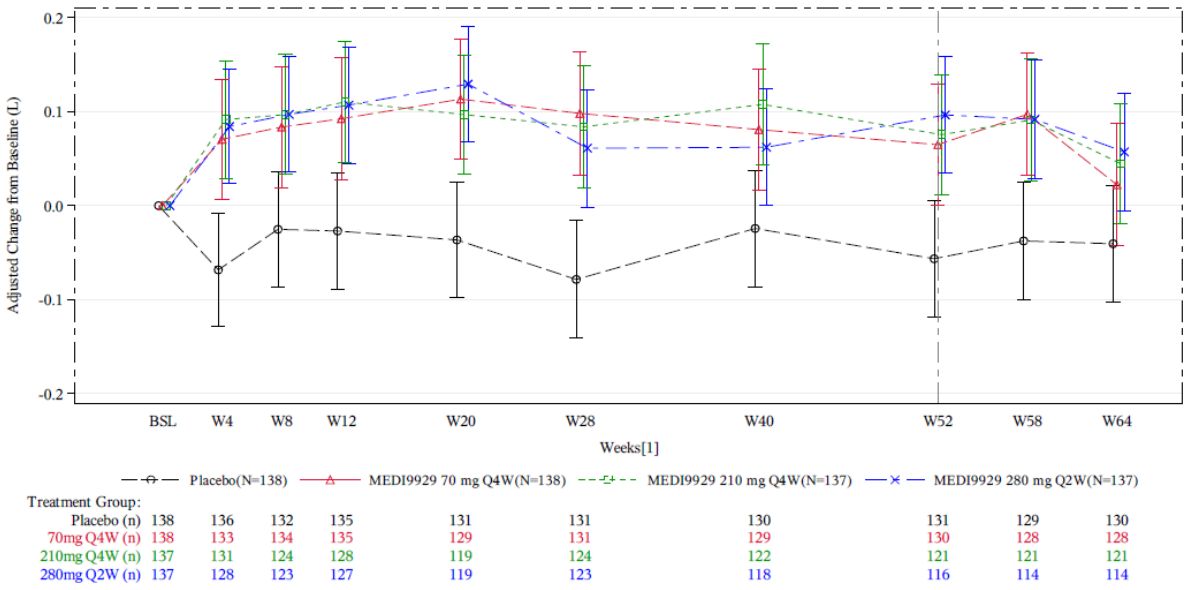
Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
n	131	130	121	116
LS mean	-0.056	0.065	0.076	0.097
Difference vs Placebo		0.121	0.132	0.153
95% CI		(0.024, 0.219)	(0.033, 0.231)	(0.054, 0.252)
p-value		0.015	0.009	0.002

Abbreviations:Q4W, every 4 weeks; Q2W, every 2 weeks; LS mean, least square mean; CI, confidence interval

Source: PATHWAY CSR, Table 14.2_2.2, confirmed by statistical reviewer

A generalized linear mixed model using a linear contrast was used, including treatment group, visit, treatment-by-visit interaction, baseline blood eosinophil count (>= or < 250 cells/uL), baseline ICS dose level (medium or high), age, gender, race, and respective baseline measure as fixed effects.

Figure 26 PATHWAY Change from baseline in FEV1 over time (ITT Population)



Abbreviations:FEV1, forced expiratory volume in 1 second; Q4W, every 4 weeks; Q2W, every 2 weeks
95% confidence intervals are displayed
Source: PATHWAY CSR, Figure 14.2 9.6.1

<u>FEV1 and eosinophil and FeNO biomarkers</u>

An exploratory analysis was conducted on FEV1 with baseline eosinophil and FeNO levels to assess their capability as predictive biomarkers. Exploratory continuous analyses and categorical analyses were conducted by the Applicant based on a request from the Agency to further investigate the predictive nature of baseline eosinophils and FeNO in FEV1, similar to what was conducted for the NAVIGATOR study.

Generally speaking, these analyses provided some support for FeNO biomarker predictability from the FEV1 endpoint. Similar results were seen with the categorical analysis.

Reviewer's comment: The lack of biomarker predictability in PATHWAY may be due in part to its smaller sample size.

<u>ACQ-6</u>

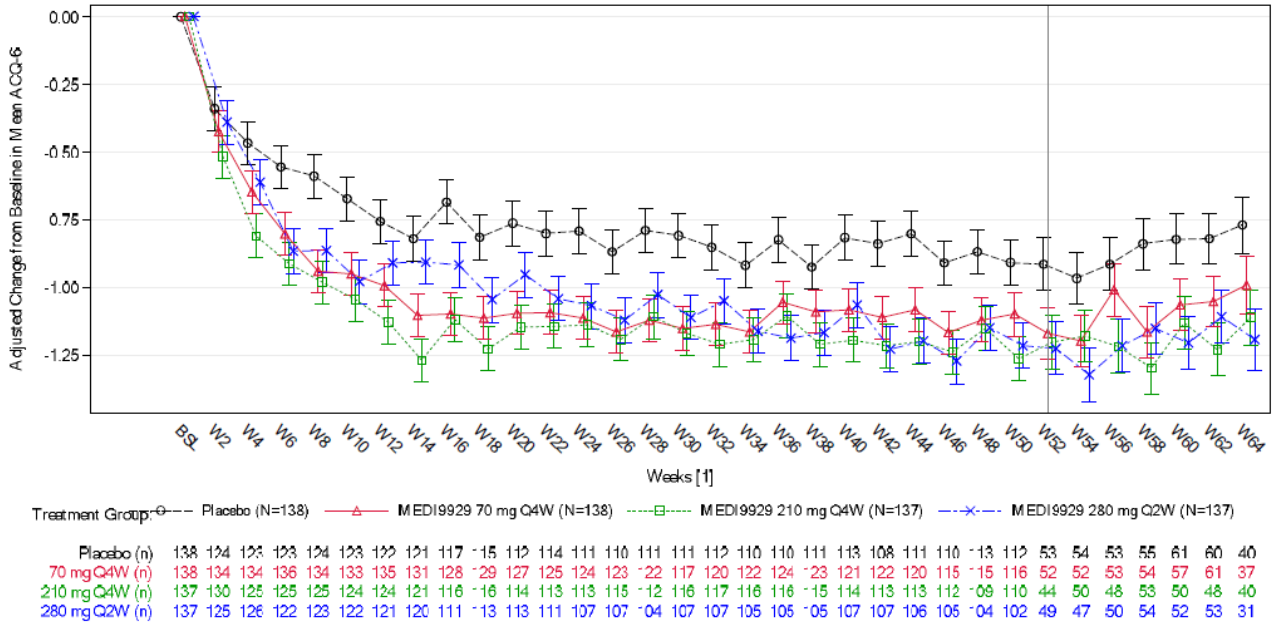
ACQ-6 was evaluated every 2 weeks using an electronic PRO device and manually triggered for Week 52 evaluation. Many study sites did not perform this function and therefore a small percentage of the randomized population completed the questionnaire at Week 52 (n=145, 35%). The Applicant provided data from Week 50 as well as more subjects completed ACQ-6 assessments from Week 50 (n=328, 80%), which showed results consistent with Week 52. Improvements in ACQ-6 were seen in all 3 tezepelumab doses when compared to placebo, with greater improvements in the two high dose groups ($p<0.05$, Table 48 and Figure 27).

Table 48 PATHWAY Summary of change from baseline in ACQ-6 (ITT Population)

Parameters	Placebo Total N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Mean ACQ-6 Score: Change from Baseline at Week 50				
n	112	116	110	102
LS mean	-0.91	-1.10	-1.26	-1.21
Difference vs Placebo		-0.19	-0.36	-0.31
95% CI		(-0.41, 0.04)	(-0.58, -0.13)	(-0.54, -0.08)
P-value [a]		0.098	0.002	0.009
Mean ACQ-6 Score: Change from Baseline at Week 52				
n	53	52	44	49
LS mean	-0.91	-1.17	-1.20	-1.22
Difference vs Placebo		-0.26	-0.29	-0.31
95% CI		(-0.52, 0.01)	(-0.56, -0.01)	(-0.58, -0.04)
P-value [a]		0.059	0.039	0.024

Abbreviations:ACQ-6, Asthma Control Questionnaire, omitting forced expiratory volume in one second; Q4W, every 4 weeks; Q2W, every 2 weeks
Source: PATHWAY CSR, Table 14.2_3.2.1
Nominal p-values were from a generalized linear mixed model using a linear contrast test including treatment group, visit, treatment-by-visit interaction, baseline blood eosinophil count (≥ or < 250 cells/μL), baseline ICS dose level (medium or high), and baseline overall ACQ-6 score as fixed effects.

Figure 27 PATHWAY Change from baseline in mean ACQ-6 score over time by treatment group (ITT Population)



Abbreviations:ACQ-6, Asthma Control Questionnaire, omitting forced expiratory volume in one second; Q4W, every 4 weeks; Q2W, every 2 weeks
Source: PATHWAY CSR, Figure 14.2 9.9, confirmed by statistical reviewer

A greater proportion of subjects in the tezepelumab groups overall (77% total) achieved clinically meaningful improvements of ≥ 0.5 from baseline in ACQ-6 compared with placebo (63%; p = 0.002) at Week 52 (LOCF), and these improvements appeared to be dose-dependent.

AQLQ(S)+12

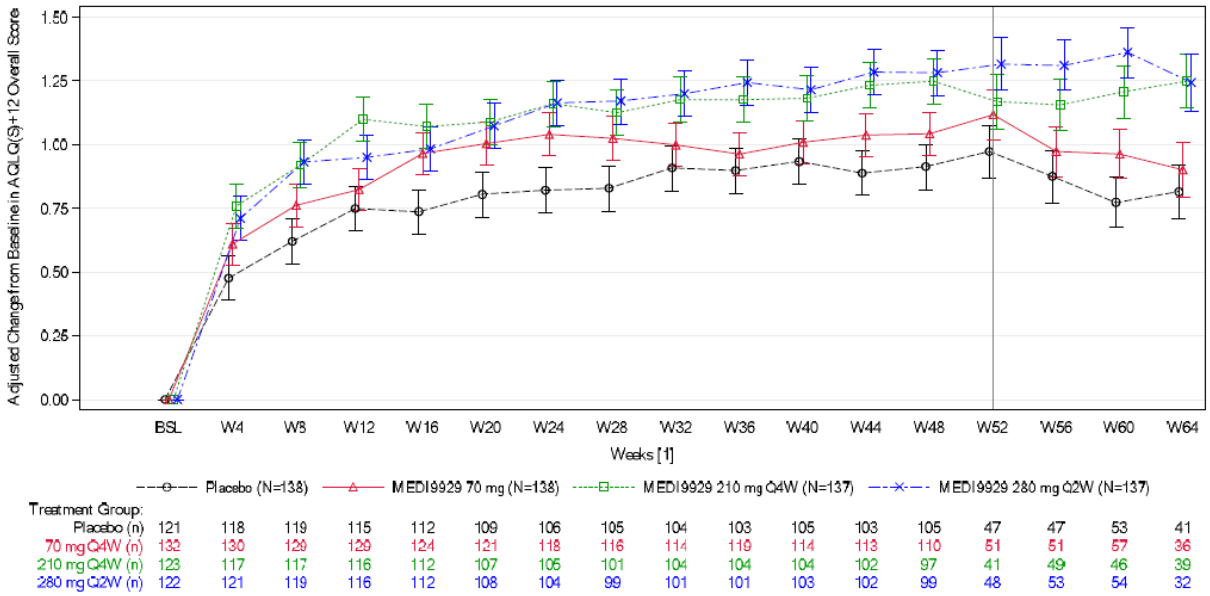
AQLQ(+12) was also completed using an electronic PRO device and was manually triggered for Week 52. As with ACQ-6, many study sites did not manually trigger Week 52 which resulted in far fewer subjects at Week 52 (n=140, 34%). As it was an every 4 week questionnaire, the Applicant also provided Week 48 data which was completed by more subjects (n=306, 74%) and which was consistent with Week 52 data. The data demonstrated improvement from baseline in AQLQ (+12) in all three treatment groups compared to placebo with the higher improvements in the two higher doses at Week 48 (Table 49, Figure 28).

Table 49 PATHWAY Change from baseline in AQLQ(S)+12 (ITT Population)

Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Overall Score: Change from Baseline at Week 48				
n	105	110	97	99
LS mean	0.91	1.04	1.25	1.28
Difference vs Placebo		0.13	0.33	0.37
95% CI		(-0.11, 0.37)	(0.09, 0.58)	(0.12, 0.61)
P-value [b]		0.293	0.008	0.003
Overall Score: Change from Baseline at Week 52				
n	47	51	41	48
LS mean	0.97	1.12	1.17	1.32
Difference vs Placebo	--	0.14	0.20	0.34
95% CI	--	(-0.13, 0.42)	(-0.09, 0.48)	(0.06, 0.63)
P-value [b]	--	0.309	0.185	0.017

Abbreviations:AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardized) for 12 years and older; Q4W, every 4 weeks; Q2W, every 2 weeks; LS mean, least square mean; CI, confidence interval
Source: PATHWAY CSR Table 14.2_5.2

Figure 28 PATHWAY Change from baseline in AQLQ (S)+12 over time (ITT Population)



Abbreviations:AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardized) for 12 years and older; Q4W, every 4 weeks; Q2W, every 2 weeks; LS mean, least square mean
95% confidence intervals are displayed
Source: PATHWAY CSR Figure 14.2 9.11, confirmed by statistical reviewer

A greater proportion of subjects in the tezepelumab groups overall (75% total) achieved clinically meaningful improvements of ≥ 0.5 from baseline in the AQLQ(S)+12 score compared with placebo (62%; p = 0.007;) at Week 52 (LOCF).

Time to first asthma exacerbation through Week 52

Tezepelumab treatment delayed the time to first exacerbation and reduced the risk of having any exacerbation by 38%, 55%, and 46% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W doses, respectively when compared to placebo (Table 50).

Table 50 PATHWAY Summary of time to first exacerbation through Week 52 (ITT Population)

Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Number of events Number censored	43 95	30 108	21 116	25 112
Hazard ratio (95% CI of Hazard ratio)		0.62 (0.39, 0.99)	0.45 (0.26, 0.75)	0.54 (0.33, 0.88)
p-value		0.044	0.002	0.013

Abbreviations: Q2W = every two weeks; Q4W = every four weeks; CI = confidence interval
Source: PATHWAY CSR, Table 14.2_1.4.1
Hazard ratio and 95% CI for HR estimated from the proportional hazard model adjusted by baseline blood eosinophil count (>= or < 250 cells/uL) and baseline ICS dose level (medium or high).
P-value based on pairwise comparison against placebo group. It is based on a stratified log-rank test with baseline blood eosinophil count (>= or < 250 cells/uL) and baseline ICS dose level (medium or high) as the stratification factors

8.1.4.10 Durability of Response

The Applicant is currently conducting a phase 3 2-year long-term extension study (DESTINATION) for eligible subjects previously randomized in one of the predecessor phase 3 asthma studies NAVIGATOR and SOURCE. The trial will be randomized, double-blind and placebo controlled throughout the 2-year treatment period. The results of this trial are not available at the time of this application.

8.1.4.11 Summary of PATHWAY Effectiveness

The PATHWAY trial was an adequate and well-controlled trial and demonstrated statistically significant and clinically relevant improvement for the primary endpoint of the AAER measured at Week 52. The ITT population showed a significant reduction in annualized AER at Week 52 in all three tezepelumab groups when compared to placebo. The treatment effect was numerically larger in the 210 mg Q2W group supporting carrying this dose forward into the NAVIGATOR trial. Although not multiplicity controlled, a nominal treatment effect was also demonstrated for the secondary endpoints of time to first asthma exacerbation, change from baseline in FEV1 at Week 52, AQLQ(S)+12 and ACQ-6.. Subgroup analysis based on baseline eosinophil and FeNO subgroups also demonstrated similar results consistent with the ITT population.

8.1.5. SOURCE Trial (D5180C00009) Design

8.1.5.1 Administrative Information

Study title: A Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma (SOURCE)
Study dates: March 5, 2018 to September 25, 2020
Study sites: Argentina, Germany, Poland, South Korea, Turkey, Ukraine, United States of America
Study report date: March 22, 2021

8.1.5.2 Objectives

The primary objective of the trial was to evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in subjects with asthma requiring chronic treatment with maintenance OCS in addition to high-dose ICS plus LABA.

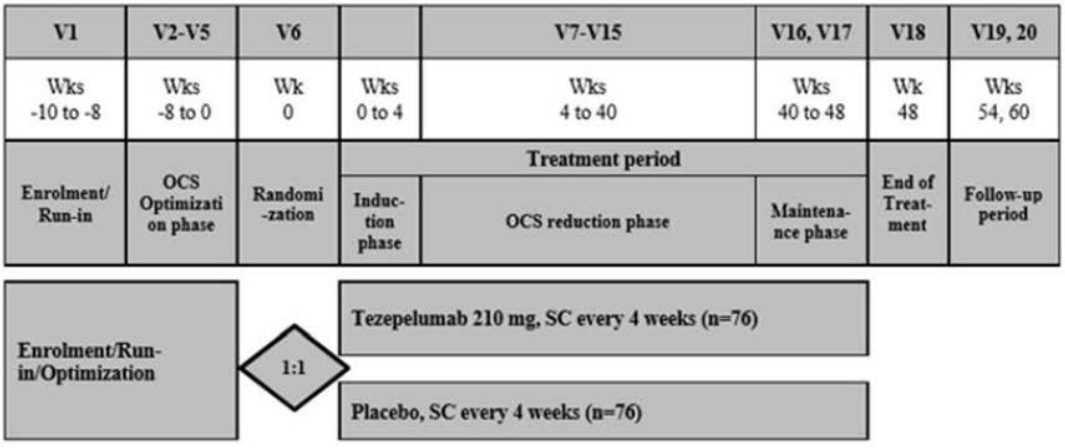
8.1.5.3 Study Design and Conduct

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group trial designed to evaluate the effect of 210 mg dose of tezepelumab administered Q4W while undergoing OCS reduction in adults with severe, OCS dependent asthma. The study enrolled and randomized 150 subjects who were receiving a stable daily dose of OCS between ≥ 7.5 mg and ≤ 30 mg prednisone daily or prednisolone equivalent. The target was to enroll approximately 35% of subjects with baseline eosinophils ≥300 cells/uL. Subjects were on baseline medium to high dose ICS the prior year and high dose ICS/LABA at least 3 months prior to screening. Additionally, subjects were required to have been on maintenance OCS for at least 6 months prior to screening. Subjects were required to have had at least one asthma exacerbation the 12 months prior to screening.

Due to the COVID-19 pandemic, changes were made to the protocol to ensure safety of subjects and minimize risk of travel. Subjects had the option of home visits or phone call/virtual visits instead of on-site visits. Decisions for OCS dose adjustments were done with remote interviewing along with eDiary data, and if applicable, home visit physical examinations.

The trial consisted of a 2 week screening/run in period followed by an OCS optimization phase of up to 8 weeks followed by a treatment period of 48 weeks (4 week induction phase, 36 weeks OCS reduction phase, and 8 week maintenance phase). Subjects who completed the 48 week trial were enrolled in a 12 week post-treatment follow up period consisting of two follow up visits. Trial study design can be found in Figure 29.

Figure 29. SOURCE trial Study Design Flow Chart



SC, subcutaneous; V, visit; Wk(s), week(s).

8.1.5.4 Procedures

Trial procedures can be seen in Table 51 and Table 52.

Table 51. SOURCE Trial Enrollment/Run In Period/Oral Corticosteroid Optimization Phase

	Run-in	OCS optimisation phase			
	V1[a]	V2	V3	V4	V5
	W -10	W -8	W -6	W -4	W -2
	Visit window (days)				
Assessment/activity	N/A	+3[c]	±3	±3	-3[c]
Informed consent	X				
Inclusion/exclusion criteria	X	X	X	X	X
Routine clinical procedures					
Demographics	X				
Medical/Surgical and asthma history	X				
Safety assessments					
Complete physical examination	X				
Weight, Height	X				
Vital Signs	X				
12-lead ECG	X				
Assessments of asthma exacerbations	X	X	X	X	X
Adverse events	X	X	X	X	X
Concomitant medications [d]	X	X	X	X	X
Safety laboratory assessments (Clinical chemistry and haematology)	X				
Urinalysis (dipstick) [e]	X				
Serology (hepatitis B, C; HIV-1; HIV-2)	X				
Serum pregnancy or FSH test [f] (Females only)	X				
Patient reported outcome assessments					
Dispense and train on eDiary [g]	X				
Daily diary	Completed twice daily at home on eDiary				
Daily diary adherence check [h]		X	X	X	X
ACQ-6	X	X			
Lung function assessments					
Pre-BD spirometry [i]	X	X			
Post-BD spirometry (Reversibility assessment) [i]	X	X			
Home peak-flow monitor (PEF meter) training and distribution	X				
Check compliance with home PEF meter		X	X	X	X

Home assessment of PEF	Measurement every morning and evening				
OCS optimisation					
OCS switch to prednisone or prednisolone if required	X				
OCS dose reduction		X [j]	X	X	
OCS dose increase, if indicated [k]					X

a Visit 1 can be performed over a period of 3-working days, with the exception of documentation of informed consent. All study assessments including withholding of asthma medications for required period for Pre-BD spirometry at visit 1 to be performed after the documentation of informed consent.
b Visit 2 and 5 will be on-site visits. Visits 3 and 4 can be performed as telephonic visits provided the subject and sites are confident to perform the visit remotely. Depending on clinical judgement, investigator may decide to call the subject on-site for visits 3 and 4 as well. Instructions for OCS dose titrations at visits 3 and 4 can be communicated to the subject on phone. The optimization phase may be extended to account for treatment of an exacerbation to allow for 2-week stable OCS dose prior to randomization.
c At a minimum there should be at least 14 days window (could be extended to 17 days) between visit 1 and 2 and also between visit 5 and 6 (randomization).
d All asthma medications taken in the 12 months prior to visit 1 must be recorded in the eCRF along with reason for treatment. All other medications taken for conditions other than asthma in the 3 months prior to visit 1 must be recorded in the eCRF along with reason for treatment.
e Urinalysis analyzed centrally only if dipstick locally is positive.
f Serum pregnancy (β-HCG) test only for WOCBP. FSH test done only in women < 50 years who have been amenorrheic for > 12months to confirm postmenopausal status.
g eDiary should be dispensed after all other assessments have been performed.
h Daily Diary: Asthma symptom diary (ASD), general asthma symptom severity item, rescue medication use, night time awakenings and adherence to maintenance medications.
i If Pre-BD FEV_1 is met and reversibility is not met or vice versa, at visit 1; only the criteria that was not met needs to be verified at visit 2. Post-BD spirometry should be performed 15-30 min after administration of 4 puffs of albuterol/salbutamol. Reversibility can be documented in the previous 12 months prior to or at visit 1 or visit 2. Note: Reversibility (both historical and during screening) is defined as FEV_1 ≥12% and ≥200 mL.
j At visit 2 OCS dose titration will be attempted without referring to the protocol-captured set of baseline eDiary data. At other optimization visits eDiary data preceding the visits, will be compared to the baseline eDiary data derived from the interval between visit 1 and 2 for OCS dose titration decisions. Refer section 8.1.1.2.
k If the subject does not meet the criteria for following OCS dose reduction schedule at visits 3 or 4, the OCS dose should preferentially be returned to one level higher, unless the judgment of the investigator is to maintain the subject on their current dose of OCS, and visit 5 should be activated instead of visit 3 or 4 on the same day. Subject must be maintained on the optimized OCS dose for at least 2 weeks before randomization.

Table 52. SOURCE Trial Treatment and Follow up Period Procedures

	Induction	Reduction phase									Maintenance phase		EOT[e]	FU	FU	IPD	UNS[b]
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20		
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 54	Wk 60		
Assessment/ Activity	Visit window (days) [a]																
	0	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	N/A	N/A
Verifying Inclusion/ exclusion criteria	X																
Weight	X						X						X			X	
Randomisation	X																
Health resource utilisation (HRU) [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete physical examination	X												X			X	
Brief physical examination		X	X	X	X	X	X	X	X	X	X	X		X	X		
Vital Signs [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessments of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG [e]	X						X						X			X	
Glucocorticoid toxicity index	X						X						X			X	
Safety laboratory assessments (Clinical chemistry and haematology) [f]	X	X		X			X				X		X		X	X	
Urinalysis (dipstick) [g]	X	X					X				X		X			X	
Urine pregnancy test (dipstick) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	

IgE (FEIA)	X																
Total serum IgE, IgA, IgG, IgM [i]	X	X					X				X		X		X	X	
PK	X	X		X			X				X		X		X	X	
ADA/nAb	X	X		X			X				X		X		X	X	
Serum for other biomarker analysis	X	X					X				X		X		X	X	
Blood sample for RNA transcriptome profiling	X	X					X				X		X		X	X	
Pharmacogenetics assessment [j] (Optional)	X										X		X			X	
Daily diary [k]	Completed twice daily at home on eDiary																

Daily diary adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X				
ACQ-6	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
AQLQ(s)+12	X	X									X	X	X			X	
WPAI+CIQ	X						X						X			X	
EQ-5D-5L	X	Completed every 2 weeks on the eDiary														X	
SGRQ	X												X			X	
FeNO [l]	X	X		X			X				X		X		X	X	
Pre-BD spirometry	X	X		X			X				X		X		X	X	

Post-BD spirometry	X	X					X						X			X	
Home assessment of PEF	Measurements every morning and evening throughout treatment period																
PEF adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X				
Administration of IP [m]	X	X	X	X	X	X	X	X	X	X	X	X					
OCS dose titration		X	X	X	X	X	X	X	X	X							X[a]

EOT – End of treatment; **FU** – Follow-up; **IPD** – Investigational product discontinuation; **UNS** – Unscheduled

a All visits are to be scheduled from the date of randomization; not from the date of previous visit.
b Unscheduled visits may be initiated as needed. At unscheduled visits for assessing an asthma exacerbation, at a minimum, these assessments need to be performed. At other unscheduled visits assessments may be performed as per investigator's judgement.
c Asthma specific resource utilization (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).
d Vital signs will be taken pre-dose prior to administration of IP. Subjects will be observed 2 hours post treatment for Visits 6 and 7. For all other visits where IP is administered, subjects will be observed for a minimum of 1 hour.
e ECG must be collected prior to any blood draws.
f During treatment period all laboratory samples should be obtained prior to IP administration. Subjects should be fasting for at least 12 hours prior to blood collection. Blood eosinophil, basophils and monocyte numbers from the visits after randomization visit will be redacted from the central laboratory reports.
g Urinalysis analyzed centrally only if dipstick locally is positive.
h For WOCBP urine pregnancy test (dipstick) to be done at site at each treatment visit prior to IP administration. Positive urine pregnancy test must be confirmed by serum β-HCG.
i All immunoglobulin results will be redacted from laboratory reports from the visits after randomization.
j Blood sample for DNA is optional and will be collected from subjects who have consented to participate in the genetic analysis component of the study
k Daily Diary: ASD, general asthma symptom severity item, rescue medication use, night time awakenings and adherence to maintenance medications.
l FENO test needs to be completed prior to spirometry. FENO results will be redacted.
m IP should be administered after all other assessments have been completed at the visit.
n Up-titration only.
o Subjects completing the EOT visit may be eligible to enrol in a separate extension study D5180C00018 and these subjects will not complete the follow-up visits at Week 54 and Week 60. During the Corona Virus Disease 2019 (COVID-19) pandemic, subjects enrolling in the separate extension study D5180C00018 will continue participation in the follow-up visit(s) (Week 54, Week 60) until the on-site (or alternate site) visit for extension study randomization and IP administration can be conducted.

8.1.5.5 Population

Key Inclusion Criteria:

1. 18 to 80 years of age.
2. On medium to high dose ICS per GINA guidelines for at least 12 months prior to Visit 1.
3. On LABA and high dose ICS for at least 3 months prior to Visit 1.
4. Additional maintenance asthma controller medications were allowed according to standard practice of care. The use of these medications must have been documented for at least 3 months prior to Visit 1.
5. Subjects had to have received OCS for the treatment of asthma for at least 6 months prior to screening and have been on a stable dose between ≥7.5 to ≤ 30 mg daily or prednisone/prednisolone or equivalent.
6. Morning pre-BD FEV1 had to be <80% predicted normal at screening or the first visit during the run-in OCS optimization phase.
7. Subjects had to have a history of at least one asthma exacerbation event within 12 months prior to screening.

Key Exclusion Criteria:

1. Any clinically important pulmonary disease other than asthma.

2. Any disorder that was not stable in the opinion of the Investigatory that could have affected the safety of the subject, influenced the findings of the trial, or imped the subject to complete the trial.
3. History of cancer.
4. History of a clinically significant infection, including upper and lower respiratory tract infection that required treatment with antibiotics or antiviral medications finalized <2 weeks before screening or during run in period.
5. A helminth parasitic infection diagnosed within 6 months prior to screening that had not been treated with, or had failed to respond to, standard of care therapy.
6. Current smokers or subjects who had a smoking history ≥10 pack years.

8.1.5.6 Treatment

Subjects were randomized to tezepelumab 210 mg Q4W vs. placebo Q4W. The subjects were given the same treatment as that given in NAVIGATOR. See Section 8.1.1.6 Treatment.

8.1.5.7 Efficacy Endpoints

Primary endpoint:
Categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control. The categories for percent change from baseline in daily OCS dose are defined as:

1. ≥ 90% to ≤ 100% reduction
2. ≥ 75% to < 90% reduction
3. ≥ 50% to < 75% reduction
4. > 0% to < 50% reduction
5. no change or any increase

Key Secondary Endpoints:

1. Annualized asthma exacerbation rate
2. Time to first asthma exacerbation
3. Rate of asthma exacerbation associated with ER visit, urgent care visit, or hospitalization
4. Proportion of subjects who did not experience an asthma exacerbation over 48 weeks

8.1.5.8 Efficacy Parameters

Oral Corticosteroid Dose

OCS Management
During the optimization phase, minimum OCS dose while maintaining asthma control was reached for all subjects. The optimized OCS dose was kept stable for 2 weeks prior to randomization and this was considered their baseline OCS use. The baseline OCS dose was maintained at the same level from Visit 5 (2 weeks prior to randomization) to Visit 7 (end of induction phase). OCS dose reduction started on Visit 7 and continued at 4 week

intervals until Visit 15. During reduction phase, a minimum stable OCS dose or complete elimination of requirements for OCS, while maintaining asthma control was reached for each subject.

OCS Titration in Optimization Period
Baseline assessments used for dose titrations during this period were the mean measures (morning PEFs, SABA use, and night-time awakenings) collected between Visit 1 and Visit 2. OCS reductions occurred every 2 weeks. In the dosing interval >10 to 30 mg prednisone or prednisolone per day, the change in daily dose was 5 mg, whereas in the interval 7.5 to 10 mg, the corresponding reduction was 2.5 mg. Subjects considered by Investigator not to be candidates for starting a reduction or noncompliant with eDiary or medication use were screen failed. If a subject reached asthma control at an OCS dose of <7.5 mg during this phase or asthma control was still obtained after 3 consecutive OCS dose reductions, then the subject was screen failed.

During the optimization phase, for all subjects who entered dose reduction, the baseline values for titration were the mean of measures (morning PEFs, SABA use, and nighttime awakenings) collected daily 2 weeks prior to randomization. OCS reduction was attempted at each visit per the schedule of assessment. Subjects had to meet all criteria listed in Table 53. It was up to the discretion of the Investigator to continue with OCS down titration even if the criteria had not been met. The Investigator had to justify and document it in the eCRF and notify the Sponsor study physician. Reasons not to reduce OCS were also captured in the eCRF. The Investigator then had the ability to either increase up one step or maintain the dose of OCS. Once the optimized dose was reached, no further OCS dose reductions were performed during the optimization phase. The subject was maintained on that OCS dose until randomization.

Table 53. Criteria for Following OCS Dose Reduction Schedule

Criteria	Definition of asthma control
1	Morning PEF ≥ 80% of mean morning measures as compared with baseline mean
2	An increase of no more than 2 nights with asthma-related awakenings (requiring rescue medication) over a 7-day period compared with baseline
3	Mean SABA rescue medication use not more than 4 puffs/day above the baseline mean and < 12 puffs/day on all days in the prior 14 days
4	No asthma exacerbation requiring increased systemic corticosteroids or hospitalization since the previous visit
5	Investigator judges subject's asthma control to be sufficient to allow OCS dose reduction
6	No signs/symptoms of adrenal insufficiency (at OCS dose reductions below 5 mg)f

OCS Titration in Treatment Period
No OCS titration occurred during the induction phase. Dose titration during the treatment phase began at Visit 7 and ended no later than Visit 15. All subjects entered the OCS dose maintenance phase at Visit 16. No further reductions were attempted after Visit 15.

Asthma Exacerbations: Assessment and Management

An asthma exacerbation was defined as a worsening of asthma that led to any of the following:

- A temporary burst of systemic steroids (at a dose at least one level higher than current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening.
- An ER or urgent care visit due to asthma that required systemic steroids.
- An inpatient hospitalization due to asthma.

Worsening of asthma was defined as new or increased symptoms and/or signs identified by physical exam, subjective interview or by the subject via eDiary. The ePRO was programmed to alert both subject and study site of any pre-specified worsening thresholds were crossed. If an exacerbation was not associated with the deterioration of at least one of the pre-specified objective measurements, the Investigator justified the decision and recorded it in the eCRF. Events that were not supported by an objective assessment were deemed not to be protocol-defined exacerbation.

Asthma Symptom Diary Score
This Asthma Symptom Diary Scores were calculated as they were in NAVIGATOR Trial. See Section 8.1.1.

ACQ-6 and AQLQ(S)+12
These scores were calculated as they were in PATHWAY and NAVIGATOR Trials. See Section 8.1.1.

8.1.5.9 Safety Parameters

Safety parameters in SOURCE were similar to that of PATHWAY and NAVIGATOR. However, in addition to the laboratory assessments, a glucocorticoid toxicity index was assessed at given timepoints as subjects were on oral corticosteroids. See Section 8.1.1.

8.1.5.10 Statistical Analysis Plan

Efficacy analyses was performed using the full analysis set. A total of 150 subjects were randomized and included in the full analysis set.

Primary analysis and its sensitivity analyses
The primary endpoint in the tezepelumab group was compared with that in the placebo group using a proportional odds (ordinal logistic regression) model. This model was used to estimate

the treatment effect and its 95% confidence interval (CI). The response variable was the ordered category number (with values ranging from 1-5). Treatment and region were included as factors in the model and baseline OCS dose was included as a linear covariate.

Three types of sensitivity analyses for the primary endpoint were performed, controlled imputation, tipping point analysis, and single imputation using an average dose approach. The controlled imputation was based on pattern mixture models. Subjects with missing baseline data were excluded from these analyses. The multiple imputations were done in 2 steps:

1. The non-monotone (intermediate) missing values were imputed first, assuming missing at random (MAR) (the Markov chain Monte Carlo method was used to partially impute the data using SAS PROC MI).
2. Then, the remaining monotone missing values at each visit were imputed using the sequential regression method. At each iteration, missing values were imputed sequentially, one time point at a time.

Different assumptions were made to impute the monotone missing data:

- MAR: Missing data in each group were imputed assuming the distribution within that treatment group.
- Missing not at random/dropout reason-based multiple imputation (MNAR/DRMI): Missing data were imputed differently depending on the reason for study withdrawal. Missing data for subjects who dropped out for a treatment-related reason were imputed assuming the subject's whole distribution, both pre-withdrawal and post-withdrawal, was the same as the placebo group (the "copy reference" approach), whereas the remaining subjects were imputed assuming MAR.

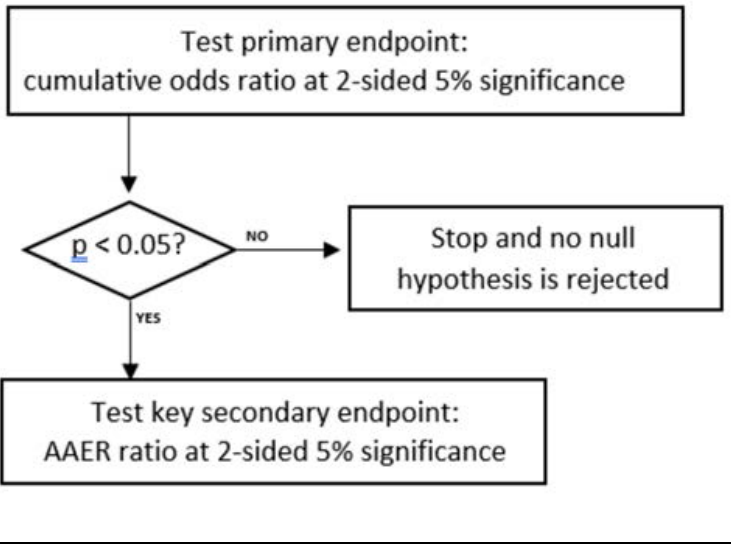
A tipping point analysis was planned for the primary endpoint using similar multiple imputation methodology as described above. Various degrees of improvement in the placebo group after withdrawal and various degrees of worsening in the tezepelumab group after withdrawal were planned to be simultaneously explored. However, the tipping point analysis was not performed since the primary endpoint was not met.

A single imputation method was also planned using average dose. Where a subject withdrew from the study or discontinued study drug and chose to discontinue the study, the final OCS dose was imputed to be the average daily dose that the subject was taking in the 14 days prior to their study drug discontinuation or withdrawal from the study.

Multiplicity control

To account for multiplicity when testing the primary and the key secondary endpoints, hypotheses were tested as displayed in Figure 30.

Figure 30 SOURCE Multiplicity strategy



Source: SOURCE CSR, Figure 2

Key secondary endpoint (AAER) analysis

The main analysis of the key secondary efficacy endpoint (AAER over 48 weeks) quantified the effect of the initially randomized treatment, regardless of the treatment that subjects actually received, or whether the subjects received other controller therapy/rescue medications post study drug withdrawal. This analysis used a treatment policy strategy and subjects were encouraged to continue to undergo applicable study-related visits/procedures for the full 48-week period. Intercurrent events included study drug discontinuation and collected data were used regardless of whether treatment discontinuation occurred. Sources of missing data were as follows: subjects lost to follow-up, subjects who withdrew their consent, and subjects who died. Missing data from early study withdrawal was modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data were MAR.

Reviewer's comment: *The Applicant describes subject death as a source of missing data, which according to ICH E9(R1) it is not missing data but a treatment failure.*

The AAER in the tezepelumab group was compared with that in the placebo group by rate ratio. The AAER in the tezepelumab group was compared with AAER in the placebo group using a negative binomial model. This model was used to estimate the rate ratio and its 95% CI. The response variable in the model was the number of asthma exacerbations experienced by a subject over the 48-week planned treatment period (or shorter duration if not followed up for the full 48 weeks). Treatment, region, and history of exacerbations (≤ 2 or > 2 in the previous 12 months) were included as factors in this model. The logarithm of the time at risk (in years) for exacerbation in the study was used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occurred.

8.1.5.11 Protocol Amendments

There were two protocol amendments (April 4, 2018 and March 12, 2019). The majority of the protocol changes were clarifications to various aspects to the procedures and did not impact the design of the trial significantly. The protocol changes did increase the number of subjects enrolled to provide more than 90% power to reject the null hypothesis along with better exploration of the effect of tezepelumab on various eosinophil levels.

8.1.6. SOURCE Trial Results

8.1.6.1 Compliance with Good Clinical Practice

The study was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

The Applicant certified that all clinical investigations in this BLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the United States were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in GCP.

8.1.6.2 Financial Disclosure

The SOURCE trial was a joint partnership between AstraZeneca and Amgen. Financial disclosure information was obtained from 100% of the investigators from AstraZeneca. All but one of the 150 financial disclosures from Amgen was obtained. See Appendix 19.2 for more information.

8.1.6.3 Data Quality and Integrity

No data quality issues were identified in the review of this trial.

8.1.6.4 Subject Disposition

Summary of the subject disposition can be found in Table 54. Overall the subject disposition was similar across treatment group. A total of 91% of subjects completed treatment and 94% completed the study. Slightly fewer subjects completed treatment in the tezepelumab group compared with placebo (89% versus 93%, respectively) and this was reflected in the proportions that completed the study (92% versus 96%).

Table 54. SOURCE Trial Subject Disposition

Disposition Outcome	Tezepelumab 210 mg Q4W N=74 n (%)	Placebo N=76 n (%)
Subjects randomized	74	76
Discontinued study	6(8)	3(4)
Death	1(1)	0(0)
Lost to follow-up	0(0)	1(1)
Due to COVID-19 pandemic	0(0)	0(0)
Withdrawal by subject	5 (7)	2(3)
Discontinued treatment	8 (11)	5 (7)
Adverse event	1 (1)	2 (3)
Development of study-specific withdrawal criteria	1 (1)	0(0)
Lost to follow-up	0 (0)	1(1)
Other	2(3)	0(0)
Due to COVID-19 pandemic	0(0)	0(0)
Withdrawal by subject	4 (5)	2 (3)

IP, investigational product; OCS, oral corticosteroid; Q4W, every 4 weeks; Teze, tezepelumab.
Source: Table 14.1.1. from SOURCE CSR

8.1.6.5 Protocol Violations/Deviations

The number of subjects with at least one important protocol deviation was similar across treatment groups (tezepelumab 23% vs. placebo 24%). The most common protocol deviation was “restrictions during the study” which was reported in 4/74 (5%) in the tezepelumab group and 8/76 (11%) in the placebo group. Within this category, the most frequent event was “changes in dose and regimen of asthma controller medications (except OCS) throughout the study (except for treatment for asthma exacerbations).” None of these protocol deviations was considered to have an effect in the overall interpretation of the results.

The COVID-19 related deviations were balanced between the treatment group, two in each treatment group. These deviations were all in the IP management category (IP missed twice or more). It is not suspected that these deviations change the conduct or quality of the study.

8.1.6.6 Subject Demographics

The demographics are summarized in Table 55. Similar to the two previous trials, the number of females randomized were more than the number of males (62% vs. 37%). The mean age enrolled was approximately 54 years old as adolescents were not included in this trial. The population was predominantly white.

Table 55. Table of Demographic Characteristics in SOURCE trial in Randomized Population

	Tezepelumab 210 mg Q4W N=74	Navigator-Placebo N=76
Sex, (n%)		
Female	49 (66)	45 (59)
Male	25 (34)	31 (41)
Age, years		
Mean (SD)	54 (12)	53 (12)
Median (min, max)	56 (24, 75)	53 (22, 76)
Age group, years, (n%)		
Adult (≥18 to <65)	58 (78)	62 (82)
Adult (≥65)	16 (22)	14 (18)
Ethnicity, (n%)		
Hispanic or Latino	10 (14)	14 (18)
Not Hispanic or Latino	64 (87)	62 (82)
Race, (n%)		
Asian	11 (15)	11 (15)
Black or African American	1 (1)	0 (0)
Other	0 (0)	1 (1)
White	62 (84)	64 (84)

Max, maximum; Min, minimum; N, number of subjects in treatment group; n, number of subjects in analysis; Q4W, every 4 weeks; SD, standard deviation.
Source: Table 14.1.10

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics can be found in Table 56. The mean baseline eosinophils count was lower compared to NAVIGATOR and PATHWAY with the mean value around 200 cells/uL versus 300s cells/uL in the other pivotal trials. This is difficult to interpret given that the SOURCE population was on OCS which is known to suppress eosinophil count. A wide range of baseline eosinophil counts while on oral corticosteroids were enrolled. The mean FeNO of the population was also generally lower, but FeNO can also be suppressed with oral corticosteroid use.

Table 56. SOURCE Trial Baseline Demographic Characteristics in Randomized Population

Characteristic	Tezepelumab 210 mg Q4W N=74 n (%)	Placebo N=76 n (%)
Baseline Eosinophils, cells/uL		
Mean (SD)	253 (203)	232 (154)
Median (min, max)	215 (20, 1160)	200 (30, 700)
Pooled Baseline Eosinophils, (n%)		
<150	138 (26)	138 (26)
150 - <300	171 (32)	171 (32)
300 - <450	99 (19)	95 (18)
≥450	120 (23)	127 (24)
Baseline FeNO, ppb		
Mean (SD)	39 (41)	42 (37)
Median (min, max)	26 (9, 279)	28 (6, 159)
Pooled Baseline FeNO, (n%)		
<25	32 (47)	26 (38)
≥25 - <50	20 (29)	27 (39)
≥50	16 (24)	16 (23)
Baseline IgE, mg/L		
Mean (SD)	299 (576)	301 (521)
Median (min, max)	109 (2, 2867)	123 (2, 3295)
Baseline IgE Status, (n%)		
All perennial FEIA negative	44 (60)	44 (60)
Any perennial FEIA positive	25 (34)	34 (45)
Unknown perennial FEIA	5 (7)	3 (4)
Smoking Status, (n%)		
Former	18 (24)	21 (28)
Never	56 (76)	55 (72)
Smoker, Pack Years		
Mean (SD)	6 (3)	5 (3)
Median (min, max)	6 (1, 9)	6 (0, 9)

Characteristic	Tezepelumab 210 mg Q4W N=74 n (%)	Placebo N=76 n (%)
Baseline ICS Level, (n%)		
High	73 (99)	73 (100)
Low	0 (0)	0 (0)
Medium	1 (1)	0 (0)
Baseline OCS Level, (n%)		
Present	74 (100)	76 (100)
Baseline FEV1 Level in Liters, (n%)		
Mean (SD)	2 (1)	2 (1)
Median (min, max)	2 (1, 3)	1 (1,3)
Baseline FEV1 % PN, (n%)		
Mean (SD)	54 (18)	53 (18)
Median (min, max)	52 (20, 104)	52 (19, 91)
Years Since First Diagnosis		
Mean (SD)	30 (17)	31 (18)
Median (min, max)	32 (0, 63)	32 (0, 70)
Exacerbations in Previous 12 months		
Mean (SD)	2 (2)	2 (1)
Median (min, max)	2 (1, 15)	2 (1, 5)
Atopic Dermatitis		
Yes	3 (4)	2 (33)
Nasal Polyps		
Yes	17 (23)	18 (244)

Max, maximum; Min, minimum; N, number of subjects in treatment group; n, number of subjects in analysis; Q4W, every 4 weeks; SD, standard deviation.
Source: Table 14.1.11-13, 14.1.17, 14.1.20

8.1.6.8 Efficacy Results – Primary Endpoint

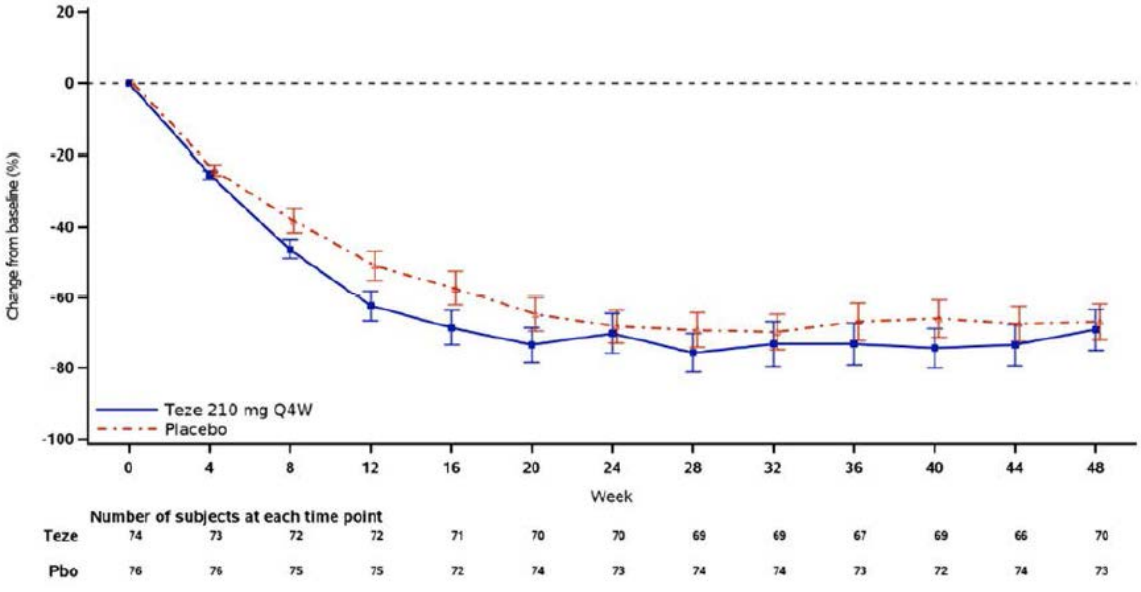
The primary endpoint assessing categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control was not met. The odds ratio of 1.28 did not meet statistical significance (95% CI, 0.69, 2.35, p = 0.434; Table 57 Figure 31). While there was treatment separation from Week 8 to Week 16, there was no treatment separation for the remainder of the 48 week trial (Figure 31). The proportions of subjects receiving a ≥90 to ≤100% reduction in maintenance OCS dose at Week 48 without losing asthma control was 54.1% in the tezepelumab group and 46.1% in the placebo group.

Table 57 Proportion of subjects in planned categories based on percent reduction from baseline in final daily OCS dose at Week 48 (Full Analysis Set)

Category	Teze 210 mg Q4W (N = 74)	Placebo (N = 76)
Reduction from baseline in final daily OCS dose, n (%)		
≥ 90% to ≤ 100% reduction	40 (54.1)	35 (46.1)
≥ 75% to < 90% reduction	5 (6.8)	4 (5.3)
≥ 50% to < 75% reduction	10 (13.5)	14 (18.4)
> 0% to <50% reduction	5 (6.8)	9 (11.8)
no change or any increase	14 (18.9)	14 (18.4)
Comparison between treatment groups		
Cumulative odds ratio (95% CI)	1.28 (0.69, 2.35)	
p-value	0.434	

Abbreviations: OCS, oral corticosteroids; Q4W, every 4 weeks; CI, confidence interval
Source: SOURCE CSR, Table 31
An odds ratio greater than 1 favors tezepelumab. The estimate of the cumulative odds ratio is obtained using a proportional odds model with treatment, region, and daily OCS dose at baseline as covariates.

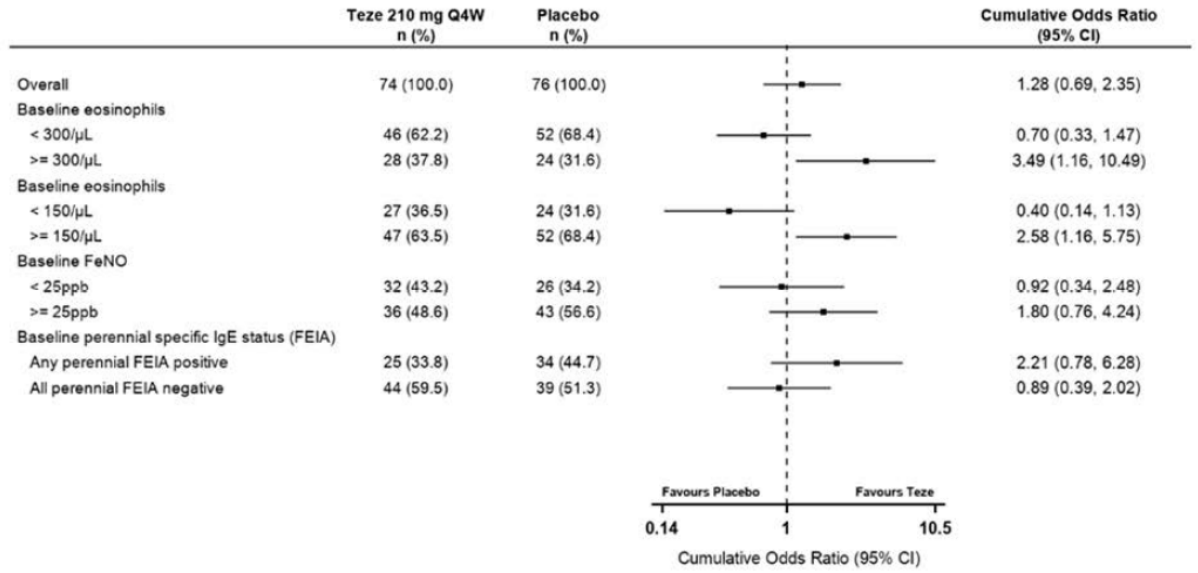
Figure 31 Mean percent change from baseline in daily OCS does over time (Full Analysis Set)



Abbreviations: OCS, oral corticosteroids
95% confidence interval displayed
Source: SOURCE CSR, Figure 5

Results were similar based on planned sensitivity analyses. Subgroup analyses, although pre specified, were difficult to interpret due to the small number of subjects. However, when assessing these subgroups, the odds ratio favored those with higher baseline levels of blood eosinophils (≥150 cells/µL), higher FeNO (≥25 ppb), positive allergic status, lower daily OCS ≤10 mg/day; Figure 32). In subjects with lower levels of eosinophils at baseline (<150 cells/µL), higher daily OCS (>10 mg/day), the odds ratio point estimates favored the placebo group.

Figure 32 Forest Plot by subgroups of proportion of subjects in different categories of reduction from baseline in final daily OCS Dose at Week 48, (Full Analysis Set)



Abbreviations: OCS, oral corticosteroids; Q4W, every 4 weeks; FeNO, fractional exhaled nitrous oxide; CI, confidence interval
Source: SOURCE CSR, Figure 14.2.1.9, Part 1
a proportional odds model with treatment group, region, OCS dose at baseline, subgroup (if not already included) and treatment * subgroup as covariates.

8.1.6.9 Efficacy Results – Secondary and other relevant endpoints

Key secondary variable: Annualized asthma exacerbation rate

AAER vs. Placebo Over 48 Weeks
The reduction in AAER did show a reduction in subjects treated with tezepelumab when compared to placebo, however this was not statistically significant (Table 58). Treatment with tezepelumab reduced the rate of exacerbations by 31% compared with placebo over 48 weeks.

A multiple imputation (annual asthma exacerbation rate) method assessed departures from the underlying assumptions. This sensitivity analysis exploring the effect of missing data on the reliability of the results using multiple imputation did not impact any conclusions.

Rate of asthma exacerbation associated with ER visit, urgent care visit, or hospitalization

The number of exacerbations in this trial that resulted in an ER visit or hospitalization was low overall (Table 58**)**. Subjects taking tezepelumab had a 41% reduction in exacerbations requiring hospitalizations or and ER visit when compared to placebo (rate ratio, 0.59, 95% CI, 0.19, 1.82).

Table 58 SOURCE annual asthma exacerbation rate ratio over 48 weeks, for all events and for those leading to hospitalization or ER visit (Full Analysis Set)

Variable	Teze 210 mg Number of Events N=74	Placebo Number of Events N = 76	Rate Ratio	95% Confidence Interval	p-value
AAER over 48 weeks [1]	78 Crude rate: 1.24	116 Crude rate: 1.82	0.69	0.44, 1.09	0.111
AAER associated with hospitalization or ER visit over 48 weeks [2]	8 Crude rate: 0.12	19 Crude rate: 0.28	0.59	0.19, 1.82	0.361

Abbreviations: ER, emergency room; AAER, annual asthma exacerbation rate

[1]Source: SOURCE CSR, Table 35. The overdispersion parameter is estimated to be 1.16.
[2]Source: SOURCE CSR, Table 37. The overdispersion parameter is estimated to be 3.52.

A negative binomial regression analysis with treatment, region, and history of exacerbations as covariates was used to establish these estimates. The logarithm of the time at risk is used as an offset variable. Crude rate: Number of exacerbation events divided by Total time at-risk (years).

Change from Baseline in Pre-bronchodilator FEV1

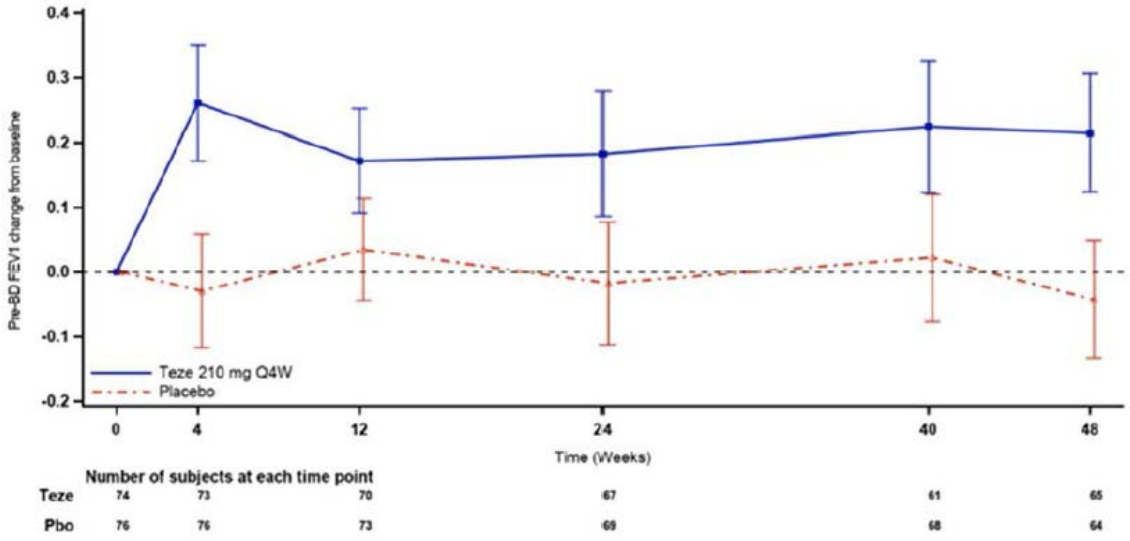
Tezepelumab treatment demonstrated an improvement in pre-BD FEV1 when compared to placebo at Week 48 despite reductions in OCS dose (least mean square changes from baseline were 0.21 L versus -0.04 L for tezepelumab and placebo; LSMean difference 0.26, 95% CI, 0.13, 0.39; Table 59). The onset of improvement was seen at Week 4 and sustained for the duration of the trial. Week 4 was prior to initiation of OCS reduction and therefore demonstrates that tezepelumab effect while the subjects were on stable dose of OCS (Figure 33). Consistent with the primary endpoint, post-hoc analysis of pre-BD FEV1 changes showed that there was a greater magnitude of effect seen in those with higher eosinophils at baseline.

Table 59 SOURCE change from baseline in FEV1 (Full Analysis Set)

Variable	Teze 210 mg (N=74) N, LS Mean, SE	Placebo (N=76) N, LS Mean, SE	LS Mean Difference	95% Confidence Interval
FEV1 (L)	65, 0.21, 0.046	64, -0.04, 0.046	0.26	0.13, 0.39

Abbreviations: FEV1, forced expiratory volume in 1 second, LS mean, least square mean, SE, standard error
Source: SOURCE CSR, Tables 14.2.3.3
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + age + baseline FEV1 + visit + treatment * visit. This analysis includes the full ITT population and a contrast for the week 52 landmark timepoint.

Figure 33 SOURCE LS means and 95% CIs over time for FEV1 change from baseline (Full Analysis Set)



Abbreviations: FEV1, forced expiratory volume in 1 second, LS mean, least square mean, Teze, Tezepelumab; Pbo, placebo
Source: SOURCE CSR, Figure 11
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + baseline FEV1 + visit + treatment * visit.

Reviewer's comment: It is noteworthy that the endpoint of change from baseline to Week 48 in FEV1 had an expected behavior, with those subjects in the higher baseline eosinophil subgroup having a greater response in comparison to those subjects in the lower baseline eosinophil subgroup.

8.1.6.10 Efficacy Results – Secondary or exploratory COA (PRO) endpoints

ACQ-6

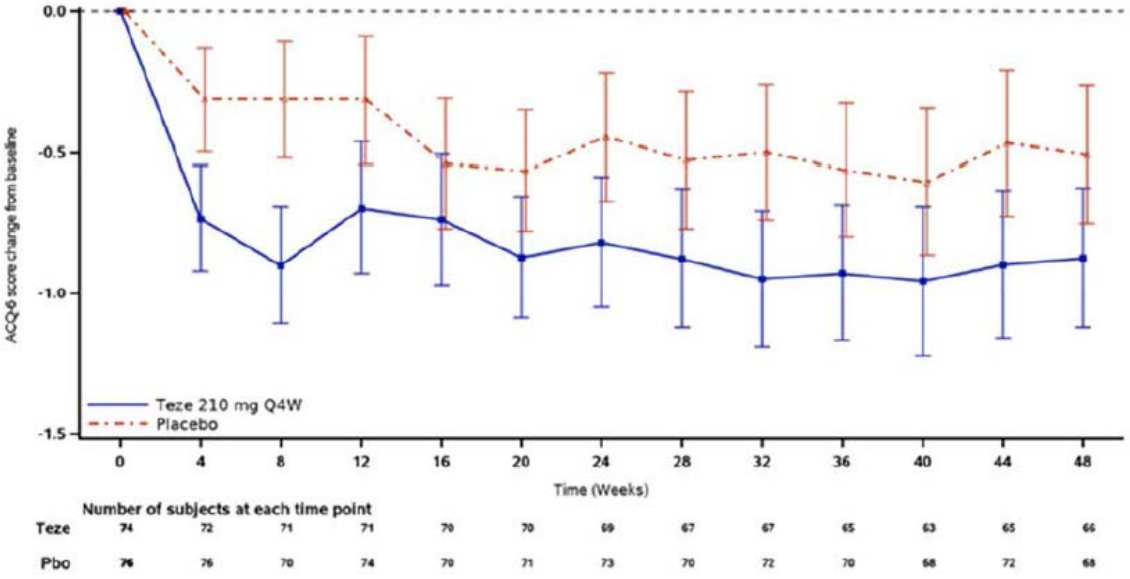
Subjects in both tezepelumab and placebo groups achieve a meaningful change in ACQ6 over time compared with baseline (-0.87 and -0.51 for tezepelumab and placebo at Week 48, respectively, for a treatment difference (95% CI) of -0.37 (-0.71, -0.02); Table 60). The change from baseline means and 95% CIs over time demonstrate an early separation at Weeks 4 and 8 that was not maintained for the duration of the treatment period.

Table 60 SOURCE change from baseline in ACQ-6, AQLQ(S)+12, and ASD scores at Week 48 (Full Analysis Set)

Variable	Teze 210 mg (N=74) N, LS Mean, SE	Placebo (N=76) N, LS Mean, SE	LS Mean Difference	95% Confidence Interval
ACQ-6	66, -0.87, 0.125	68, -0.51, 0.123	-0.37	-0.71, -0.02
AQLQ(S) +12	66, 0.94, 0.124	67, 0.58, 0.123	0.36	0.01, 0.70
Asthma Symptom Diary	58, -0.36, 0.071	68, -0.26, 0.068	-0.10	-0.29, 0.09

Abbreviations: ACQ-6, Asthma Control Questionnaire, omitting forced expiratory volume in one second; AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardized) for 12 years and older; ASD, asthma symptom diary; , Teze, Tezepelumab; LS mean, least square mean, SE, standard error
Source: SOURCE CSR, Tables 14.2.5.2, 14.2.4.2, 14.2.7.2
Estimate of the mean change from baseline at each week in Tezepelumab is compared to the Placebo using a repeated measures analysis. Estimates are least squares means. The model with Unstructured covariance structure is: Change from baseline in FEV1 = Treatment group + region + age + baseline FEV1 + visit + treatment * visit. This analysis includes the full ITT population and a contrast for the week 52 landmark timepoint.

Figure 34 SOURCE Adjusted means and 95% CIs over time for ACQ-6 score change from baseline (Full Analysis Set)

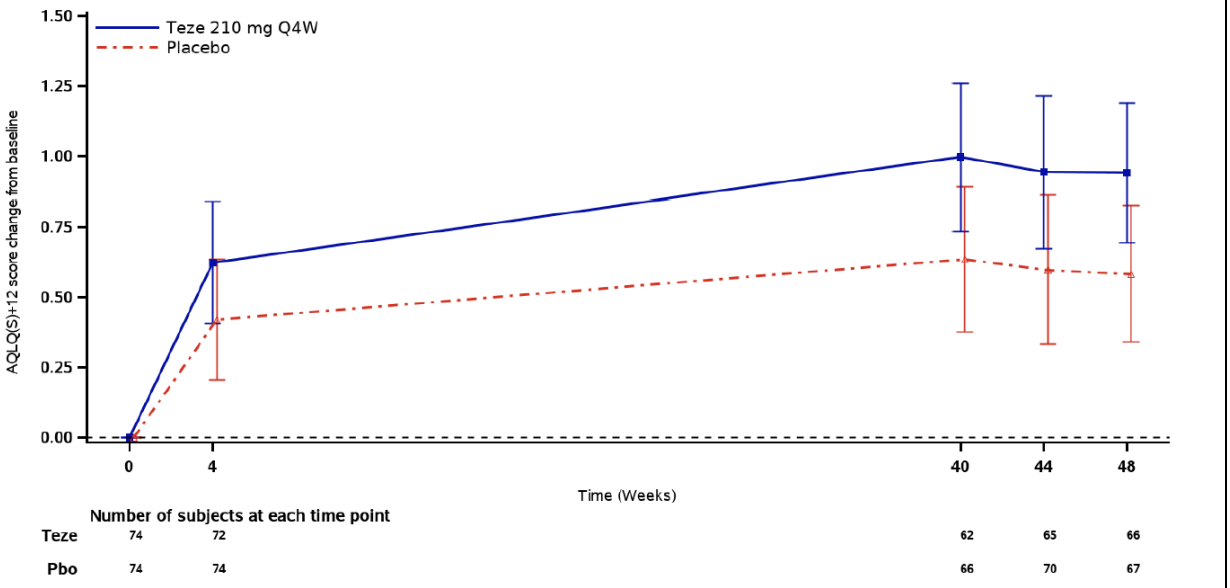


Abbreviations: ACQ-6, Asthma Control Questionnaire, omitting forced expiratory volume in one second; Teze, Tezepelumab; Pbo, placebo
Source: SOURCE CSR, Figure 16
The model with Unstructured covariance structure is: Change from baseline in ACQ-6 = Treatment group + region + baseline ACQ-6 + visit + treatment * visit.

AQLQ(S)+12

Subjects in both the tezepelumab and placebo groups achieved a clinically meaningful change in AQLQ1(S)+12 over time compared with baseline (total score LSMean change at Week 48 was 0.94 and 0.58 for tezepelumab and placebo, for a treatment difference (95% CI) of 0.36 (0.01, 0.70)). However, the change from baseline means and 95% CIs over time (Figure 35), demonstrate a lack of treatment separation throughout the entire course of the treatment period.

Figure 35 SOURCE adjusted means and 95% CIS over time for AQLQ(S)+12 total score change from baseline (Full Analysis Set)

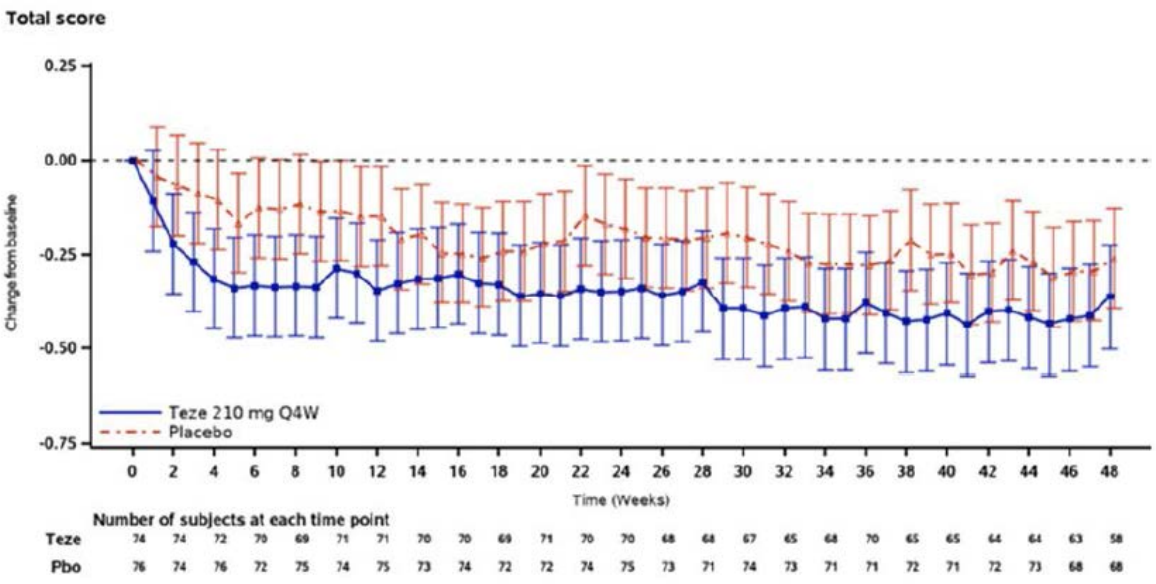


Abbreviations: AQLQ(S)+12, Asthma Quality of Life Questionnaire (Standardized) for 12 years and older; Teze, Tezepelumab; Pbo, placebo
95% confidence intervals displayed
Source: SOURCE CSR, Figure 14.2.4.1
The model with Unstructured covariance structure is: Change from baseline in AQLQ(S)+12 = Treatment group + region + baseline AQLQ(S)+12 + visit + treatment * visit.

Asthma Symptom Diary Score

Subjects in both the tezepelumab and placebo groups achieved a clinically meaningful change in ASD over time compared with baseline (total score LSMean change at Week 48 was -0.36 and -0.26 for tezepelumab and placebo, for a treatment difference (95% CI) of -0.10 -0.29, 0.09)). The change from baseline means and 95% CIs over time (Figure 36), demonstrate a lack of treatment separation throughout the entire course of the treatment period.

Figure 36 SOURCE adjusted means and 95% CI over time for asthma symptom diary score change from baseline (Full Analysis Set)



Abbreviations: Teze, Tezepelumab; Pbo, placebo
95% confidence intervals displayed
Source: SOURCE CSR, Figure 14.2.7.1
The model with Compound symmetry covariance structure is: Change from baseline in Asthma Symptom Diary score = Treatment group + region + baseline Asthma Score + week + treatment * week.

8.1.6.11 Summary of SOURCE Effectiveness

This phase 3 trial did not meet statistical significance for its primary endpoint, the percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control. This was an unexpected outcome given the efficacy demonstrated in both the NAVIGATOR and PATHWAY trials. Although this OCS sparing trial is a smaller trial compared with NAVIGATOR and PATHWAY, the trial enrolled a similar number of subjects when compared to OCS reduction trials with other asthma biologics. The trial design was similar to the other OCS sparing trials, however, there are some notable differences. First, the overall trial length was longer. The OCS reduction phase was longer (8 weeks vs 4 weeks) to allow more subjects to reduce daily OCS dose to zero mg. The more aggressive titration to establish the baseline OCS dose may have led to fewer subjects showing a reduction during the maintenance phase. The maintenance phase was also longer (48 weeks versus 24-28 weeks) to evaluate the sustainability of the treatment effect. The longer maintenance phase may have allowed more time for subjects on placebo to titrate their OCS within the protections of a clinical trial supporting clinical care. Second, the SOURCE trial design also allowed investigators to titrate down OCS even if subjects did not meet criteria, but investigators would need to provide an explanation in the CRF. The more aggressive approach to OCS titration may have decreased the difference between treatment and placebo.

The population enrolled could also have potentially had an effect. In a post hoc analysis, the Applicant relayed that a nominally significant reduction was seen in the tezepelumab treated subjects who had baseline eosinophils ≥150 cells/µL The magnitude of effect was greater in subjects in the ≥ 300 cells/uL eosinophil group. In subjects with < 150 cells/ul, the point estimate for the primary endpoint favored placebo. However, making conclusions based on eosinophil subgroups in a patient population that is OCS dependent is challenging as OCS use can affect eosinophils. Also, other OCS sparing trials for products approved for asthma with an eosinophilic phenotype did not enrich for a higher eosinophilic population and were able to demonstrate efficacy. Conclusions based on these subgroups is also uncertain due to the small sample sizes.

A limitation of use statement was not included in the label. Limitations of use identify a particular patient population in which a drug should generally not be used. The above failed OCS sparing trial (SOURCE) does not support a limitation of use for subjects on maintenance OCS. Although the results did not meet statistical significance, the trends favored tezepelumab for the primary endpoint, the percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control. The point estimate also favored tezepelumab for reduction of AAER and improvement in change from baseline in FEV1 at Week 48 despite subjects reducing their maintenance OCS dose. Subgroup analyses for subjects on maintenance OCS in NAVIGATOR further supports the efficacy trends noted in SOURCE. Based on these results, efficacy was supported for subjects on maintenance OCS.

8.1.7. Assessment of Efficacy Across Trials

No efficacy assessments were integrated across trials. See individual trial results. A summary of the efficacy primary endpoints for the two pivotal trials can be seen in Table 61.

Table 61 Efficacy primary endpoint summary for NAVIGATOR and PATHWAY

Variable	Teze 210 mg N	Placebo N	Rate Ratio	Confidence Interval
NAVIGATOR: AAER over 52 weeks using primary analysis	528	531	0.44	95%: (0.37, 0.53) 99% (0.34, 0.57)
Navigator: AAER over 52 weeks in subjects with baseline eosinophils < 300	309	309	0.58	95% (0.45, 0.75)

cells/µL				
PATHWAY: AAER over 52 weeks using primary analysis	137	138	0.29	95% (0.20, 0.58)

Abbreviations: Teze, Tezepelumab; AAER annual asthma exacerbation rate
Source: Table 29 and Table 45 of this review

8.1.8. Integrated Assessment of Effectiveness

Substantial evidence effectiveness was demonstrated for tezepelumab for the add-on maintenance treatment of severe asthma in subjects ≥12 years of age based on two adequate and well-controlled trials. The 1-year dose-ranging trial (PATHWAY) and 1-year efficacy trial (NAVIGATOR) demonstrated a statistically significant difference in their primary endpoint, the AAER. Clinically significant change in AAER compared to placebo was seen across baseline eosinophil levels, with larger treatment differences compared to placebo in the higher baseline eosinophils level. These efficacy trends were also demonstrated regardless of baseline FeNO (a related biomarker). Effectiveness was further supported by an improvement in the change from baseline in FEV1, decreased annualized rate of exacerbations associated with emergency room visits or hospitalizations, increased time to first exacerbation, and favorable AQLQ(6)+12 and ACQ-6 responder rates compared to placebo.

Although the adolescent subgroup was not powered to demonstrate statistical significance, numerical and clinically meaningful reductions in asthma exacerbations along with improvement in lung function compared to placebo were demonstrated in NAVIGATOR. Partial extrapolation of efficacy is supported as adolescents have the same pathophysiology for asthmatics and there were no age-related differences in the pharmacokinetics (PK).

The oral steroid reduction study (SOURCE) failed to meet its primary endpoint of the percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control, although the point estimates favored tezepelumab for the primary endpoint, reduction of AAER and improvement in change from baseline in FEV1 at Week 48 despite subjects reducing their maintenance OCS dose. Subgroup analyses for subjects on maintenance OCS in NAVIGATOR further supports the efficacy trends noted in SOURCE. Based on these results, a limitation of use for subjects on maintenance OCS is not supported.

Given that tezepelumab is the first biologic for asthma to demonstrate efficacy across the spectrum of baseline eosinophil level in the subjects with severe asthma, tezepelumab meets an unmet medical need for patients with severe asthma without an eosinophilic phenotype. It is the first product available with substantial evidence of effectiveness in this population.

8.2. Review of Safety

8.2.1. Safety Review Approach

This safety review begins with review of the PATHWAY trial to assess for potential dose related safety signals. The main review for safety focuses on the pooled safety data containing the two 52 week trials, PATHWAY and NAVIGATOR. These trials were pooled together due to similar patient population, study design and duration. The OCS-sparing trial, SOURCE, was not pooled for safety given the different trial population and is assessed separately in the supplementary safety analysis in 8.2.8.1 SOURCE Trial.

8.2.2. Review of Dose Related Safety (PATHWAY)

8.2.2.1 Extent of Exposure

The majority of subjects received all 26 planned doses of the investigational product (70% in the placebo group, and 73%, 70%, and 57% in the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups). The mean total tezepelumab exposures increased across the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W dose groups (See Table 62).

Table 62. Total Tezepelumab Exposure, As-Treated Population

Total Exposure (mg)	Tezepelumab		
	70 mg Q4W N=138	210 mg Q4W N=137	280 mg Q2W N=137
N	138	137	137
Mean	877.0	2493.9	6574.9
SD	116.9	640.4	1630.2
Median	910.0	2730.0	7280.0
(Min, Max)	(70, 910)	(210, 2730)	(560, 7280)

Max = maximum; Min = minimum; N = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks;
SD = standard deviation.
Source: CSR Section 14, Table 14.3.1_1.2.

8.2.2.2 Overview of Adverse Events in PATHWAY Trial

This dose range finding trial assessed three doses of tezepelumab: 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W. The final dose to be marketed and carried forward in the phase 3 trials, NAVIGATOR and SOURCE, was the 210 mg Q4W dose. Overall, the incidence of adverse events was similar between the three tezepelumab groups and placebo group (Table 63). There was no dose dependent safety signal detected in the PATHWAY Trial.

Table 63. Overview of Adverse Events, Safety Population, Trial Pathway (All dosage)

Event Category	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Placebo N=138 n (%)
SAE	17 (12)	13 (10)	18 (13)	18 (13)
SAEs with fatal outcome	1 (1)	0	0	0
Life-threatening SAEs	0	0	0	0
AE leading to permanent discontinuation of study drug	0	2 (2)	3 (2)	1 (1)
AE leading to dose modification of study drug	14 (10)	11 (8)	13 (10)	15 (11)
AE leading to interruption of study drug	0	1 (1)	0	0
AE leading to dose delay of study drug	14 (10)	10 (7)	13 (10)	15 (11)
Other	0	0	0	0
AE	93 (67)	90 (66)	89 (65)	91 (66)
Death	1 (1)	0	0	0
Life-threatening	0	0	0	0
Severe	16 (12)	13 (10)	18 (13)	18 (13)
Moderate	0	0	0	0
Mild	0	0	0	0

Source: adae.xpt; Software: R
Adverse events defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; Q2W = every 2 weeks; Q4W = every 4 weeks.

8.2.2.3 Serious Adverse Events in PATHWAY trial

The SAEs for the PATHWAY trial are summarized in Table 64. SAEs were generally equal across all treatment arms. The most commonly reported SAEs were in the Respiratory, Thoracic and Mediastinal SOC, Infections and Infestations SOC, and Injury, Poisoning and Procedural SOC.

Two SAEs occurred in more than one subject (pneumonia and asthma). Based on PT terms, there were no SAEs >1 in tezepelumab treatment groups when compared to placebo group.

Table 64. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial Pathway (All dosage)

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Any SAE	23 (16)	19 (14)	24 (18)	66 (16)	21 (15)
Cardiac disorders (SOC)	2 (1)	1 (1)	0	3 (1)	2 (1)
Atrial flutter	1 (1)	0	0	1 (<1)	0
Cardiac failure	0	1 (1)	0	1 (<1)	1 (1)
Myocardial infarction	1 (1)	0	0	1 (<1)	0
Atrial fibrillation	0	0	0	0	1 (1)
Gastrointestinal disorders (SOC)	1 (1)	0	3 (2)	4 (1)	1 (1)
Abdominal pain	1 (1)	0	0	1 (<1)	0
Hiatus hernia	0	0	1 (1)	1 (<1)	0
Large intestine polyp	0	0	1 (1)	1 (<1)	0
Pancreatitis acute	0	0	1 (1)	1 (<1)	0
Abdominal pain lower	0	0	0	0	1 (1)
General disorders and administration site conditions (SOC)	0	1 (1)	0	1 (<1)	1 (1)
Non-cardiac chest pain	0	1 (1)	0	1 (<1)	1 (1)
Hepatobiliary disorders (SOC)	0	0	1 (1)	1 (<1)	0
Cholelithiasis	0	0	1 (1)	1 (<1)	0
Immune system disorders (SOC)	0	0	1 (1)	1 (<1)	0
Anaphylactic shock	0	0	1 (1)	1 (<1)	0

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Infections and infestations (SOC)	6 (4)	1 (1)	4 (3)	11 (3)	4 (3)
Staphylococcal infection	0	1 (1)	0	1 (<1)	0
Viral infection	0	1 (1)	0	1 (<1)	0
Bronchitis	1 (1)	0	0	1 (<1)	0
Erysipelas	0	0	1 (1)	1 (<1)	0
Genitourinary tract infection	0	0	1 (1)	1 (<1)	0
Influenza	1 (1)	0	0	1 (<1)	0
Pyelonephritis chronic	1 (1)	0	0	1 (<1)	0
Urinary tract infection	1 (1)	0	0	1 (<1)	0
Cellulitis	0	0	0	0	1 (1)
Chronic sinusitis	1 (1)	0	0	1 (<1)	1 (1)
Pneumonia	3 (2)	0	2 (2)	5 (1)	1 (1)
Sinusitis	0	0	0	0	1 (1)
Tooth abscess	0	0	0	0	1 (1)
Injury, poisoning and procedural complications (SOC)	2 (1)	2 (2)	2 (2)	6 (2)	0
Cartilage injury	0	1 (1)	0	1 (<1)	0
Foreign body aspiration	0	1 (1)	0	1 (<1)	0
Ligament sprain	0	1 (1)	0	1 (<1)	0
Concussion	0	0	1 (1)	1 (<1)	0
Lower limb fracture	1 (1)	0	0	1 (<1)	0
Lumbar vertebral fracture	0	0	1 (1)	1 (<1)	0
Post procedural complication	1 (1)	0	0	1 (<1)	0
Upper limb fracture	1 (1)	0	0	1 (<1)	0

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Musculoskeletal and connective tissue disorders (SOC)	0	3 (2)	1 (1)	4 (1)	1 (1)
Intervertebral disc protrusion	0	1 (1)	0	1 (<1)	0
Rhabdomyolysis	0	1 (1)	0	1 (<1)	0
Osteoarthritis	0	1 (1)	0	1 (<1)	1 (1)
Osteochondrosis	0	0	1 (1)	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	3 (2)	2 (2)	5 (1)	1 (1)
Basal cell carcinoma	0	1 (1)	0	1 (<1)	0
Pancreatic carcinoma metastatic	0	1 (1)	0	1 (<1)	0
Prostate cancer	0	1 (1)	0	1 (<1)	0
Adenocarcinoma of colon	0	0	1 (1)	1 (<1)	0
Lipoma	0	0	1 (1)	1 (<1)	0
Prostate cancer stage I	0	0	0	0	1 (1)
Nervous system disorders (SOC)	2 (1)	2 (2)	0	4 (1)	0
Cervicobrachial syndrome	0	1 (1)	0	1 (<1)	0
Guillain-Barre syndrome	0	1 (1)	0	1 (<1)	0
Cerebrovascular accident	1 (1)	0	0	1 (<1)	0
Sciatica	1 (1)	0	0	1 (<1)	0

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Pregnancy, puerperium and perinatal conditions (SOC)	0	1 (1)	1 (1)	2 (1)	0
Abortion threatened	0	1 (1)	1 (1)	2 (1)	0
Hyperemesis gravidarum	0	1 (1)	0	1 (<1)	0
Renal and urinary disorders (SOC)	1 (1)	0	0	1 (<1)	0
Calculus urinary	1 (1)	0	0	1 (<1)	0
Reproductive system and breast disorders (SOC)	1 (1)	0	2 (2)	3 (1)	0
Cervical leukoplakia	0	0	1 (1)	1 (<1)	0
Ovarian cyst	0	0	1 (1)	1 (<1)	0
Testicular pain	1 (1)	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders (SOC)	6 (4)	4 (3)	6 (4)	16 (4)	10 (7)
Pulmonary embolism	1 (1)	0	0	1 (<1)	0
Asthma	5 (4)	4 (3)	6 (4)	15 (4)	10 (7)
Skin and subcutaneous tissue disorders (SOC)	1 (1)	0	0	1 (<1)	1 (1)
Dermatitis contact	1 (1)	0	0	1 (<1)	0
Dermatitis atopic	0	0	0	0	1 (1)

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Vascular disorders (SOC)	1 (1)	1 (1)	1 (1)	3 (1)	0
Deep vein thrombosis	1 (1)	1 (1)	0	2 (1)	0
Hypertensive crisis	0	0	1 (1)	1 (<1)	0

Source: adae.xpt; Software: R
Adverse events defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date. Duration is 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; Q2W = every 2 weeks; Q4W = every 4 weeks.

8.2.2.4 Deaths

There was one death in the 70 mg Q4W tezepelumab arm. This death is not included in the pooled safety database as it occurred in the 70 mg Q4W dosing arm. The subject was a 74 year old female with severe asthma, hypertension, and hypertensive encephalopathy. Sixty seven days after the last active dose, the subject experienced a cerebrovascular accident that was fatal. Postmortem diagnosis of cerebral infarction was made by the doctor in the ambulance based on history of significant weakness, loss of orientation and speech difficulties from family history. No autopsy was performed. Prior to this event, the subject also had adverse events of neutropenia, leukopenia, and thrombocytopenia starting on Day 30 of the last active dose. It's unclear whether this death was drug related; however given the subjects previous history of hypertensive encephalopathy it's possible that the death was due to her underlying disease. Although continued pharmacovigilance should be continued, there is insufficient evidence to support including this event in labeling.

8.2.2.5 Adverse Events Leading to Discontinuation

There were only six adverse events that led to discontinuation. Based on PT terms, there was no imbalance in adverse events leading to discontinuation when comparing tezepelumab treatment arms and placebo. There was no AE that had >1 event. There was one event of Guillan Barre in the tezepelumab 210 mg Q4W dose. This is discussed in detail in the AESI section of the main safety database review below.

Table 65. Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial Pathway (All dosage)

System Organ Class Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Gastrointestinal disorders (SOC)	0	0	2 (2)	2 (1)	0
Abdominal pain upper	0	0	1 (1)	1 (<1)	0
Tongue oedema	0	0	1 (1)	1 (<1)	0
Investigations (SOC)	0	1 (1)	0	1 (<1)	0
Hepatic enzyme increased	0	1 (1)	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	1 (1)	1 (<1)	1 (1)
Adenocarcinoma of colon	0	0	1 (1)	1 (<1)	0
Prostate cancer stage I	0	0	0	0	1 (1)
Nervous system disorders (SOC)	0	1 (1)	0	1 (<1)	0
Guillain-Barre syndrome	0	1 (1)	0	1 (<1)	0

Source: adae.xpt; Software: R
Adverse events defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; Q2W = every 2 weeks; Q4W = every 4 weeks.

8.2.2.6 Common Adverse Events

The number of adverse events were balanced across treatment arms. The most frequently reported AE by preferred term were asthma, nasopharyngitis, bronchitis, and headache (Table 66). In terms of overall percentage, headache, nasopharyngitis, rhinitis, tracheitis were slightly higher when comparing all of the tezepelumab treated groups compared to placebo, however only slightly at 1-2% higher than placebo. However, none of these AEs appeared treatment dose related. Arthralgia was noted to occur more frequently as treatment dose increased (tezepelumab 70 mg Q4W, 2 events; 210 mg Q4W 5 events; 280 mg Q2W 7 events; placebo, 5 events). This may be a dose related event, however, it is difficult to truly determine given the small sample size. Arthralgia was noted to occur more frequently in the tezepelumab treatment arm compared to placebo in the NAVIGATOR trial and is listed in Section 6 in the label. Asthma occurred at a greater frequency in the placebo group compared to the tezepelumab groups which was expected given the efficacy results.

Table 66. Common Adverse Events Occurring at ≥3% Frequency, Safety Population, Trial PATHWAY (All dosage)

Preferred Term	Tezepelumab 70 mg Q4W N=138 n (%)	Tezepelumab 210 mg Q4W N=137 n (%)	Tezepelumab 280 mg Q2W N=137 n (%)	Tezepelumab Total N=412 n (%)	Placebo N=138 n (%)
Any AE	93 (67)	90 (66)	89 (65)	272 (66)	91 (66)
Headache	6 (4)	11 (8)	5 (4)	22 (5)	6 (4)
Nasopharyngitis	19 (14)	19 (14)	15 (11)	53 (13)	16 (12)
Rhinitis	11 (8)	4 (3)	3 (2)	18 (4)	2 (1)
Influenza	5 (4)	5 (4)	1 (1)	11 (3)	4 (3)
Arthralgia	2 (1)	5 (4)	7 (5)	14 (3)	5 (4)
Tracheitis	1 (1)	1 (1)	5 (4)	7 (2)	1 (1)
Cough	5 (4)	3 (2)	2 (2)	10 (2)	4 (3)
Respiratory tract infection	5 (4)	5 (4)	6 (4)	16 (4)	6 (4)
Sinusitis	0 (0)	4 (3)	3 (2)	7 (2)	5 (4)
Upper respiratory tract infection	4 (3)	4 (3)	4 (3)	12 (3)	5 (4)
Back pain	5 (4)	3 (2)	5 (4)	13 (3)	5 (4)
Bronchitis	8 (6)	5 (4)	9 (7)	22 (5)	7 (5)
Hypertension	7 (5)	5 (4)	6 (4)	18 (4)	7 (5)
Rhinitis allergic	1 (1)	2 (2)	0	3 (1)	5 (4)
Diarrhea	3 (2)	1 (1)	2 (2)	6 (2)	5 (4)
Viral infection	4 (3)	1 (1)	6 (4)	11 (3)	5 (4)
Asthma	35 (25)	27 (20)	38 (28)	100 (24)	50 (36)

Source: adae.xpt; Software: R
Duration is 64 weeks (on-study period).
Adverse events defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Coded as MedDRA preferred terms.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event.

8.2.2.7 Adverse Events of Special Interest

For this trial, adverse events of special interest included helminth infections, serious infections, injection site reactions, anaphylactic reactions, hypersensitivity reactions, and malignancies. One subject in the 280 mg Q2W tezepelumab group with known peanut allergy did experience an anaphylactic reaction due to accidental ingestion of peanut containing food. There were no instances of helminth infections identified in this trial. The incidence of SAES in the Infections and Infestations SOC were similar between tezepelumab and placebo groups. The AEs in the Neoplasm SOC occurred at a similar proportion between treatment group. For further discussion of AESI, see review of pooled safety database below.

8.2.3. Review of the Pooled Safety Database

8.2.3.1 Overall Exposure

The overall exposure for the tezepelumab program is summarized in Table 67. The exposure was balanced across treatment groups for both trials. A total of 620 (93%) were subjects treated with tezepelumab for at least 44 weeks and 431 (65%) subjects were treated with tezepelumab for at least 52 weeks.

Table 67. Duration of Exposure, Primary Safety Population (NAVIGATOR and PATHWAY)

	Tezepelumab 210 mg Q4W N=665	Placebo N=669
Duration of exposure, weeks		
Mean (SD)	50 (10)	49 (10.1)
Median (Q1, Q3)	52 (50, 53)	52 (50, 52)
Min, Max	0, 58	3, 57
Total exposure (person years)	631	626
Patients treated, by duration, n (%)		
<4 weeks	7 (1)	1 (<1)
≥4 to <8 weeks	5 (1)	6 (1)
≥8 to <12 weeks	4 (1)	9 (1)
≥12 to <16 weeks	4 (1)	9 (1)
≥16 to <20 weeks	11 (2)	13 (2)
≥20 to <24 weeks	4 (1)	6 (1)
≥24 to <28 weeks	1 (<1)	3 (0)
≥28 to <36 weeks	4 (1)	7 (1)
≥36 to <44 weeks	5 (1)	4 (1)
≥44 to <52 weeks	189 (28)	197 (29)
≥52 to <60 weeks	431 (65)	414 (62)

Source: adex.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, every 4 weeks; SD, standard deviation.

8.2.3.2 Adequacy of the safety database

Overall, the safety database is of sufficient size and duration for severe asthma to assess the safety of the proposed doses of tezepelumab.

8.2.4. Adequacy of Applicant's Clinical Safety Assessments

8.2.4.1 Issues Regarding Data Integrity and Submission Quality

See Section 4.1 for overview of data integrity and submission quality.

8.2.4.2 Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols. AEs were captured from signing of informed consent through the final follow up visit. Treatment emergent adverse events were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using the MedDRA dictionary version 23.1. The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. Adverse events of special interest included anaphylactic reactions, hypersensitivity, injection-site reaction, severe infection, parasitic infection, opportunistic infection, malignancy, and Guillain-Barre syndrome. The Applicant analyzed Standardized MedDRA Queries (SMQs) during their analysis.

8.2.5. Safety Results

8.2.5.1 Overview

An overview of the adverse events in the primary safety pool can be found in Table 68.

Table 68. Overview of Adverse Events, Primary Safety Population (NAVIGATOR and PATHWAY)

Event Category	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Total-Risk Difference Between Teze and Placebo (95% CI)
SAE	65 (10)	91 (14)	-3.8 (-7.3, -0.4)
SAEs with fatal outcome	0	2 (<1)	-0.3 (-0.7, 0.1)
Life-threatening SAEs	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	13 (2)	20 (3)	-1.0 (-2.7, 0.6)
AE leading to dose modification of study drug	34 (5)	43 (6)	-1.3 (-3.8, 1.2)
AE leading to interruption of study drug	24 (4)	28 (4)	-0.6 (-2.7, 1.5)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	10 (2)	15 (2)	-0.7 (-2.2, 0.7)
Other	0	0	0 (0, 0)

Event Category	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Total-Risk Difference Between Teze and Placebo (95% CI)
AE	497 (75)	520 (78)	-3.0 (-7.6, 1.6)
Death	0	2 (<1)	-0.3 (-0.7, 0.1)
Life-threatening	0	0	0 (0, 0)
Severe	53 (8)	79 (13)	-3.8 (-7.0, -0.6)
Moderate	238 (36)	246 (37)	-1.0 (-6.1, 4.2)
Mild	129 (19)	120 (18)	1.5 (-2.7, 5.6)

Source: adae.xpt; Software: R
AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration is 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; Q4W, every 4 weeks; SAE, serious adverse event; Teze, Tezepelumab.

8.2.5.2 Deaths

There were no deaths in the tezepelumab 210 mg Q4W or placebo groups in the on-treatment period of the Primary Safety Pool. However, two deaths secondary to cardiac failure occurred in the placebo group of the NAVIGATOR study in the on-treatment period (Refer to Table 69). As discussed in the PATHWAY safety section, a death secondary to cerebrovascular accident also occurred in the tezepelumab 70 mg Q4W group of PATHWAY during the on-study period (67 days after last active dose); this death is not included in the Primary Safety Pool summaries because the pool comprises AE data for the tezepelumab 210 mg dose group and placebo group only.

Table 69. Deaths, Primary Safety Population (NAVIGATOR and PATHWAY)

Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Any AE leading to death	0	2 (<1)	-0.3 (-0.7, 0.1)
Cardiac failure	0	1 (<1)	-0.1 (-0.4, 0.1)
Death	0	1 (<1)	-0.1 (-0.4, 0.1)

Source: adae.xpt; Software: R
AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration is 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every 4 weeks; Teze, Tezepelumab.

8.2.5.3 Serious Adverse Events

Serious adverse events are summarized in Table 70. The SAE SOCs that occurred in more than one subject in the tezepelumab treatment arm and greater than the placebo arm includes the cardiac disorders SOC, injury, poisoning and procedural complications SOC, and musculoskeletal and connective tissue disorders SOC. After reviewing the individual PT terms along with the accompanying narratives of each SAE, the imbalance of the above SOCs does not appear to reflect a true imbalance.

In terms of the cardiac SOC, the only PT term with greater than 1 event was cardiac failure congestive. The Applicant also performed a MACE evaluation on the cardiac events in the NAVIGATOR and SOURCE trials. In NAVIGATOR, one subject in the tezepelumab group reported 2 AEs and 5 subjects in the placebo group reported 6 AEs, that were submitted to the MACE committee for blinded adjudication. One event in each group was adjudicated as MACE.

For the injury, poisoning and procedural SOC the imbalance appears to be driven by events of ligament rupture and sprain with each PT term having 2 events in the tezepelumab group for each term and 0 events in the placebo group. Review of the narratives showed that these events were explained by accidents (i.e., skiing, slipping by pool). Review of the PT terms that produced the imbalance in the musculoskeletal and connective tissue SOC did not appear to be drug-related and there were no events greater than one in each PT term.

Table 70. Serious Adverse Events by System Organ Class and Preferred Term, Primary Safety Population (NAVIGATOR and PATHWAY)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Cardiac disorders (SOC)	6 (1)	3 (<1)	0.5 (-0.4, 1.3)
Cardiac failure congestive	2 (<1)	0	0.3 (-0.1, 0.7)
Aortic valve stenosis	1 (<1)	0	0.2 (-0.1, 0.4)
Coronary artery disease	1 (<1)	0	0.2 (-0.1, 0.4)
Coronary artery occlusion	1 (<1)	0	0.2 (-0.1, 0.4)
Ventricular extrasystoles	1 (<1)	0	0.2 (-0.1, 0.4)
Atrial fibrillation	0	1 (<1)	-0.1 (-0.4, 0.1)
Cardiac failure	1 (<1)	2 (<1)	-0.1 (-0.7, 0.4)
Congenital, familial and genetic disorders (SOC)	0	1 (<1)	-0.1 (-0.4, 0.1)
Hypertrophic cardiomyopathy	0	1 (<1)	-0.1 (-0.4, 0.1)
Ear and labyrinth disorders (SOC)	0	1 (<1)	-0.1 (-0.4, 0.1)
Vertigo positional	0	1 (<1)	-0.1 (-0.4, 0.1)
Eye disorders (SOC)	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Cataract	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Uveitis	0	1 (<1)	-0.1 (-0.4, 0.1)
Gastrointestinal disorders (SOC)	4 (1)	6 (1)	-0.3 (-1.2, 0.6)
Colitis	1 (<1)	0	0.2 (-0.1, 0.4)
Diverticular perforation	1 (<1)	0	0.2 (-0.1, 0.4)
Obstruction gastric	1 (<1)	0	0.2 (-0.1, 0.4)
Rectal haemorrhage	1 (<1)	0	0.2 (-0.1, 0.4)
Umbilical hernia	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Abdominal pain lower	0	1 (<1)	-0.1 (-0.4, 0.1)
Colitis ischaemic	0	1 (<1)	-0.1 (-0.4, 0.1)
Inguinal hernia	0	1 (<1)	-0.1 (-0.4, 0.1)
Oesophageal achalasia	0	1 (<1)	-0.1 (-0.4, 0.1)
Pancreatitis acute	0	1 (<1)	-0.1 (-0.4, 0.1)
Pancreatitis necrotising	0	1 (<1)	-0.1 (-0.4, 0.1)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
General disorders and administration site conditions (SOC)	2 (<1)	2 (<1)	0.0 (-0.6, 0.6)
Non-cardiac chest pain	2 (<1)	1 (<1)	0.2 (-0.4, 0.7)
Death	0	1 (<1)	-0.1 (-0.4, 0.1)
Hepatobiliary disorders (SOC)	1 (<1)	2 (<1)	-0.1 (-0.7, 0.4)
Cholelithiasis	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Cholecystitis chronic	0	1 (<1)	-0.1 (-0.4, 0.1)
Immune system disorders (SOC)	0	1 (<1)	-0.1 (-0.4, 0.1)
Anaphylactic reaction	0	1 (<1)	-0.1 (-0.4, 0.1)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Infections and infestations (SOC)	14 (2)	17 (3)	-0.4 (-2.1, 1.2)
Anal abscess	1 (<1)	0	0.2 (-0.1, 0.4)
Atypical pneumonia	1 (<1)	0	0.2 (-0.1, 0.4)
Breast abscess	1 (<1)	0	0.2 (-0.1, 0.4)
COVID-19	1 (<1)	0	0.2 (-0.1, 0.4)
Gastroenteritis salmonella	1 (<1)	0	0.2 (-0.1, 0.4)
Gastroenteritis viral	1 (<1)	0	0.2 (-0.1, 0.4)
Herpes zoster oticus	1 (<1)	0	0.2 (-0.1, 0.4)
Influenza	1 (<1)	0	0.2 (-0.1, 0.4)
Osteomyelitis	1 (<1)	0	0.2 (-0.1, 0.4)
Staphylococcal infection	1 (<1)	0	0.2 (-0.1, 0.4)
Upper respiratory tract infection	1 (<1)	0	0.2 (-0.1, 0.4)
Viral infection	1 (<1)	0	0.2 (-0.1, 0.4)
Diverticulitis	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Pneumonia bacterial	2 (<1)	2 (<1)	0.0 (-0.6, 0.6)
Chronic sinusitis	0	1 (<1)	-0.1 (-0.4, 0.1)
Lower respiratory tract infection	0	1 (<1)	-0.1 (-0.4, 0.1)
Lung abscess	0	1 (<1)	-0.1 (-0.4, 0.1)
Pneumonia	1 (<1)	2 (<1)	-0.1 (-0.7, 0.4)
Pneumonia klebsiella	0	1 (<1)	-0.1 (-0.4, 0.1)
Pneumonia streptococcal	0	1 (<1)	-0.1 (-0.4, 0.1)
Pneumonia viral	0	1 (<1)	-0.1 (-0.4, 0.1)
Septic shock	0	1 (<1)	-0.1 (-0.4, 0.1)
Sinusitis	0	1 (<1)	-0.1 (-0.4, 0.1)
Tooth abscess	0	1 (<1)	-0.1 (-0.4, 0.1)
Viral upper respiratory tract infection	0	1 (<1)	-0.1 (-0.4, 0.1)
Gastroenteritis	0	2 (<1)	-0.3 (-0.7, 0.1)
Lower respiratory tract infection bacterial	0	2 (<1)	-0.3 (-0.7, 0.1)
Cellulitis	0	3 (<1)	-0.4 (-1.0, 0.1)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Injury, poisoning and procedural complications (SOC)	9 (1)	4 (1)	0.8 (-0.3, 1.8)
Ligament rupture	2 (<1)	0	0.3 (-0.1, 0.7)
Ligament sprain	2 (<1)	0	0.3 (-0.1, 0.7)
Cartilage injury	1 (<1)	0	0.2 (-0.1, 0.4)
Foreign body aspiration	1 (<1)	0	0.2 (-0.1, 0.4)
Hip fracture	1 (<1)	0	0.2 (-0.1, 0.4)
Incisional hernia	1 (<1)	0	0.2 (-0.1, 0.4)
Radius fracture	1 (<1)	0	0.2 (-0.1, 0.4)
Tendon rupture	1 (<1)	0	0.2 (-0.1, 0.4)
Ulna fracture	1 (<1)	0	0.2 (-0.1, 0.4)
Head injury	0	1 (<1)	-0.1 (-0.4, 0.1)
Lumbar vertebral fracture	0	1 (<1)	-0.1 (-0.4, 0.1)
Road traffic accident	0	1 (<1)	-0.1 (-0.4, 0.1)
Skin laceration	0	1 (<1)	-0.1 (-0.4, 0.1)
Tibia fracture	0	1 (<1)	-0.1 (-0.4, 0.1)
Investigations (SOC)	0	1 (<1)	-0.1 (-0.4, 0.1)
Blood creatine phosphokinase increased	0	1 (<1)	-0.1 (-0.4, 0.1)
Metabolism and nutrition disorders (SOC)	0	4 (1)	-0.6 (-1.2, -0.0)
Diabetes mellitus inadequate control	0	1 (<1)	-0.1 (-0.4, 0.1)
Diabetic ketoacidosis	0	1 (<1)	-0.1 (-0.4, 0.1)
Gout	0	1 (<1)	-0.1 (-0.4, 0.1)
Type 1 diabetes mellitus	0	1 (<1)	-0.1 (-0.4, 0.1)
Type 2 diabetes mellitus	0	1 (<1)	-0.1 (-0.4, 0.1)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	8 (1)	4 (1)	0.6 (-0.4, 1.6)
Bone cyst	1 (<1)	0	0.2 (-0.1, 0.4)
Intervertebral disc protrusion	1 (<1)	0	0.2 (-0.1, 0.4)
Lumbar spinal stenosis	1 (<1)	0	0.2 (-0.1, 0.4)
Myositis	1 (<1)	0	0.2 (-0.1, 0.4)
Rhabdomyolysis	1 (<1)	0	0.2 (-0.1, 0.4)
Spinal stenosis	1 (<1)	0	0.2 (-0.1, 0.4)
Osteoarthritis	2 (<1)	2 (<1)	0.0 (-0.6, 0.6)
Muscle necrosis	0	1 (<1)	-0.1 (-0.4, 0.1)
Polyarthritis	0	1 (<1)	-0.1 (-0.4, 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	8 (1)	6 (1)	0.3 (-0.8, 1.4)
Malignant melanoma in situ	2 (<1)	0	0.3 (-0.1, 0.7)
Prostate cancer	2 (<1)	0	0.3 (-0.1, 0.7)
Benign neoplasm of thyroid gland	1 (<1)	0	0.2 (-0.1, 0.4)
Pancreatic carcinoma metastatic	1 (<1)	0	0.2 (-0.1, 0.4)
Squamous cell carcinoma	1 (<1)	0	0.2 (-0.1, 0.4)
Basal cell carcinoma	2 (<1)	2 (<1)	0.0 (-0.6, 0.6)
Colon adenoma	0	1 (<1)	-0.1 (-0.4, 0.1)
Endometrial cancer	0	1 (<1)	-0.1 (-0.4, 0.1)
Prostate cancer stage I	0	1 (<1)	-0.1 (-0.4, 0.1)
Squamous cell carcinoma of the oral cavity	0	1 (<1)	-0.1 (-0.4, 0.1)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Nervous system disorders (SOC)	5 (1)	5 (1)	0.0 (-0.9, 0.9)
Cervicobrachial syndrome	1 (<1)	0	0.2 (-0.1, 0.4)
Guillain-Barre syndrome	1 (<1)	0	0.2 (-0.1, 0.4)
Migraine	1 (<1)	0	0.2 (-0.1, 0.4)
Myelopathy	1 (<1)	0	0.2 (-0.1, 0.4)
Transient ischaemic attack	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Cubital tunnel syndrome	0	1 (<1)	-0.1 (-0.4, 0.1)
Haemorrhagic stroke	0	1 (<1)	-0.1 (-0.4, 0.1)
Idiopathic generalised epilepsy	0	1 (<1)	-0.1 (-0.4, 0.1)
Seizure	0	1 (<1)	-0.1 (-0.4, 0.1)
Pregnancy, puerperium and perinatal conditions (SOC)	3 (1)	0	0.5 (-0.1, 1.0)
Abortion spontaneous	2 (<1)	0	0.3 (-0.1, 0.7)
Abortion threatened	1 (<1)	0	0.2 (-0.1, 0.4)
Hyperemesis gravidarum	1 (<1)	0	0.2 (-0.1, 0.4)
Renal and urinary disorders (SOC)	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Ureterolithiasis	1 (<1)	0	0.2 (-0.1, 0.4)
Acute kidney injury	0	1 (<1)	-0.1 (-0.4, 0.1)
Reproductive system and breast disorders (SOC)	0	1 (<1)	-0.1 (-0.4, 0.1)
Ovarian cyst	0	1 (<1)	-0.1 (-0.4, 0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	18 (3)	53 (8)	-5.2 (-7.6, -2.8)
Eosinophilic pneumonia	0	1 (<1)	-0.1 (-0.4, 0.1)
Epistaxis	0	1 (<1)	-0.1 (-0.4, 0.1)
Nasal polyps	0	1 (<1)	-0.1 (-0.4, 0.1)
Pulmonary embolism	0	1 (<1)	-0.1 (-0.4, 0.1)
Asthma	18 (3)	49 (7)	-4.6 (-6.9, -2.3)

System Organ Class Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Skin and subcutaneous tissue disorders (SOC)	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Dermatitis contact	1 (<1)	0	0.2 (-0.1, 0.4)
Dermatitis atopic	0	1 (<1)	-0.1 (-0.4, 0.1)
Vascular disorders (SOC)	3 (1)	0	0.5 (-0.1, 1.0)
Cyanosis	1 (<1)	0	0.2 (-0.1, 0.4)
Deep vein thrombosis	1 (<1)	0	0.2 (-0.1, 0.4)
Thrombosis	1 (<1)	0	0.2 (-0.1, 0.4)

Source: adae.xpt; Software: R
AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration is 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every 4 weeks; SOC, system organ class8.2.5.4 Dropouts and/or Discontinuations Due to Adverse Effects

AEs leading to discontinuation that were more common in the tezepelumab groups compared to placebo are summarized in Table 71. AEs leading to discontinuation were generally similar between groups. The most common adverse event leading to discontinuation was malignancy, but this was equal in both the placebo and tezepelumab groups. Arthralgia is included in the common adverse reactions table in the label and one subject on tezepelumab discontinued due to arthralgia compared to zero subjects in placebo.

Table 71. Adverse Events Leading to Discontinuation by System Organ Class and FDA Medical Query (Narrow), Occurring More Frequently in Treatment Arm than Placebo, Primary Safety Population, Trial ISS

System Organ Class FMQ (Narrow)	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
General disorders and administration site conditions (SOC)			
Peripheral edema	1 (<1)	0	0.2 (-0.1, 0.4)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia	1 (<1)	0	0.2 (-0.1, 0.4)

System Organ Class FMQ (Narrow)	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Risk Difference Between Teze and Placebo (95% CI)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy	4 (1)	4 (1)	0.0 (-0.8, 0.8)
Nervous system disorders (SOC)			
Headache	1 (<1)	0	0.2 (-0.1, 0.4)
Psychiatric disorders (SOC)			
Depression	1 (<1)	0	0.2 (-0.1, 0.4)
Skin and subcutaneous tissue disorders (SOC)			
Pruritus	1 (<1)	0	0.2 (-0.1, 0.4)
Rash	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)

Source: adae.xpt; Software: R
AEs in the on-study period are defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date.
Duration is 64 weeks (on-study period).
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
For specific preferred terms under each FMQ, see the table "Adverse Events Leading to Discontinuation by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…"
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every 4 weeks; SC, SOC, system organ class; Teze, Tezepelumab.

8.2.5.5 Common Adverse Events

Adverse events that occurred in at least 3% of subjects and occurred more often in the tezepelumab treatment group as compared to placebo are summarized in Table 72. Overall, adverse events were similar across treatment groups. The most common adverse event which occurred more often with tezepelumab when compared to placebo and which occurred in greater than or equal to 3% of the population included pharyngitis, arthralgia, bronchitis bacterial, viral upper respiratory tract infection, and back pain.

Table 72. Common Adverse Events Occurring at ≥3% Frequency and Occurring More Frequently in Treatment Arm than Placebo, Primary Safety Population, Trial ISS

Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Tezepelumab Q4W vs Placebo Risk Difference (%) (95% CI)
Pharyngitis	28 (4)	18 (3)	1.5 (-0.4, 3.5)

Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Tezepelumab Q4W vs Placebo Risk Difference (%) (95% CI)
Arthralgia	25 (4)	18 (3)	1.1 (-0.8, 3.0)
Bronchitis bacterial	25 (4)	18 (3)	1.1 (-0.8, 3.0)
Viral upper respiratory tract infection	21 (3)	15 (2)	0.9 (-0.8, 2.7)
Back pain	24 (4)	20 (3)	0.6 (-1.3, 2.5)

Source: adae.xpt; Software: R
Adverse events defined as those with onset between day of first dose of study treatment and the day of study completion or withdrawal date. Duration 64 weeks (on-study period).
Pharyngitis includes: Pharyngitis, Pharyngitis bacterial, Pharyngitis streptococcal and Viral pharyngitis.
Rash includes: Rash, Rash pruritic, Rash erythematous, Rash maculo-papular, Rash macular.
Injection site reaction includes: Injection site reaction, Injection site swelling, Injection site erythema, Injection site induration, Injection site haematoma, Injection site pain, Injection site oedema, Injection site cellulitis, Injection site bruising, Injection site pruritus, Injection site hypoaesthesia, Injection site warmth, and Injection site urticaria.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; Teze, Tezepelumab

Reviewer Comments: (b) (4) (b) (4) *When pooling the PTs of bronchitis (bronchitis (4% tezepelumab vs 5% placebo), bronchitis bacterial (4% tezepelumab vs 3% placebo), bronchitis pneumococcal (0.2% tezepelumab vs. 0% placebo) and bronchitis viral (0% tezepelumab vs. 0.3% placebo)), the incidence between the treatment arms was balanced so it was agreed not to include bronchitis bacterial.*

With viral upper respiratory tract infections and pooling other similar terms (upper respiratory tract infection (9% tezepelumab vs. 13% placebo), viral upper respiratory tract infection (3% tezepelumab vs. 2% placebo), upper respiratory tract infection bacterial (0.8% tezepelumab vs. 0.3% placebo), the incidence favored tezepelumab. Therefore, (b) (4) *pharyngitis, arthralgia, and back pain as the common AEs.*

8.2.5.6 Vital Signs and Electrocardiograms (ECGs)

Vital signs and ECGs were not pooled across trials. Assessment of the individual trials, NAVIGATOR and PATHWAY, there were no clinically meaningful changes in vital signs or ECG shifts over time and no meaningful differences between tezepelumab and placebo groups.

8.2.5.7 QT

Due to the large size and high target specificity, mABs have a very low likelihood of ion channel interactions and therefore thorough QT/QTc studies are generally not required. No formal tQT clinical study was conducted for tezepelumab as there were no relevant nonclinical findings, no mechanistic rational, and no relevant findings from limited ECG/AE data in the clinical trials. This was reviewed by the IRT Interdisciplinary Review Team for Cardiac Safety Studies who agreed with the above.

8.2.6. Analysis of Submission-Specific Safety Issues

8.2.6.1 Serious Infections

In the pooled data, SAEs for the Infections and Infestations SOC were pooled and evaluated. The 95% CI risk differences and incidence of SAEs in the Infections and Infestations SOC were similar between the tezepelumab (2%) and placebo groups (3%) (Table 70). The adverse events of serious/severe infections that occurred more frequently in treatment group than placebo can be found in Table 73. Overall, the AE related to this adverse vent os special interest was higher in placebo group (7%) when compared to tezepelumab group (6%).

Reviewer comments: The Applicant included in the label, a precaution with using tezepelumab with live vaccines due to the theoretical immunomodulatory risk, but no actual studies were performed at the time of submission. The Applicant has an ongoing study to assess humoral immune response to the flu vaccine, but it is not completed yet. Given that there is no data to justify the risk or lack of potential risk, the Division agreed with including the live vaccine warning in the label and placed it in Section 5 Warning and Precautions section.

Table 73. Adverse Events of Special Interest Serious/Severe Infections, Occurring More Frequently in Treatment Arm than Placebo, Primary Safety Population (NAVIGATOR and PATHWAY)

Infections and Infestation Assessment	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Total-Risk Difference Between Teze and Placebo (95% CI)
AE grouping related to AESI	42 (6)	44 (7)	-0.3 (-2.9, 2.4)
Acute sinusitis	1 (<1)	0	0.2 (-0.1, 0.4)
Anal abscess	1 (<1)	0	0.2 (-0.1, 0.4)
Atypical pneumonia	1 (<1)	0	0.2 (-0.1, 0.4)
Breast abscess	1 (<1)	0	0.2 (-0.1, 0.4)
COVID-19	1 (<1)	0	0.2 (-0.1, 0.4)
Diverticulitis	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Gastroenteritis salmonella	1 (<1)	0	0.2 (-0.1, 0.4)
Gastroenteritis viral	1 (<1)	0	0.2 (-0.1, 0.4)
Genital herpes simplex	1 (<1)	0	0.2 (-0.1, 0.4)
Herpes zoster	7 (1)	6 (1)	0.2 (-0.9, 1.2)
Herpes zoster oticus	1 (<1)	0	0.2 (-0.1, 0.4)
Influenza	8 (1)	8 (1)	0.0 (-1.2, 1.2)
Nasopharyngitis	11 (2)	4 (1)	1.1 (-0.1, 2.2)
Oral herpes	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)

Infections and Infestation Assessment	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)	Total-Risk Difference Between Teze and Placebo (95% CI)
Osteomyelitis	1 (<1)	0	0.2 (-0.1, 0.4)
Pneumonia	1 (<1)	1 (<1)	0.0 (-0.4, 0.4)
Pneumonia bacterial	5 (1)	3 (<1)	0.3 (-0.5, 1.1)
Tracheitis	2 (<1)	1 (<1)	0.2 (-0.4, 0.7)
Maximum severity			
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	9 (1)	13 (2)	-0.6 (-2.0, 0.8)
Moderate	29 (4)	22 (3)	1.1 (-1.0, 3.1)
Mild	4 (<1)	9 (1)	-0.7 (-1.8, 0.3)
Serious	13 (2)	13 (2)	0.0 (-1.5, 1.5)
Deaths	0	0	0 (0, 0)
Resulting in discontinuation	0	0	0 (0, 0)

Source: adae.xpt; Software: R
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every 4 weeks.

8.2.6.2 Opportunistic Infections

There were no events of opportunistic infections reported in the Primary Safety Pool.

8.2.6.3 Helminth Infections

No helminth infections were reported in the Primary Safety Pool.

8.2.6.4 Anaphylactic of Serious Allergic Reactions

Given the known risk of anaphylaxis for biologics and the higher incidence in the atopic populations, anaphylaxis was included as an adverse event of special interest. Anaphylaxis was identified based on a narrow SMQ query. There were no reports of anaphylaxis for subjects treated with tezepelumab in the Primary Safety Pool. In NAVIGATOR, there was a patient who had anaphylaxis in the placebo arm. The subject, with a known reaction to beef, had a reaction to beef and had acute symptoms 10-15 minutes after having beef. This occurred 21 days after dose 3.

8.2.6.5 Hypersensitivity Reactions

Similar to anaphylaxis, since there is a known risk of hypersensitivity for biologics with a higher incidence in atopic study populations, hypersensitivity was included as an AESI. The

hypersensitivity adverse events that were reported on treatment can be seen in Table 74. In the Primary Safety Pool, within the narrow SMQ of hypersensitivity, the incidence of hypersensitivity reactions reported during the on-treatment period was similar in both treatment groups (8.4% in tezepelumab and 8.7% in placebo group). Across both treatment groups, the most common hypersensitivity reaction was rhinitis allergic (2.7% in tezepelumab vs. 3.3% placebo) with the other hypersensitivity reactions occurring in the Skin and Subcutaneous Disorder SOC (PT terms: rash, dermatitis contact, eczema, dermatitis atopic, dermatitis) and Gastrointestinal disorders SOC (PT terms: lip swelling, allergic gastroenteritis). The only PT term in which was greater in the tezepelumab arm when compared to placebo was conjunctivitis allergic and various rashes. Thus, allergic conjunctivitis and rashes are included as examples of hypersensitivity reactions in Section 5 of the prescribing information.

Table 74. Hypersensitivity reactions reported during on treatment period by SOC and PT in Safety Population (NAVIGATOR and PATHWAY)

System organ class/Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)
Subjects with any Hypersensitivity	56 (8)	58(9)
Immune system disorders	1(<1)	4 (1)
Hypersensitivity	1(<1)	1(<1)
Anaphylactic reaction	0(0)	1(<1)
Drug hypersensitivity	0(0)	2(0)
Eye disorders	5(1)	2(0)
Conjunctivitis allergic	4(1)	1(<1)
Eye allergy	1(<1)	0(0)
Eyelid oedema	0(0)	1(<1)
Respiratory, thoracic, and mediastinal disorders	19(3)	27(4)
Rhinitis allergic	18(3)	22(3)
Bronchospasm	1(0)	3(0)
Allergic sinusitis	0(0)	2(0)
Gastrointestinal disorders	1(<1)	2(0)
Lip swelling	1(<1)	1(<1)
Eye allergy	1(<1)	0(0)
Allergic gastroenteritis	0(0)	1(<1)
Skin and subcutaneous tissue disorders	32(5)	30(5)
Rash	7(1)	7(1)
Dermatitis contact	5(1)	3(0)
Eczema	5(1)	5(1)
Dermatitis atopic	4(1)	4(1)

System organ class/Preferred Term	Tezepelumab 210 mg Q4W N=665 n (%)	Placebo N=669 n (%)
Dermatitis	3(1)	2(0)
Urticaria	3(1)	6(1)
Idiopathic urticaria	2(0)	0(0)
Rash pruritic	2(0)	0(0)
Eczema nummular	1(<1)	0(0)
Rash erythematous	1(<1)	0(0)
Rash maculo-papular	1(<1)	0(0)
Angioedema	0(0)	1(<1)
Dermatitis allergic	0(0)	2(0)
Pruritus allergic	0(0)	1(<1)
Rash macular	0(0)	1(<1)
Toxic skin eruption	0(0)	1(<1)

Source: ISS, Table 1.7.8.1
Abbreviations: AESI, adverse events of special interest; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every 4 weeks; SOC, system organ glass; PT, preferred term

8.2.6.5 Malignancy

A total of 11 subjects reported malignancy in the on-treatment period with 6 subjects in the tezepelumab group and 5 subjects in the placebo group in the primary safety pool. The malignancies reported in the tezepelumab group include basal cell carcinoma, malignant melanoma in situ, prostate cancer, and squamous cell carcinoma. Malignancies in the placebo group included basal cell carcinoma, endometrial cancer, prostate cancer, and squamous cell carcinoma of the oral cavity. For the NAVIGATOR trial, all investigator reported malignancies were assessed by an independent adjudication committee. In the on-treatment group, 4 subjects from each treatment group reported malignancy events (5 total events in tezepelumab group and 4 total events in the placebo group). Four events in each group were determined to be new malignancies. Of the 2 subjects reporting malignant melanomas in situ in the study, one was reported to be causally related to tezepelumab by the Investigator and the other was thought not to be due to tezepelumab. However, both subjects had pre-existing lesions. The tezepelumab group also included one subject with basal cell carcinoma, one with prostate cancer, one with squamous cell carcinoma. None of these events were considered casually related to tezepelumab per the Applicant.

8.2.6.6 Injection Site Reactions

The incidence of injection site reactions for both tezepelumab and placebo groups were low (3.3% vs. 2.8%). The most frequent PT reported was erythema. Injection site reactions were non-serious and transient in nature, with majority reported as mild.

8.2.6.7 Guillain-Barre Syndrome

There was one event of Guillain-Barre syndrome that occurred in the tezepelumab group. The subject was a 56 year old female who presented with a viral infection 6 days after Dose 10. The subject required hospitalization with fevers and joint pain. Symptoms resolved. Six days after onset of symptoms, the subject developed acute muscular weakness in all four limbs. Four days later, the subject was diagnosed with Guillain-Barre syndrome and the investigational product was permanently discontinued. The investigator relayed the above event may be related to the Investigational Product; however, an alternative etiology could be due to the preceding viral infection.

8.2.7. Safety Analyses by Demographic Subgroups

8.2.7.1 Intrinsic Factors

Safety assessing AE and SAE rates was by subgroups of baseline blood eosinophil count, age, gender, race, and BMI. Per the Applicant analysis, the safety profile is generally similar regardless of baseline blood eosinophil count, age, gender, race, or BMI. No clinically meaningful differences were observed in the frequency or pattern of AEs.

8.2.7.2 Extrinsic Factors

In general, the safety profile of tezepelumab is similar in the subgroups assessed. The safety profile in terms of AEs by geographic region or country showed no meaningful difference in frequency or pattern. No meaningful difference or frequency in pattern was seen when based by OCS use at baseline and dose of ICS at baseline.

8.2.7.3 Pregnancy

Incidence and outcome for the pregnancies reported by 11 subjects from NAVIGATOR and PATHWAY were provided by the Applicant. Four subjects were enrolled in PATHWAY (2 received tezepelumab 210 mg Q4W and 2 received tezepelumab 280 mg Q2W) and 7 subjects were enrolled in NAVIGATOR (3 subjects received tezepelumab 210 mg Q4W and 4 received placebo). All four subjects who received placebo, resulted in healthy full term infants. For the 7 subjects with pregnancies who received tezepelumab, 4 resulted in either a pre-term delivery or a spontaneous abortion and 3 patients delivered healthy, full term infants. One patient in the PATHWAY trial delivered pre-term twins after developing pre-eclampsia. One patient in PATHWAY had a spontaneous abortion at 11 weeks. Two patients in NAVIGATOR had a spontaneous absorption at 6 and 9 weeks.

No pregnancies were reported in any of the other completed tezepelumab asthma clinical studies.

Reviewer's Comment: A total of 3 of the 7 pregnancies for subjects on tezepelumab led to miscarriage which is higher than the U.S. general population estimated background miscarriage risk of 15-20%. Both the higher rate in the tezepelumab group and overall is likely due to the small sample size and to the underlying disease. Also, the event of pre-eclampsia could have also been due to the underlying disease as women with poorly or moderately controlled asthma have an increased risk of pre-eclampsia and prematurity.

Nonclinical studies did not demonstrate adverse effects on maternal health, pregnancy outcomes, embryo-fetal development, or neonatal growth and development up to 6.5 months of age (See Section 5.5.4).

Overall, the development program took standard measures to limit the incidence of pregnancy during the clinical trials. Once approved, women of child-bearing potential may be exposed to tezepelumab. There are limited data from the clinical program in pregnant women. The Applicant has proposed to not include a pregnancy registry for tezepelumab given that severe asthma is a small segment of the overall asthma population and so an adequately powered disease based pregnancy registry for tezepelumab is likely not feasible. The Applicant relayed they plan to conduct a retrospective database pregnancy safety study using routinely collected data from electronic health records and administrative healthcare claims database, in addition to gathering relevant data from existing pregnancy registries from Europe and the United States. The Division agrees with the above plan.

8.2.8. Specific Safety Studies/Clinical Trials

8.2.8.1 SOURCE Trial

The SOURCE trial was not included in the primary safety pool as it enrolled only oral corticosteroid dependent patients and therefore is different from the population in PATHWAY and NAVIGATOR which enrolled subjects that were primarily not OCS dependent. A total of 74 subjects received tezepelumab 210 mg Q4W and 76 subjects received placebo. The demographics were generally balanced between both treatment arms.

There was one death in this trial secondary to cardiac arrest, in the tezepelumab group. The subject had a history of angina, atrial fibrillation, coronary artery disease, pulmonary hypertension, and obesity. He had a previous event of non-fatal cardiac failure 16 days after dose 4, which required hospitalization. Eighteen days after dose 7 of tezepelumab, the subject experienced a fatal AE of cardiac arrest.

A total of 11 (15%) tezepelumab treated subjects and 16 (21%) placebo treated subjects reported an SAE in the on-treatment period. The most common SAE in both treatment groups was asthma (27% in tezepelumab group and 11% in placebo group). Apart from asthma, no SAE PT was reported in >1 subject in the tezepelumab group.

AEs leading to discontinuation were similar in both treatment arms, with 2 in each treatment

arm (2.7% in tezepelumab group and 2.6% in the placebo group).

The incidence of subjects with AEs in the on-treatment period was 72% in the tezepelumab group and 86% in the placebo group. The most common AEs reported in SOURCE were in the Infections and Infestations SOC (47% vs 57% of the subjects in the tezepelumab and placebo group). AEs occurring in ≥3% of subjects in either treatment group during the on-treatment period are summarized in Table 75. The 4 most common AEs in the tezepelumab group that occurred more commonly in subject on tezepelumab compared to placebo were upper respiratory tract infection, bronchitis, fall, and myalgia.

Overall, the safety assessment is similar to what was seen in the Primary Safety Pool.

Table 75. Most Common Adverse Events (Frequency of ≥ 3%), Reported During On-Treatment Period by Preferred Term (SOURCE, Safety Analysis Set)

Preferred Term	Number (%) of subjects[a]	
	Teze 210 mg Q4W (N = 74)	Placebo (N = 76)
Subjects with any AE	53 (72)	65 (86)
Nasopharyngitis	11 (15)	19 (25)
Upper respiratory tract infection	9 (12)	7 (9)
Asthma	7 (10)	13 (17)
Bronchitis bacterial	6 (8)	7 (9)
Bronchitis	4 (5)	3 (4)
Oral candidiasis	4 (5)	4 (5)
Fall	3 (4)	1 (1)
Headache	3 (4)	8 (11)
Myalgia	3 (4)	1 (1)
Hypertension	2 (3)	5 (7)
Sinusitis	1 (1)	5 (7)
Cataract	0 (0)	3 (4)
Influenza like illness	0 (0)	5 (7)
Muscle spasms	0 (0)	3 (4)
Nasal polyps	0 (0)	4 (5)

Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms. Includes adverse events with an onset date between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).

MedDRA version 23.1.

AE, adverse event; IP, Investigational product; N, number of subjects in treatment group; Q4W, Every 4 weeks; Teze, Tezepelumab.

SOURCE: Table 14.3.2.6 SOURCE CSR (Module 5.3.5.1).

8.2.8.2 120 Day Safety Update

Overview

The Applicant provided a 3 month safety update report that consisted of the blinded adverse event data from the ongoing randomized, double-blind, placebo controlled, parallel group phase 3 long term extension study DESTINATION (data cut off April 30 2021) and provided an update on the safety data from the phase 3 asthma exacerbation trial NAVIGATOR as per their final database lock on February 17, 2021. Their phase 3 NAVIGATOR trial was locked on October 29, 2020.

NAVIGATOR Trial

No new safety findings were identified based on evaluation of the additional safety data from NAVIGATOR. The additional safety data were from 8 subjects, 4 subjects in the tezepelumab group and the other 4 in the placebo arm, who had completed treatment prior to the primary database lock, but subsequently either completed the safety follow up period or rolled over into the DESINATION study at the NAVIGATOR Week 48 study visit.

A total of 9 AEs for 4 subjects randomized into DESTINATION were recorded as starting in NAVIGATOR the predecessor trial, but were not reported in the primary analysis CSR for NAVIGATOR. One subject experienced post-COVID AEs with PTs of disturbance in attention, fatigue, headache, and hypersomnia. One subject reported AEs with PTs of spinal osteoarthritis, upper respiratory tract infection, and hypercholesterolemia. The remaining 2 subjects experienced a single AE each, with PTs of spinal stenosis and helicobacter infection. After review of this additional safety data, it is concluded that the original safety conclusions from NAVIGATOR remain unchanged.

DESTINATION Trial

The primary objective of DESTINATION is to assess the long term safety of tezepelumab for a total of 104 weeks on treatment (with the first year of treatment coming from the predecessor studies). A total of 951 subjects from the predecessor studies were randomized into DESTINATION (827 from NAVIGATOR and 124 from SOURCE). Of the 950 subjects who received treatment, 72 were ≥12 to 18 years of age, 726 were ≥18 to <65 years of age, and 152 were ≥65 years of age. As DESTINATION is still ongoing and blinded, no detailed comparison by treatment group is available. However, the Applicant relays the overall AE profile of the combined treatment groups appears consistent from the Primary Safety Pool.

As of the data cut off for this 3 month safety update, a total of 801 (84%) subjects had completed treatment in DESTINATION and 58 (6%) had discontinued treatment. The most common reason for discontinuing treatment were withdrawal by subject (27 (3%) of subjects) and 'other' (21 (2%)). A total of 91 (10%) subjects were continuing in the study on-treatment as of the 3 month safety update data cut off.

Deaths

Twelve AEs (1%) with an outcome of death were reported in this 3 month safety update. One subject died without receiving the investigational product in DESTINATION. For the remaining 11 subjects, 9 subjects died while on treatment, 1 subject died during the follow up period and 1 subject died during the Extended follow up period. Of the 9 AEs with outcomes of death on treatment, 8 were not considered causally related to IP by the investigator (PTs: COVID-19 pneumonia (2 cases), pneumonia, periprocedural myocardial infarction, acute left ventricular failure, death (2 cases), and myocardial infarction). For 1 fatal AE (PT: colorectal cancer), the investigator considered a reasonable possibility it may be related to IP. This event occurred in a 64 year old female who rolled over into DESTINATION from NAVIGATOR. The subject who died during the follow up period reported the PT term pneumonia staphylococcal. The subject who died during the Extended follow up period was reported as PT: sudden death.

Serious Adverse Events

A total of 95 of the 950 subjects (10%) experience an SAE in the on study period of DESTINATION. The most common SAEs by PT occurring in 2 or more subjects were as follows: asthma (19 [2.0%] subjects), COVID-19 pneumonia (7 [0.7%]), COVID-19 (4 [0.4%]), inguinal hernia (3 [0.3%]), diverticulitis (2 [0.2%]), pneumonia bacterial (2 [0.2%]), acute myocardial infarction (2 [0.2%]), coronary artery disease (2 [0.2%]), death (2 [0.2%]), and lower limb fracture (2 [0.2%]).

Discontinuation of Investigational Product due to Adverse Events
A total of 8 (1%) subjects reported a discontinuation due to AE, with 6 while on treatment and 2 during the on-study period in DESTINATION. All of the AEs were reported at an incidence of 1 (0.1%) subject per PT with the following PTs: COVID-19 pneumonia, colorectal cancer, drug-induced liver injury, rash, arthralgia, and liver function test increased.

Common Adverse Events

Adverse events by PT occurring in ≥ 3% of subjects in the LTE on-study period of DESTINATION are summarized in Table 76. The AE PTs with highest incidence were nasopharyngitis (68%), headache (7%), and upper respiratory tract infection (568%).

Table 76. The Most Common Adverse Events (Frequency of ≥ 3%), Reported During LTE On-study Period by Preferred Term (DESTINATION SAF-LTE Analysis Set)

Preferred term	Total (N = 950)	
	Number (%) of subjects[a]	Incidence rate (per 100 subject-years)[b]
Total time at risk across all subjects (years)		993
Subjects with any AE		
Nasopharyngitis	647 (68)	65
Headache	69 (7)	7
Upper respiratory tract infection	51 (5)	5
COVID-19	38 (4)	4
Back pain	36 (4)	4
Hypertension	32 (3)	3
Asthma	31 (3)	3
Urinary tract infection	29 (3)	3

a Number (%) of subjects with AEs, sorted by decreasing frequency for preferred term in subjects treated.
b Number of subjects with AEs divided by the total time at risk across all subjects treated, multiplied by 100.
Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms.
Includes AEs that occur within the defined study period.
Total represents combination of tezepelumab- and placebo-treated subjects.
MedDRA version 24.0
AE, adverse event; COVID-19, coronavirus disease 2019; LTE, long-term extension; N, number of subjects treated; SAF-LTE, safety analysis set long-term extension.
Source: Table 6, 3MSU Summary Data Output (Appendix A).

Adverse Event of Special Interest

Serious infections
During the LTE on-study period of DESTINATION, a total of 22 (2%) subjects reported SAEs in the infections and infestations SOC. The most common of these SAEs were COVID-19 pneumonia (7 [0.7%] subjects), COVID-19 (4 [0.4%] subjects), diverticulitis (2 [0.2%] subjects), and pneumonia bacterial (2 [0.2%] subjects). All remaining SAEs in the Infections and infestations SOC were reported by 1 (0.1%) subject per PT.

Opportunistic infections
No events reported in the LTE on study period of DESITINATION.

Helminth infections
No events were reported.

Anaphylactic or serious allergic reactions
No events were reported.

Hypersensitivity reactions
No anaphylaxis cases were reported. A total of 67 subjects with 84 events were reported during the LTE on-study period. The majority of the reactions were reported in the skin and subcutaneous tissue disorders SOC. Hypersensitivity events occurring in 2 or more subjects by PT were as follows: rhinitis allergic (27 [3%] subjects, 32 events), urticaria (7 [0.7%] subjects, 7 events), dermatitis atopic (5 [0.5%] subjects, 5 events), dermatitis contact (4 [0.4%] subjects, 5 events), rash (4 [0.4] subjects, 4 events), dermatitis (3 [0.3%] subjects, 3 events), eczema (3 [0.3%] subjects, 3 events), drug hypersensitivity (3 [0.3%] subjects, 3 events), drug eruption (2 [0.2%] subjects, 2 events), and conjunctivitis allergic (2 [0.2%] subjects, 2 events). Three serious hypersensitivity reactions were reported. The serious hypersensitivity reactions reported were immune thrombocytopenia, drug hypersensitivity, and rash, occurring in 1 (0.1%) subject each by PT.

Malignancy
A total of 4 subjects reported malignancies in the LTE on-study period of DESTINATION. Malignancies were reported at an incidence of 1 (0.1%) subject per PT and included PTs of colon cancer stage IV, colorectal cancer, squamous cell carcinoma, and thymoma.

Injection Site Reactions
A total of 7 subjects reported 10 events of injection site reactions. Reported PT include: injection site bruising, injection site discoloration, injection site hematoma, injection site edema, injection site pain, injection site swelling, and injection site urticaria. The above were single events except injection site urticaria which reported four events with one subject.

Guillain-Barre syndrome
No events reported.

Pregnancy
Five subjects receiving blinded study therapy in DESTINATION reported pregnancies as of the 3 month safety update. One subject delivered a healthy full-term infant, 1 subject had an elective abortion, and pregnancy outcomes are not yet known for 3 subjects.

8.2.9. Additional Safety Explorations

8.2.9.1 Overdose

In clinical trials, doses of up to 280 mg SC every 2 weeks (Q2W) and doses of up to 700 mg IV Q4W were administered to subjects with asthma without evidence of dose-related toxicities.

Clinical study data regarding overdose of tezepelumab are limited to 2 occurrences to date.

One subject in the NAVIGATOR study and 1 subject in the SOURCE study received an unintentional overdose of 420 mg of tezepelumab; for both studies, the definition of overdose was any dose greater than 280 mg within a 2-week period. These 2 instances of overdose were not associated with an AE.

8.2.9.2 Drug Abuse Potential

There is no evidence for and no anticipation of drug abuse or dependence potential with tezepelumab.

8.2.9.3 Withdrawal and Rebound

No formal studies have been conducted to assess withdrawal or rebound effects.

8.2.10. Safety in the Postmarket Setting

As this is a new biologic and has yet to be marketed, there is no data obtained in the postmarket setting.

8.2.11. Integrated Assessment of Safety

Safety analyses were based on the 1-year safety pool of the 210 mg Q4W dose from the 1-year dose range finding trial (PATHWAY) and the 1-year efficacy and safety trial (NAVIGATOR). Independent review of the PATHWAY trial assessed dose related adverse events. SOURCE was not included in the primary safety pool due to differences in population as all participants were on baseline OCS and therefore may have a different safety profile.

For the primary safety pool, there were no deaths in subjects on tezepelumab during the on-treatment period. There was a death secondary to a cerebrovascular accident in PATHWAY during the on study period in the tezepelumab 70 mg Q4W group. The SAE SOCs that occurred in more than one subject in the tezepelumab treatment arm and greater than the placebo arm includes the cardiac disorders SOC, injury, poisoning and procedural complications SOC, and musculoskeletal and connective tissue disorders SOC. Review of the individual PT terms along with the accompanying narratives of each SAE showed that many of the PTs were clearly not related to tezepelumab.

The overall common adverse event incidence was similar across treatment groups (tezepelumab 75%, placebo 78%). The most common adverse events that occurred more often in treatment group compared placebo were pharyngitis, arthralgia, and back pain.

No events of anaphylaxis were reported for subjects on tezepelumab. The incidence of hypersensitivity reactions was similar across treatment groups (8% in tezepelumab and 9% in placebo group). Amongst the hypersensitivity reactions, allergic conjunctivitis and various rashes showed a higher incidence in the tezepelumab arm when compared to placebo.

Safety analyses by intrinsic factors such as baseline blood eosinophil count, age, gender, race and BMI showed a similar safety profile regardless of the above factor. This was also seen when extrinsic factors such as OCS use at baseline and ICU status was considered. No safety differences were noted in these subgroups including age <18 years.

Overall, the safety issues identified from the tezepelumab development program can be adequately described in product labeling. There were no unique serious safety issues identified for this first in class product. Given the benefits of tezepelumab, the safety profile in subjects ≥12 years of age with severe asthma is favorable.

8.3. Statistical Issues

We did not agree with the Applicant's approach for assessing efficacy on several points:

- In the NAVIGATOR trial, the Applicant describes H02, AAER – subjects with baseline eosinophils < 300/µL, as part of the primary analysis. We disagreed, because the primary estimand and estimator are used for regulatory decision-making. Therefore, H02 was denoted in our review as the first secondary estimand and first secondary analysis.
- The Applicant's main analysis for the secondary endpoints, change from baseline to Week 52 for pre-BD FEV1, AQLQ(S)+12 Total Score, ACQ-6 Score, and weekly mean asthma symptom diary score, had anywhere from 43 to 176 patients apparently excluded from a given treatment arm. Communication from the Applicant clarified that the number of subjects contributing to the analysis were higher than originally reported, with at most, 5 subjects in a treatment arm not contributing.
- In order to further understand the effect of biomarkers, an assessment of eosinophils and FeNO by both a continuous assessment and a subgroup approach was required to demonstrate the predictive nature of these endpoints. The Applicant conducted the analyses we requested, resulting in significant results that supported inclusion of information in labelling for these two biomarkers.
- Based on the Applicant's data and our assessment, perennial specific IgE did not meet the criteria for use as a predictive biomarker.
- We note that PATHWAY as a phase 2 dose ranging trial lacks statistical rigor seen in typical confirmatory trials such as statistical significance level of 0.05 and multiplicity adjustment plan regarding secondary endpoints. The planned Type I error of 0.10 for the PATHWAY trial does not meet criteria for a confirmatory trial. A Type I error of 0.05 or less is recommended so the trial may achieve statistical persuasiveness. Further, this trial had no multiplicity plan to control Type I error for secondary endpoints. Despite not powering the study to achieve statistical persuasiveness, the primary endpoint was statistically persuasive and secondary endpoints achieved nominal significance in concordance with the NAVIGATOR study that were compelling.

8.4. Conclusions and Recommendations

The recommended regulatory action from a clinical and statistical perspective is approval of tezepelumab 210 mg SC Q4W as add-on maintenance treatment in patients 12 years of age and older with severe asthma as substantial evidence of effectiveness was met and there were no major safety concerns. Substantial evidence of effectiveness is based on two adequate and well-controlled trials, NAVIGATOR and PATHWAY.

Both trials demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations in patients with severe asthma. Improvements in secondary endpoints of lung function and PROs (AQLQ(6)+12 and ACQ-6) were also supportive. Efficacy was demonstrated regardless of baseline blood eosinophil levels.

In the NAVIGATOR trial, the adolescent subgroup demonstrated a similar numerical trend in exacerbation rate and lung function, but the subgroup was not powered to demonstrate statistical significance. This review team recommends approval in this age group based on partial efficacy extrapolation from the adult subjects as the disease characteristics and the effects of the drug are known to be the same in adults and children and therefore, extrapolation is appropriate. In addition there were no age-related differences in the pharmacokinetics and no safety concerns for tezepelumab in adolescents.

A third trial was conducted in a severe asthma population where all participants were on baseline OCS, but it did not demonstrate a statistically significant reduction in daily oral corticosteroid use. A limitation of use was not supported as the efficacy trends for the primary and secondary endpoints favored tezepelumab and was similar to subgroup analyses for subjects on maintenance OCS in NAVIGATOR.

The program included an assessment of safety related to immunomodulatory therapy and biologics including infections, malignancy, hypersensitivity events, and immunogenicity. No episodes of anaphylaxis were reported related to tezepelumab and hypersensitivity events were overall equal amongst tezepelumab and placebo groups, except rash and allergic conjunctivitis were slightly higher in those treated with tezepelumab. There was no increases in serious infections in the tezepelumab group. Arthralgia was noted to be a dose-related adverse event and more frequent in tezepelumab treated subjects when compared to placebo. Pharyngitis was the most common adverse event reported more frequently for tezepelumab compared to placebo. No safety concerns that offset the efficacy benefits provided by tezepelumab were identified for the overall or adolescent populations. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Overall, the benefit risk assessment is favorable for tezepelumab 210 mg SC Q4W as add-on maintenance treatment in patients 12 years of age and older with severe asthma and addresses an unmet medical need for patients with severe asthma without an eosinophilic phenotype.

9 Advisory Committee Meeting and Other External Consultations

Tezepelumab is a first in class biologic. However, the review team did not identify any controversial or precedent setting issue, identify any questions regarding the clinical trial design, conduct or analysis, or identify any safety issue that would benefit from discussion at an Advisory Committee meeting.

10 Pediatrics

Agreed iPSP

In this BLA submission, AstraZeneca is supporting efficacy and safety with one 52-week double-blind, placebo-controlled trials in adolescents and adults with severe asthma (NAVIGATOR) and another 52-week dose-ranging trial of similar design in adults (PATHWAY). In NAVIGATOR, the adolescent subgroup was not powered to demonstrate statistical significance, but did show numerical and clinically meaningful reductions in asthma exacerbations and an improvement in lung function compared to placebo. The approval for 12-18 years of age is based on partial extrapolation given the same pathophysiology for adolescents with asthma, no PK age-related differences, and no safety concerns for the use of tezepelumab in this age group.

AstraZeneca submitted an Agreed iPSP in December 2020 whichproposed a waiver in children <2 year of age because studies are impossible or highly impractical since it is difficult to identify asthma in children below 2 year of age. AstraZeneca also proposed a deferral for 2- to 11-year-olds. In the Agreed iPSP, the Applicant proposed to conduct a phase 1 PK/safety trial in 5–11-year-olds, a phase 3 safety and efficacy trial in 5–11-year-olds, and then a phase 1 PK/PD safety trial in 2–4-year-olds.

In an earlier version of the iPSP, the Applicant initially asked for a waiver in (b) (4)-year-olds, but the Division recommended the Sponsor plan to request a waiver in <2-year-olds as there are patients with severe asthma who are 2 to 4 years of age that could benefit from the availability of this biologic and none of the waiver criteria (including that clinical trials are impossible or highly impracticable) are met.

Amended iPSP

When the Applicant submitted their BLA in May 2021, they proposed an amended iPSP which proposed to replace the safety and efficacy trial in 5- to 11-year-olds with a PK/PD/safety trial with a plan (b) (4)

5–11-year-old deferral

The Division disagrees with the amended iPSP and recommends a safety and efficacy trial in 5–11-year-olds. Specifically, the Division has concerns (b) (4)

(b) (4)

Establishing efficacy in patients 5 to 11 years of age would requirea phase 3 efficacy and safety trial as we had agreed in the Agreed iPSP submitted in December 2020.

2 to <5-year-old deferral

Although the Division initially agreed to a phase 1 PK/PD/safety trial in 2- to 4-year-olds, after further consider, including concerns (b) (4)

the Division in conjunction with the Pediatric Review Committee, is requiring the Applicant conduct a phase 3 efficacy/safety/PK trial in this age range. (b) (4)

The benefit risk assessment in this age group will also be challenging due to potential immunomodification which further supports the need for an efficacy and safety trial.

0 to < 2 year-old waiver

The Division agrees that pediatric studies can be waived in this age group as studies are impossible or highly impractical due to insufficient numbers of pediatric patients to study in this age group with severe asthma who require add-on treatment

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following table reflects major changes to the Prescribing Information (PI) that have been agreed upon between the Agency and the Applicant. The final label was submitted by the Applicant on December 14, 2021.

Section	Proposed Labeling	Approved Labeling
Section 1 Indications and Usage	For the add-on maintenance treatment of patients aged 12 years and older (b) (4)	For the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. The Division removed the terms (b) (4) as the terms did not add to the indication statement. The Division removed (b) (4)
	The Applicant described tezepelumab (b) (4) (in Highlights).	The Division changed the term (b) (4) to "blocker" as the drug prevents a ligand receptor interaction, not only by binding to the receptor, but also by binding to the ligand.
Section 5 Warnings and Precautions	(b) (4)	The Division modified this section to include examples of hypersensitivity reactions that occurred more frequently in the tezepelumab group compared to placebo.
Section 6 Clinical Trials Experience	The Applicant provided a summary of the two pivotal trials and table of (b) (4) (b) (4) adverse reactions	The Division revised the summary according to current labeling practices. The Division revised the common adverse reaction table to include those events with greater than or equal to 3% and more common than placebo.
Section 7 Drug Interactions	The Applicant provided a statement relaying the use of live attenuated vaccines should be avoided in patients receiving tezepelumab.	The Division agreed with inclusion of this statement, but moved it to Section 5 Warnings and Precautions given this is not a drug interaction.

Section	Proposed Labeling	Approved Labeling
Section 12 Clinical Pharmacology	A summary of the pharmacokinetic and pharmacodynamic findings from the development was provided.	The Division removed information regarding (b) (4) The Division also removed information regarding (b) (4) The prescribing information describes a decrease in blood eosinophils. The Division instead placed in Section 12 that TSLP is involved in submucosal eosinophils which was supported by the CASCADE study[30] (See Section 6.3.2)
Section 14 Clinical Studies	The Applicant provided a (b) (4) The Applicant added (b) (4) The Applicant added efficacy data from the Asthma Symptom Diary PRO.	The Division provided the following edits: Removed (b) (4) and provided a less detailed summary at the bottom of Section 14 ('Additional Trial') since the trial failed on the primary endpoint. The Division removed (b) (4) from the description in the clinical summary as the Division does not agree (b) (4) The Division removed the PRO as it has not been fully validated.

[30] Diver S., Khalfaoui L., Emson C., Wenzel S.E., et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): A double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir. 2021 Nov;9(11):1299-1312

12 Risk Evaluation and Mitigation Strategies (REMS)

The Division did not find any safety issues that requires a Risk Evaluation and Mitigation Strategy. The safety findings that were identified can be adequately addressed through labeling and will be followed with routine pharmacovigilance.

13 Postmarketing Requirements and Commitment

Three Postmarketing Requirement (PMR) trials are being included with this approval. All three PMRs are required under PREA as outlined below and reflect timelines agreed upon with the Applicant.

PMR 4188-1: Conduct a PK/safety trial in children 5-11 years of age with asthma requiring daily controller medication.

Final Protocol Submission: 11/2020 (submitted)
Study Completion: 12/2023
Final Report Submission: 05/2024

PMR 4188-2: Conduct a 52-week efficacy and safety trial in children 5 to < 12 years of age with severe asthma.

Draft Protocol Submission: 02/2024
Final Protocol Submission: 06/2024
Study Completion: 04/2028
Final Report Submission: 09/2028

PMR 4188-3: Conduct an efficacy, safety, and PK trial in children 2 years to < 5 years of age with severe asthma with a continued safety evaluation out to a minimum of 52 weeks.

Draft Protocol Submission: 06/2029
Final Protocol Submission: 12/2029
Study Completion: 03/2036
Final Report Submission: 09/2036

14 Division Director (Clinical) Comments

Background and Regulatory History

Tezepelumab is a first-in-class monoclonal antibody that binds TSLP and prevents the interaction of TSLP with the TSLP receptor (TSLP blocker). Currently approved biologics for moderate-to-severe asthma target a specific asthma population, e.g. eosinophilic phenotype or allergic asthma. The Applicant proposed a (b) (4) indication for tezepelumab, add-on maintenance treatment in patients with (b) (4) severe asthma aged 12 years and older, (b) (4) The Applicant also proposed tezepelumab (b) (4) The proposed dose is 210 mg every 4 weeks by SC injection in a healthcare setting and the presentations are a single dose vial and single dose prefilled syringe.

Tezepelumab was granted Breakthrough Drug Designation in September 2018 because it showed preliminary efficacy in asthma patients not only with eosinophilic phenotype, but in asthma patients without an eosinophilic phenotype, i.e. a broader asthma population. The BLA was granted priority review because data continued to support that tezepelumab demonstrated evidence of safety and effectiveness (b) (4)

Nonclinical Pharmacology and Toxicology and Clinical Pharmacology

The Applicant submitted a complete nonclinical pharmacology and toxicology program for tezepelumab and there are no outstanding issues. The nonclinical pharmacology and toxicology team recommended approval. The Applicant submitted a complete clinical pharmacology program for tezepelumab. Based upon submitted data, adjustment in dosing is not necessary in patients with renal or hepatic impairment or in adolescents. ADA were detected in 5% of patients treated with the proposed dose of tezepelumab, but there was no evidence of ADA impact on PK, efficacy or safety. Since tezepelumab is a large molecule monoclonal antibody, it has low potential for clinically relevant drug-drug interactions; therefore, drug-drug interaction studies were not conducted. The clinical pharmacology team recommends approval.

Clinical Development Program

To support the efficacy and safety of tezepelumab, the Applicant submitted results from three adequate and well-controlled clinical trials: PATHWAY, NAVIGATOR, and SOURCE.

PATHWAY was a randomized, double-blind, placebo-controlled, 52 week, dose ranging trial in 552 adult patients with severe asthma. Randomization of patients was stratified by several factors, including baseline eosinophil count: low (< 250 cells/uL) vs. high (≥250 cell uL). Three doses of tezepelumab were evaluated: 70 mg SC every 4 weeks, 210 mg SC every 4 weeks, and 280 mg SC every 2 weeks. The primary endpoint for PATHWAY was the annualized exacerbation rate at week 52. Results from PATHWAY showed that tezepelumab significantly reduced the annualized rate of asthma exacerbations (62-71% compared to placebo) in all 3

dose groups. Results were consistent in subgroup analyses in patients with and without elevated eosinophils. Although there was no clear dose response, the tezepelumab 210 mg SC every 4 weeks had a numerically greater reduction in the rate of exacerbations, including hospitalizations related to exacerbations, so the Applicant chose this dose to carry forward into phase 3.

NAVIGATOR was a phase 3, randomized, double-blind, placebo-controlled, 52 week trial that evaluated tezepelumab 210 mg SC every 4 weeks in 1061 patients 12 years and older with severe asthma. Patients were required to have a history of 2 or more exacerbations in the previous 12 months. Patients were enrolled regardless of baseline eosinophil count. The primary endpoint for NAVIGATOR was the annualized exacerbation rate at week 52. Results from NAVIGATOR showed that treatment with tezepelumab significantly reduced the annualized rate of exacerbations compared with placebo (RR 0.44 [95% CI 0.37, 0.53]). There was also a significant reduction in exacerbations associated with ER visits and/or hospitalizations. Response based upon baseline eosinophils and FeNO are of interest. The reduction in exacerbations was significant, regardless of baseline eosinophil or baseline FeNO; however, the treatment effect was greater in patients with increasing baseline eosinophils and FeNO. Treatment with tezepelumab was also associated with an increase in FEV1 compared to placebo (0.13 L [95% CI 0.08, 0.18]) in the overall population. Finally, compared to placebo, more patients treated with tezepelumab had an improvement in ACQ-6 and AQLQ(S)+12.

SOURCE was a randomized, double-blind, placebo-controlled, 48 week clinical trial in 150 adult patients with severe asthma requiring OCS to evaluate the effect of tezepelumab 210 mg SC every 4 weeks in reducing daily OCS dose. The trial included an 8 week optimization phase (determine the minimum OCS dose to maintain asthma control) followed by a 48 week treatment period. During the treatment period, the OCS dose was reduced based upon protocol criteria. The primary endpoint was the categorized percent reduction from baseline in daily OCS dose without loss of asthma control at week 48. Results from SOURCE did not meet statistical significance for the primary endpoint. The odds ratio for percent reduction in daily OCS dose was 1.28 (95% CI, 0.69, 2.35). Although the primary endpoint was not significant, some secondary endpoints were numerically supportive of treatment with tezepelumab, including reduction in asthma exacerbation rate and improvement in FEV1.

Substantial evidence of effectiveness for tezepelumab is based upon results from two adequate and well-controlled trials, NAVIGATOR and PATHWAY. Although PATHWAY had some statistical issues that could have limited its utility to support substantial evidence of effectiveness (not powered for statistical significance level of 0.05 and no multiplicity adjustment plan for secondary endpoints), the results for the primary endpoint were statistically robust for all 3 tezepelumab treatment groups. In both trials, tezepelumab showed a significant reduction in the annualized rate of asthma exacerbations. This benefit was demonstrated regardless of baseline eosinophil or FeNO levels. This distinguishes tezepelumab from other biologic products that are indicated for a specific asthma population, such as eosinophilic phenotype or allergic asthma. Secondary endpoints in NAVIGATOR were also supportive of the benefit of tezepelumab, including an improvement in the change from baseline in FEV1, decreased

annualized rate of exacerbations associated with emergency room visits or hospitalizations, increased time to first exacerbation, and favorable AQLQ(6)+12 and ACQ-6 responder rates compared to placebo. SOURCE was also an adequate and well-controlled trial; however, SOURCE did not meet the primary endpoint, reduction in daily OCS use. Therefore, SOURCE is not considered one of the adequate and well controlled trials that support substantial evidence of effectiveness. However, SOURCE does provide some supportive evidence of the effectiveness of tezepelumab, including a numerical improvement in FEV1 with use of tezepelumab.

Safety

The safety of tezepelumab was based upon safety data from PATHWAY, NAVIGATOR, and SOURCE. The team focused the safety review on PATHWAY and NAVIGATOR, since these trials were similar in design and patient population and they provide substantial evidence of effectiveness. In the pooled safety database, there were 665 patients who received tezepelumab 210 mg Q 4 weeks and 669 patients who received placebo. The size of the database and the duration of exposure are adequate to assess the safety of this new biologic product intended for chronic use. There were no deaths in the tezepelumab group. SAEs were reported more frequently in the placebo group (14%) compared to tezepelumab (10%). Review of the SAE SOC and PT did not reveal a serious safety signal that was clearly related to tezepelumab. Common AEs include pharyngitis, arthralgia, and back pain. These will be included in the product label. Although data from the clinical program do not show a significant increase in hypersensitivity events with tezepelumab, the product label will include a warning regarding hypersensitivity reactions, given the known potential for hypersensitivity with biologic products and the patient population.

Benefit Risk Assessment

The overall benefit risk assessment of tezepelumab is favorable. The clinical development program showed that tezepelumab reduces exacerbations and increases lung function in patients with severe asthma regardless of baseline eosinophil count or FeNO level. Tezepelumab also showed improvement in patient reported assessments of asthma control and asthma quality of life. There were no serious safety concerns identified with tezepelumab that would outweigh the potential benefits. Since currently approved biologics for moderate to severe asthma target a specific asthma population, e.g. eosinophilic phenotype or allergic asthma, tezepelumab fulfills an unmet need by providing a treatment option for patients with severe asthma who do not have an eosinophilic phenotype.

Labeling

The Applicant proposed an indication for add on maintenance treatment (b) (4) (b) (4) The clinical team carefully reviewed the patient population enrolled in PATHWAY and NAVIGATOR. The team compared the enrolled patient population with GINA and NHLBI guidelines and to patient populations enrolled in other biologic development program. Considering baseline medication use, symptoms, asthma control, and exacerbations, the team determined the population was most consistent with severe asthma.

Therefore, the indication will be for patients with severe asthma. (b) (4) Results for exacerbations and lung function will be described in Section 14 of the product label. The approved indication will be the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

Pediatrics

The clinical program supports the efficacy and safety of tezepelumab for patients 12 years of age and older. There were a limited number of adolescents (n=82) enrolled in NAVIGATOR, with 41 adolescents treated with tezepelumab. Assessment of the available PK data showed that the serum trough concentration in adolescents was approximately 30% higher compared to adults. The clinical pharmacology team determined that no dose adjustment is needed in adolescents. Review of the clinical data in adolescents does not suggest a difference in efficacy or safety compared to adults. Given the similarity in disease between adolescents and adults, the available data are sufficient to support approval of tezepelumab in adolescents 12 years and older. Under PREA, the Applicant will be required to obtain additional data in pediatric patients < 12 years of age. Studies in children 2 to < 12 years of age will be deferred, while studies in children < 2 years of age will be waived because studies are impossible or highly impractical due to insufficient numbers of pediatric patients to study in this age group with severe asthma who require add-on treatment.

Recommendation

Although tezepelumab is a new first in class original biologic, the review team did not identify any issues that would benefit from discussion at an Advisory Committee meeting. The clinical program to support an asthma indication is well-established and results of the program clearly demonstrated efficacy. No serious safety concerns were identified. Therefore, an Advisory Committee was not convened for this application.

Overall, the submitted data support a favorable benefit risk profile for tezepelumab for the add on maintenance treatment of patients with severe asthma. All disciplines recommend approval and I agree with approval of this application. Labeling has been agreed upon between FDA and the Applicant. Tezepelumab provides a new treatment option for patients with severe asthma and importantly, the indication is not limited to patients with a specific asthma phenotype. Other than the PREA requirement noted above, there are no other post-marketing requirements or commitments.

15 Office Director Comments

I concur with the recommendation of the Division of Pulmonology, Allergy and Critical Care to approve BLA 761224 for tezepelumab. This is a first-in-class original biologic monoclonal antibody product that blocks thymic stromal lymphopoietin intended as add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. The recommended dose is 210 mg administered subcutaneously every 4 weeks. The approval of tezepelumab meets an unmet medical need for patients with severe asthma without an eosinophilic phenotype.

Effectiveness was demonstrated in two adequate and well-controlled trials enrolling a broad population of severe asthma patients, that is, not limited to an eosinophilic or allergic phenotype. Unlike other approved biologic products for moderate to severe asthma, tezepelumab treatment resulted in a significant reduction in annualized asthma exacerbation rate relative to placebo regardless of baseline eosinophil levels. Tezepelumab treatment was generally well tolerated. Development of anti-tezepelumab antibodies was infrequent and did not adversely impact the pharmacokinetics, pharmacodynamics, or safety of tezepelumab.

Given the similarity of the disease in adults and adolescents and the available pharmacokinetic, safety and efficacy data for adolescents in the clinical development program, approval is recommended for patients 12 years and older.

16 Appendices

16.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): PATHWAY (CD-RI-MEDI9929-1146)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 401		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study:0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 112		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NAVIGATOR (D5180C0007)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 1448		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 14		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): SOURCE (D5180C0009)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 256		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.2. OCP Appendices (Technical documents supporting OCP recommendations)

16.2.1. Pharmacometrics Review

16.2.1.1. Population Pharmacokinetics Analysis

In general, the Applicant's population pharmacokinetics analysis is considered acceptable to support the labeling claims. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Table 77. Specific Comments on the Applicant's Final Population PK Model

	Utility of the Final Model	Reviewer's Comments
Support labeling statements about PK parameters	Based on population pharmacokinetic analysis, the estimated absolute bioavailability was approximately 77%. Based on population pharmacokinetic analysis, central and peripheral volume of distribution of tezepelumab were 3.9 L and 2.2 L, respectively, for a 70 kg individual. Based on population pharmacokinetic analysis, the estimated clearance for tezepelumab was 0.17 L/d for a 70 kg individual.	The statements are acceptable
Support labeling statements about intrinsic factors	Based on population pharmacokinetic analysis, age, gender and race had no clinically meaningful effects on the pharmacokinetics of tezepelumab. Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure: patients with body weight of 49 kg and 114 kg (the 5th and 95th percentiles of NAVIGATOR) were expected to have 45% higher and 40% lower steady state exposure, respectively, compared with a typical subject with body weight of 70 kg. The population pharmacokinetic analysis included 320 volunteers or asthma patients (23%) with mild renal impairment and 38 asthma patients (3%) had moderate renal impairment. Tezepelumab clearance was similar in patients with mild renal impairment (estimated creatinine clearance 60 to 89 mL/min), moderate renal impairment (estimated creatinine clearance 30 to 59 mL/min) and those with normal renal function (estimated creatinine clearance ≥ 90 mL/min). Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no effect on tezepelumab clearance.	The statements are acceptable. Covariate analysis by the Applicant demonstrates no evident difference based on age, gender, and race. The higher exposure in lighter patients is not expected to cause safety issues, and the lower exposure in heavier patients is not expected to lead to compromised efficacy. Thus no dose adjustment is recommended.
Support labeling statements about extrinsic factors	Based on the population pharmacokinetic analysis, commonly co-administered asthma medications (leukotriene receptor antagonist, theophylline/aminophylline, oral and inhaled corticosteroid) had no clinically meaningful effect on tezepelumab clearance.	The statement is acceptable

Source: Pharmacometrics Reviewer

Abbreviations: AUC_{tau}, area under the curve over the dosing interval; C_{max}, maximum concentration; CV, coefficient of variation

Introduction

The primary objectives of the Applicant's analysis were to:

- Characterize the structural PK model and quantify the population variability in the PK parameters of tezepelumab.
- Evaluate the effects of intrinsic and extrinsic factors on tezepelumab exposure.

Model Development

Data

The population PK analysis dataset included data from 8 clinical studies: Phase 3 NAVIGATOR, Phase 2b PATHWAY, and 6 supportive Phase 1 studies (Studies 0620 [Part A], 0390, 1183, 0002, 0003, and PATH-BRIDGE). The original dataset included 12608 measurable serum samples and 33 BLQ samples (0.261%) from 1372 subjects. BLQ data were omitted from the popPK analysis. Of the 12608 measurable samples, a total of 67 (0.531%) were excluded from the popPK analysis (Table 78). The reasons for exclusion of PK samples were implausibly high or low concentrations, sampling time error, and outliers. The final Nonlinear Mixed-Effects Modeling data file for analysis contained 12541 PK observations from 1368 subjects. Table 79 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 78. Summary of Studies With PK Sampling Included in the Population PK Analysis

Study	Original Dataset	Data Exclusions (EXCLFL) [a]			Final Analysis Dataset
	No. Subject (No. Sample [b])	1	2	3	No. Subject (No. Sample [b])
0620	48 (817)	-	-	1	48 (816)
0390	37 (481)	-	-	-	37 (481)
1183	16 (299)	-	1	-	16 (298)
0002	21 (209)	-	-	-	21 (209)
0003	18 (294)	-	-	-	18 (294)
PATH-BRIDGE	313 (5295)	-	-	5	313 (5290)
PATHWAY	393 (2591)	25	-	28	389 (2538)
NAVIGATOR	526 (2622)	5	-	2	526 (2615)
Total	1372 (12608)	30	1	36	1368 (12541)

a. EXCLFL = 1 indicates implaus bly high or low concentrations; EXCLFL = 2 indicates scheduled post-dose sample taken during infusion; EXCLFL = 3 indicates outliers identified during initial model exploration, including |CWRES| > 5 and data from 2 subjects (ID = 454 and ID = 459) who had extremely high Vc values (40.8 L and 79.3 L versus population estimate of 4.35 L) based on model 11 (see Appendix C).
b. Samples that were below the limit of quantification (BLQ) are not included.

Abbreviations: CWRES, Conditional weighted residuals; EXCLFL, Exclusion flag; Vc, Volume of distribution of the central compartment.
Source: Table 3 in Applicant's population PK report.

Table 79. Summary of Baseline Covariates for Analysis

Covariate (unit)	Studies								
	0620 (Part A)	**0390**	**1183**	**0002**	**0003**	**PATH-BRDIGE**	**PATHWAY**	**NAVIGATOR**	**All Studies**
Number of subjects	48	37	16	21	18	313	389	526	1368
Number of PK samples	816	481	298	209	294	5290	2538	2615	12541
Continuous Covariates (Median [min-max])									
Age (years)	33 (20-44)	33 (19-45)	27 (18-50)	14 (12-17)	23 (20-42)	48 (19-65)	53 (20-75)	53 (12-80)	49 (12-80)
Body weight (kg)	75.8 (58.9-99.1)	76.9 (61.2-156)	63.8 (50-104)	56.5 (39.3-91.8)	60.5 (54.2-84 3)	73.1 (50.4-89.8)	77 (45-133)	75.6 (40 2-161)	75 (39.3-161)
Height (cm)	171 (150-187)	172 (153-194)	165 (156-188)	167 (145-193)	171 (157-182)	174 (137-197)	167 (147-198)	164 (139-192)	168 (137-198)
BMI (kg/m^2)	25.8 (20 5-31.6)	26.5 (19.8-64.1)	24.3 (20.5-29.8)	20.8 (16.9-27)	21.7 (18.9-25.8)	24.3 (18.5-29.8)	27.7 (18.3-39.8)	27.6 (17.1-62.9)	26.1 (16.9-64.1)
TBL (µmol/L)	12 (3.42-34.2)	8.55 (3.42-20.5)	7 (4-14)	6.84 (1.71-18.8)	17.1 (8.55-25.6)	11.6 (4.6-35.3)	6.84 (1.71-27.4)	7 (3-50)	8.55 (1.71-50)
AST (U/L)	21.5 (12-33)	20 (15-38)	17.5 (10-28)	24 (15-30)	17 (11-21)	22.9 (11.9-55.3)	19 (10-161)	18 (7.98-89)	20 (7.98-161)
ALT (U/L)	20 (9-51)	20 (9-69)	15.5 (10-39)	16 (9-26)	16 (10-35)	19.1 (7.2-54.6)	19 (6-105)	18 (4.02-106)	19 (4.02-106)
Creatinine (µmol/L)	78.7 (52 2-115)	78.7 (39.8-104)	77 (49-108)	67.2 (44 2-81.3)	79.6 (64.5-89.3)	72 (47.4-107)	71.6 (38.9-155)	71 (39-124)	71 (38 9-155)
CRCL (mL/min)	121 (80.1-170)	128 (95.3-458)	110 (90.5-160)	131 (91.7-188)	113 (86.6-154)	107 (59.3-209)	104 (37.3-217)	106 (35.7-294)	108 (35.7-458)
GFR (mL/min/1.73 m^2)	95.8 (62 5-131)	99.3 (72.6-166)	85.2 (62.8-137)	137 (94.3-235)	104 (81-136)	88.4 (58-145)	84.7 (36.1-163)	88.3 (42.9-249)	88 (36 1-249)
ALB (g/L)	46 (38-52)	45 (40-51)	43 (36-50)	48 (42-53)	45 (41-50)	43.8 (36.5-51.3)	45 (36-51)	-	44.5 (36-53)
Baseline CRP (mg/L)	-	-	-	-	-	0.63 (0.08-8.58)	-	2.18 (0.2-89.4)	1.25 (0.08-89.4)
Baseline FeNO (ppb)	-	-	-	-	-	-	22 (2-349)	31 (5-235)	26 (2-349)
Baseline EOS (cells/µL)	200 (100-900)	100 (100-900)	300 (98-600)	190 (40-970)	175 (80-590)	120 (20-800)	280 (10-3990)	250 (10-3650)	210 (10-3990)
Baseline total IgE (IU/mL)	-	-	-	-	-	-	131 (2-11400)	194 (1.5-12800)	162 (1 5-12800)
Categorical Covariates (N [%])									
Sex									
Male	37 (77.1%)	32 (86.5%)	6 (37.5%)	15 (71.4%)	18 (100%)	166 (53.0%)	137 (35.2%)	191 (36.3%)	602 (44.0%)
Female	11 (22.9%)	5 (13.5%)	10 (62.5%)	6 (28.6%)	-	147 (47.0%)	252 (64.8%)	335 (63.7%)	766 (56.0%)
Age group									
12 to < 18	-	-	-	21 (100%)	-	-	-	40 (7.6%)	61 (4.5%)
18 to < 65	48 (100%)	37 (100%)	16 (100%)	-	18 (100%)	307 (98.1%)	335 (86.1%)	391 (74.3%)	1152 (84.2%)
≥ 65	-	-	-	-	-	6 (1.9%)	54 (13.9%)	95 (18.1%)	155 (11 3%)

Race									
Asian	2 (4.2%)	-	2 (12.5%)	-	18 (100%)	1 (0.3%)	13 (3.3%)	146 (27.8%)	182 (13 3%)
Black or African American	5 (10.4%)	2 (5.4%)	-	-	-	-	13 (3.3%)	29 (5.5%)	49 (3.6%)
White	13 (27.1%)	13 (35.1%)	14 (87.5%)	21 (100%)	0 (0%)	306 (97.8%)	358 (92.0%)	332 (63.1%)	1057 (77.3%)
Other	28 (58.3%)	22 (59.5%)	-	-	-	6 (1.9%)	5 (1.3%)	19 (3.6%)	80 (5.8%)
Ethnicity									
Non-Japanese	48 (100%)	37 (100%)	16 (100%)	21 (100%)	-	313 (100%)	376 (96.7%)	468 (89.0%)	1279 (93.5%)
Japanese	-	-	-	-	18 (100%)	-	13 (3.3%)	58 (11.0%)	89 (6.5%)
Disease status									
Healthy Volunteer	48 (100%)	37 (100%)	-	-	18 (100%)	313 (100%)	-	-	416 (30.4%)
Asthma Patient	-	-	16 (100%)	21 (100%)	-	-	389 (100%)	526 (100%)	952 (69.6%)
Inhaled corticosteroid (ICS) dose									
No	48 (100%)	37 (100%)	16 (100%)	-	18 (100%)	313 (100%)	-	-	432 (31.6%)
Low	-	-	-	16 (76.2%)	-	-	-	-	16 (1.2%)
Medium	-	-	-	5 (23.8%)	-	-	196 (50.4%)	131 (24.9%)	332 (24.3%)
High	-	-	-	-	-	-	193 (49.6%)	395 (75.1%)	588 (43.0%)
Subject-level ADA status (IM)									
Negative	48 (100%)	36 (97.3%)	16 (100%)	20 (95.2%)	18 (100%)	303 (96.8%)	378 (97.2%)	500 (95.1%)	1319 (96.4%)
Positive	-	1 (2.7%)	-	1 (4.8%)	-	10 (3.2%)	11 (2.8%)	26 (4.9%)	49 (3.6%)
Subject-level nAb status									
Negative	48 (100%)	37 (100%)	16 (100%)	21 (100%)	18 (100%)	303 (96.8%)	389 (100%)	525 (99.8%)	1357 (99.2%)
Positive	-	-	-	-	-	-	-	1 (0.2%)	1 (0.1%)
Missing	-	-	-	-	-	10 (3.2%)	-	-	10 (0.7%)
Concomitant leukotriene receptor antagonist (LTRA)									
No	48 (100%)	37 (100%)	16 (100%)	16 (76.2%)	18 (100%)	313 (100%)	296 (76.1%)	311 (59.1%)	1055 (77.1%)
Yes	-	-	-	5 (23.8%)	-	-	93 (23.9%)	215 (40.9%)	313 (22.9%)
Concomitant theophylline/aminophylline (PHL)									
No	48 (100%)	37 (100%)	16 (100%)	21 (100%)	18 (100%)	313 (100%)	355 (91.3%)	466 (88.6%)	1274 (93.1%)
Yes	-	-	-	-	-	-	34 (8.7%)	60 (11.4%)	94 (6.9%)
Concomitant oral corticosteroids (OCS)									
No	48 (100%)	37 (100%)	16 (100%)	21 (100%)	18 (100%)	313 (100%)	366 (94.1%)	476 (90.5%)	1295 (94.7%)
Yes	-	-	-	-	-	-	23 (5.9%)	50 (9.5%)	73 (5.3%)
Smoking history									
Never	-	-	-	21 (100%)	-	189 (60.4%)	305 (78.4%)	428 (81.4%)	943 (68.9%)

Former	-	-	-	-	-	124 (39.6%)	84 (21.6%)	98 (18.6%)	306 (22.4%)
Missing	48 (100%)	37 (100%)	16 (100%)	-	18 (100%)	-	-	-	119 (8.7%)
Formulation									
(b) (4)	48 (100%)	37 (100%)	16 (100%)	21 (100%)	18 (100%)	-	389 (100%)	-	529 (38.7%)
(b) (4)	-	-	-	-	-	313 (100%)	-	526 (100%)	839 (61.3%)

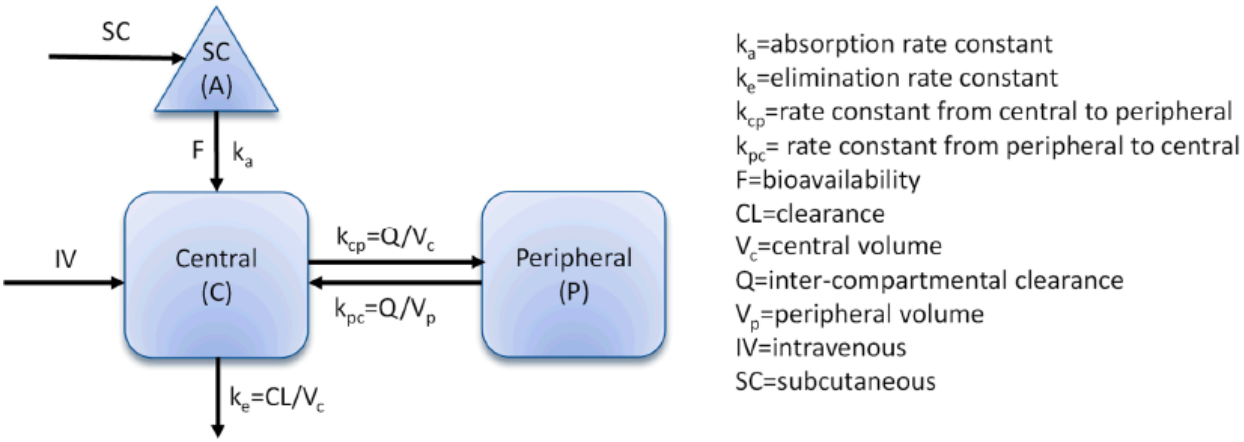
- Creatinine clearance is calculated as: (140 - Age) × Body weight / (72 × Creatinine [µmol/L] / 88.4) × 0.85 (if Female).
- Estimated glomerular filtration rate is calculated as: (175 × (Creatinine [µmol/L] / 88.4)-1.154 × Age-0.203 × 0.742 (if Female) × 1.212 (if Black).
- Subject-level ADA status is positive if ADA is positive at any time; negative if all ADA samples are negative.
- Subject-level nAb status is positive if nAb is positive at any time; negative if all samples are negative for ADA or all ADA positive samples are tested negative for nAb; missing if any sample is positive for ADA but not tested for nAb.

Abbreviations: ADA, Anti-drug ant bodies; ALB, Albumin; ALT, Alanine aminotransferase; AST, Aspartate transaminase; BMI, Body mass index; CRCL, Creatinine clearance; CRP, C-reactive protein; EOS, Blood eosinophil count; FeNO, Fractional exhaled nitric oxide; GFR, Estimated glomerular filtration rate; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; IM, Subject-level ADA status; LTRA, Leukotriene receptor antagonist; max, Maximum; MAXTIT, Maximum ADA titre within a subject; min, Minimum; max, Maximum; N, Number of subjects; nAb, Neutralising antibodies; OCS, Oral corticosteroids; PHL, Theophylline/aminophylline; TBL, Total bilirubin.
Source: Revised from Table 4 in Applicant's population PK report.

Base Model

The base model for tezepelumab was a linear two-compartment model with first-order absorption and linear elimination (Figure 37). Interindividual variability was modelled assuming a log-normal distribution for patient-level random effects. A combined additive and proportional error model was selected based on model fitness.

Figure 37. Population PK Model Diagram for Tezepelumab



Source: Figure 1 in Applicant's Population PK report.

Covariate Analysis

The covariate modelling process begins with the univariate testing, where each covariate was added to the base model one at a time. The effects of sex, race, TBL, disease status, ICS dose level and formulation on CL and age, age group, race, disease status, ICS dose level, and formulation on Vc were found significant ($p < 0.01$) in this univariate testing. The coveriate showed the most significant decrease in OFV was added to the base model in the first forward

selection step. And the other significant covariates were then tested on this first forward model. This procedure was repeated until all significant covariate relationships identified in the forward selection steps were included (full covariate model). Next, covariates were excluded from the full covariate model one at a time using a stepwise backward elimination method. The criterion for retention was $p < 0.001$ for the likelihood ratio test, corresponding to an increase in OFV of greater than 10.83 for removal of one parameter.

Final Model

The final model (Model 66a) was a two-compartment model with first-order absorption and linear elimination. The final popPK model includes the covariate effects of body weight on CL, Vc, Q, and Vp (as part of the base model), ICS dose level on CL and Vc, Asian race on CL, formulation on CL, as well as age on Vc.

The parameter estimates for the final model are listed in Table 80, and the goodness-of-fit plots in Figure 38. Selected visual predictive check plots for the final model are shown in Figure 39. The parameter-covariate relationships in the final popPK model, namely the effect of body weight on CL, Q, Vc, and Vp, ICS dose level on CL and Vc, race and formulation on CL, and age on Vc are illustrated in Figure 40.

The influence of each statistically significant covariate in the final popPK model (body weight, age, race, formulation, and ICS dose level) was evaluated independently on the predicted steady state exposure (AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$) of tezepelumab in a sensitivity analysis. Each covariate was varied one at a time from its typical value to a high/low value of continuous covariates or possible values of categorical covariates, and the steady state exposures of tezepelumab following 210 mg SC Q4W dosing for 52 weeks were predicted for each of the scenarios based on the final popPK model. The sensitivity analysis results are shown in

Figure 41. Body weight was shown to be the most influential covariate on tezepelumab exposure. Compared with a typical subject with body weight of 70 kg, subjects with body weight at the 5th percentile of the NAVIGATOR population (49 kg) were expected to have 43.2%, 41.8%, and 46.1% higher AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, respectively, while subjects with the 95th percentile of body weight (114 kg) were expected to have 38.8%, 38.0%, and 40.5% lower AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$, respectively. The effects of ICS dose level, formulation, race, and age on tezepelumab exposure were relatively small (≤20% exposure change).

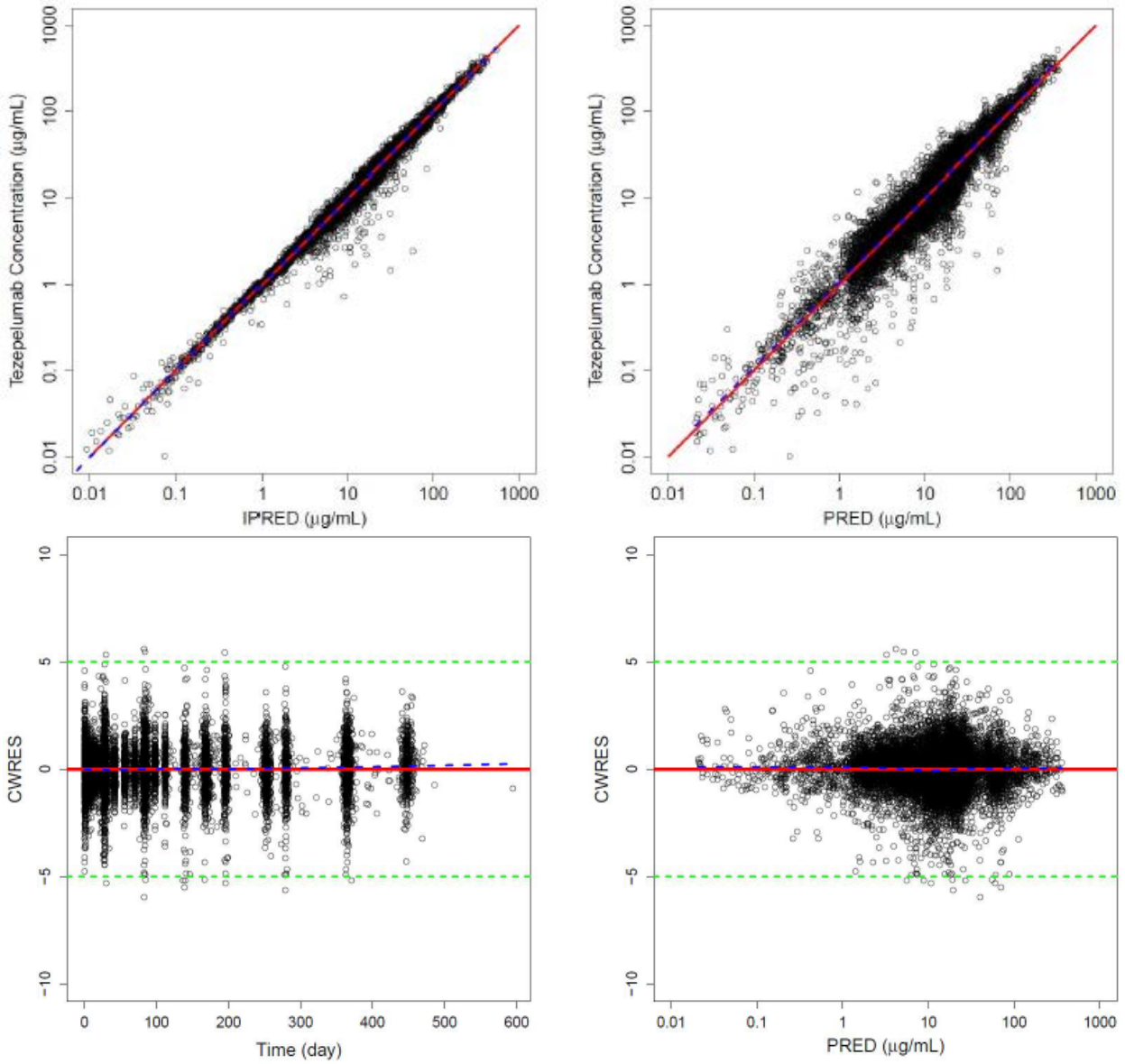
Table 80. Summary of Final Population PK Parameters (Model 66a)

Parameter	Parameter Description	Final popPK Model [a]		
		Estimate (% RSE)	95% CI from Bootstrapping	Shrinkage (%)
$exp(\theta_1)$	Clearance (CL) (L/day)	0.172 (3.89%)	(0.159, 0.186)	-
θ_7	Influence of body weight on CL	1.01 (4.28%)	(0.915, 1.09)	-
θ_{11}	Influence of no or low ICS dose level on CL	-0.168 (11.0%)	(-0.203, -0.133)	-
θ_{13}	Influence of Asian race on CL	0.0867 (24.1%)	(0.0444, 0.127)	-
θ_{15}	Influence of Clinical Process 1 formulation on CL	0.0955 (14.7%)	(0.0671, 0.127)	-
$exp(\theta_2)$	Central volume, V_c (L)	3.91 (5.68%)	(3.47, 4.32)	-
θ_8	Influence of body weight on V_c	0.963 (11.8%)	(0.677, 1.21)	-
θ_{12}	Influence of no or low ICS dose level on V_c	-0.102 (26.9%)	(-0.161, -0.0402)	-
θ_{14}	Influence of age on V_c	0.195 (14.7%)	(0.132, 0.261)	-
$exp(\theta_3)$	Inter-compartmental clearance (Q) (L/day)	0.568 (4.95%)	(0.506, 0.647)	-
θ_9	Influence of body weight on Q	0.588 (48.8%)	(3.42e-6, 1.19)	-
$exp(\theta_4)$	Peripheral volume, V_p (L)	2.17 (3.46%)	(1.98, 2.37)	-
θ_{10}	Influence of body weight on V_p	0.609 (20.5%)	(0.346, 0.895)	-
$exp(\theta_5)$	Absorption rate constant, k_a (1/day)	0.316 (3.41%)	(0.292, 0.34)	-
$exp(\theta_6)/(1+exp(\theta_6))$	Bioavailability after SC administration, F (%)	76.8 (3.61% [b])	(71.6, 82.7)	-
ω_{CL}	IIV for CL (CV%)	29.9 (2.13%)	(28.2, 31.7)	2.67
ω_{Vc}	IIV for V_c (CV%)	35.8 (3.87%)	(32.2, 40.0)	17.2
ω_Q	IIV for Q (CV%)	47.9 (9.66%)	(32.5, 64.6)	62.1
ω_{Vp}	IIV for V_p (CV%)	13.1 (13.1%)	(8.15, 16.3)	67.4
ω_{ka}	IIV for k_a (CV%)	38.8 (4.77%)	(33.2, 43.4)	49.4
$\Omega_{CL\sim Vc}$	Covariance (CL~V_c)	0.0734 (6.81%)	(0.0608, 0.0879)	-
σ_a	Additive residual error (µg/mL)	0.0191 (12.5%)	(3.30e-6, 0.0298)	11.3
σ_p	Proportional residual error (%)	13.9 (0.774%)	(13.3, 14.5)	11.3

a. The final popPK model is model 66a (see Appendix C).
b. The relative standard error for the original non-transformed bioavailability estimate (RSE_F) was calculated from the standard error of the logit transformed parameter θ_6 (SE_θ_6) by linear approximation using the following equation: RSE_F = (1-F) × SE_θ_6 × 100%.

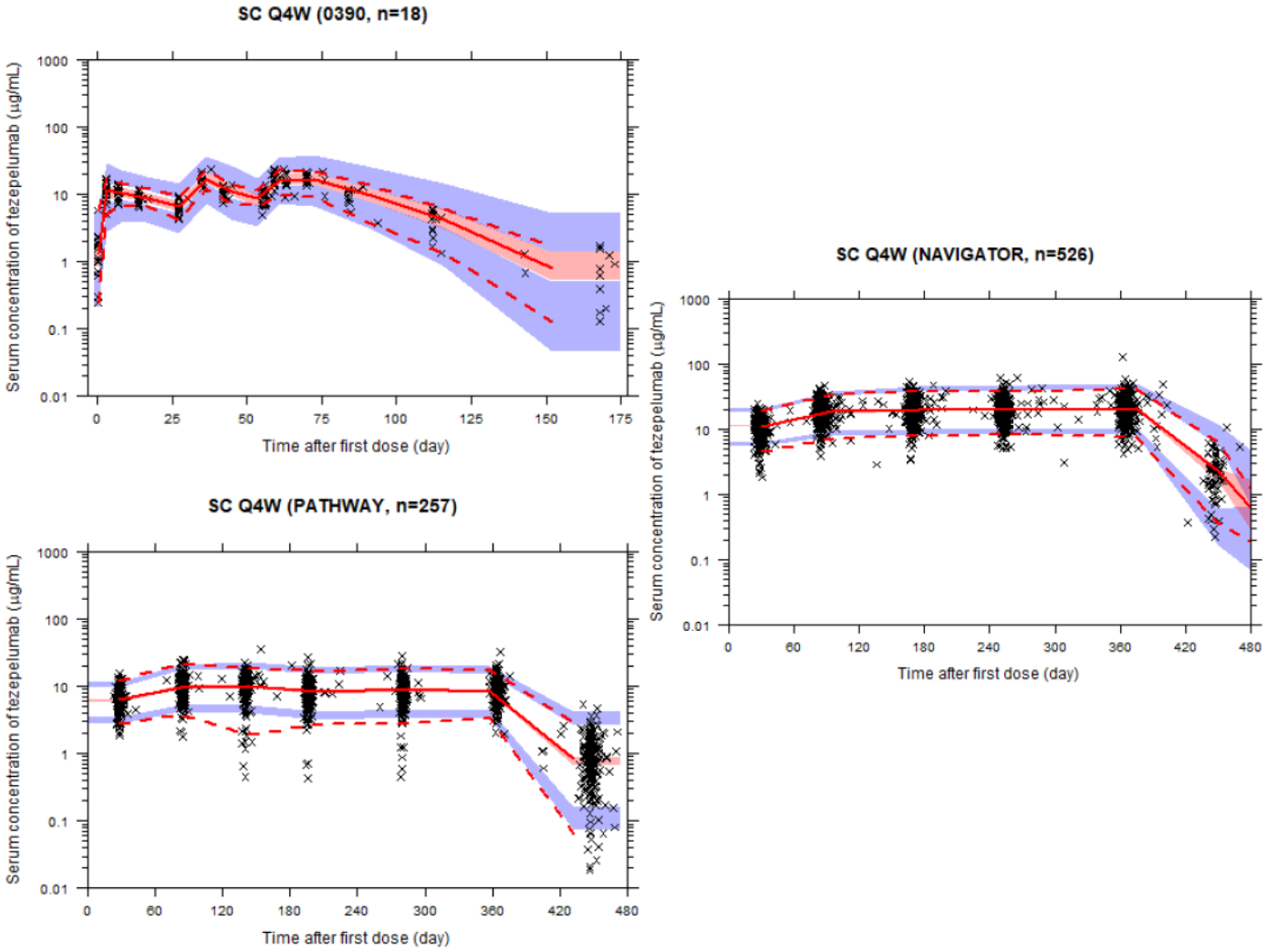
Abbreviations: CI, Confidence interval; CV, Coefficient of variation; ICS, Inhaled corticosteroid; IIV, Interindividual variability; RSE, Relative standard error; SC, Subcutaneous; SE, Standard error.
Source: Table 7 in Applicant's Population PK report.

Figure 38. Goodness-of-Fit Plots for the Final Model



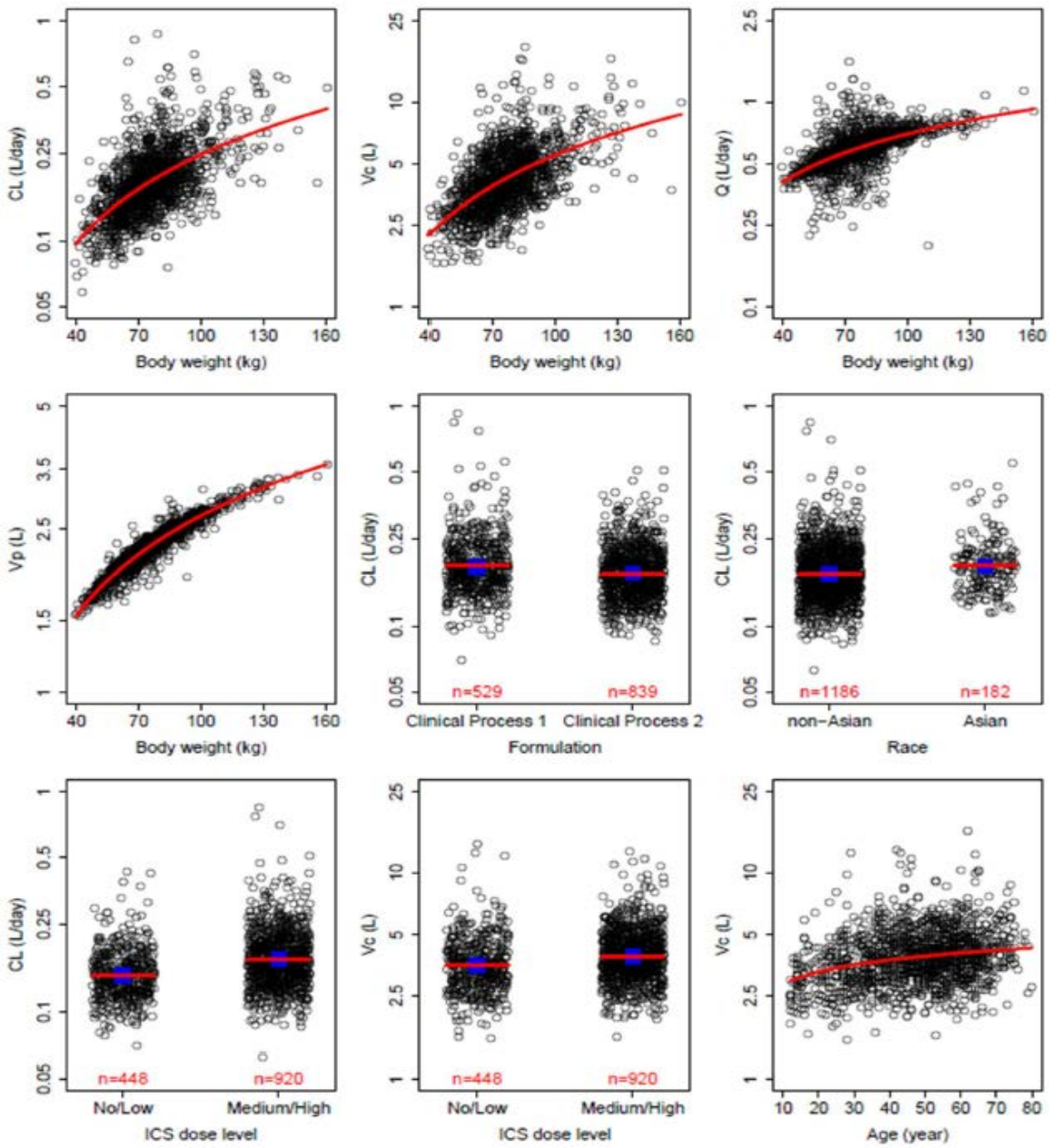
Circles are individual data points. Red solid lines represent the line of equality. The blue dashed lines are LOWESS smooth curves showing the relationship between the 2 variables.
Abbreviations: IPRED, Individual predicted concentrations; PRED, Population predicted concentrations; LOWESS, Locally weighted scatterplot smoothing; CWRES, Conditional weighted residuals.
Source: Figure 5 and 6 in the Applicant's Population PK report.

Figure 39 Prediction-corrected Visual Predictive Check Plots for the Final Model Following SC Q4W Administration: Studies 0390, PATHWAY, and NAVIGATOR



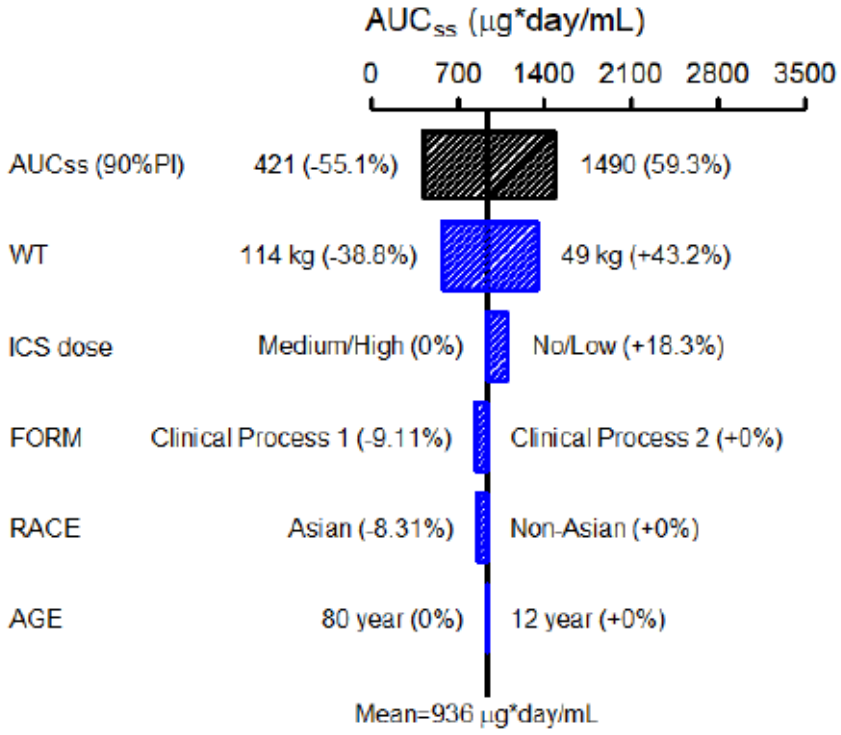
Black cross symbols are individual observed concentrations, solid red lines represent the median observed concentrations, and dashed red lines represent 2.5th and 97.5th percentiles of the observed concentrations over time. Pink shaded areas represent the 95% CI of the predicted median concentrations, and blue shaded areas represent the 95% CI of the predicted 2.5th and 97.5th percentiles of the concentrations over time.
Abbreviations: CI, Confidence interval; Q4W, Once every 4 weeks; n, Number of subjects; SC, Subcutaneous.
Source: Figure 15 in the Applicant's Population PK report.

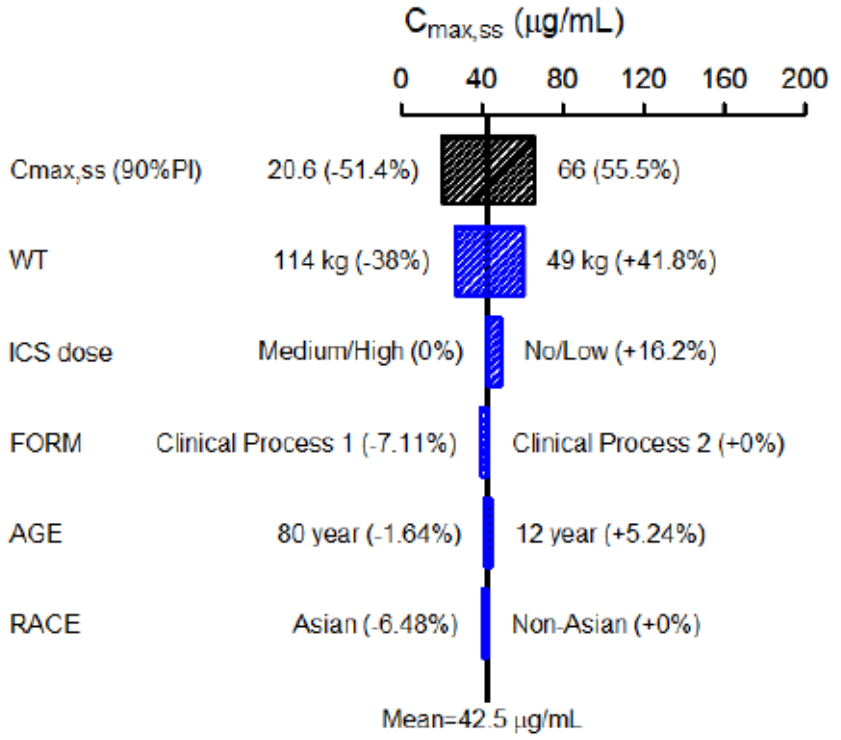
Figure 40. Pharmacokinetic Parameter-covariate Relationships for the Final Population PK Model

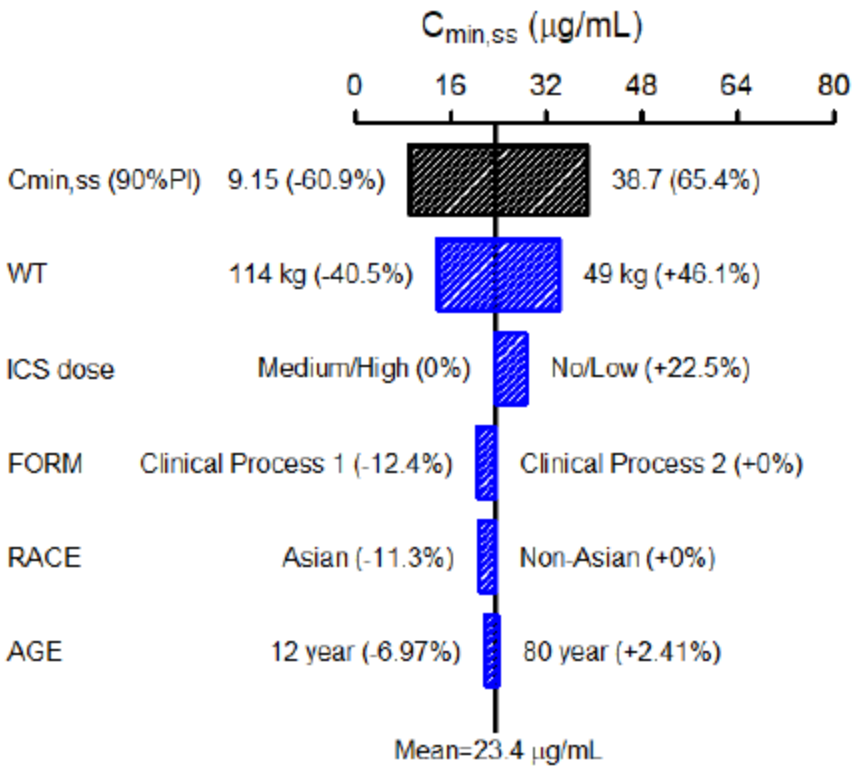


Circles are the empirical Bayes estimates of individual PK parameters after correcting for all other covariates (except for the one plotted in the x-axis). Blue squares represent the geometric mean values within the group for categorical covariates. Red lines represent the typical (population) predicted parameter-covariate relationship based on the model.
Abbreviations: CL, Clearance from the central compartment; ICS, Inhaled corticosteroid; n, Number of subjects; Q, Intercompartmental clearance between the central and peripheral compartments; Vc, Volume of distribution of the central compartment; Vp, Volume of distr bution of the peripheral compartment.
Source: Figure 9 in the Applicant's Population PK report.

Figure 41 The Effect of Significant Covariates on Tezepelumab Exposure (AUCss, Cmax,ss, and Cmin,ss)







The black vertical line refers to the predicted exposure (AUCss, Cmax,ss, and Cmin,ss) of tezepelumab in a typical subject after 210 mg tezepelumab Q4W SC dosing for 52 weeks which serve as the reference values. All percentage values shown in each plot are the relative changes in exposure compared with the reference value. The black shaded bar with values at each end shows the 5th to 95th percentile exposure range across the NAVIGATOR population. Each blue shaded bar represents the magnitude of influence of the respective covariate on the exposure. The length of each bar represents the magnitude of change in predicted exposure caused by changing the covariate from its reference to the low or high values or other possible values (indicated on the 2 sides of the bars). The covariates shown in each plot are ordered from the most influential covariate at the top to the least influential covariate at the bottom.
Abbreviations: AUCss, Area under curve at steady state (over 4 weeks); Cmax,ss, Maximum concentration at steady state; Cmin,ss, Trough concentration at steady state; FORM, Formulation; ICS, Inhaled corticosteroid; PI, Prediction interval; Q4W, Every 4 weeks; SC, Subcutaneous; WT, Body weight.
Source: Figure 16 in the Applicant's Population PK report.

Simulations

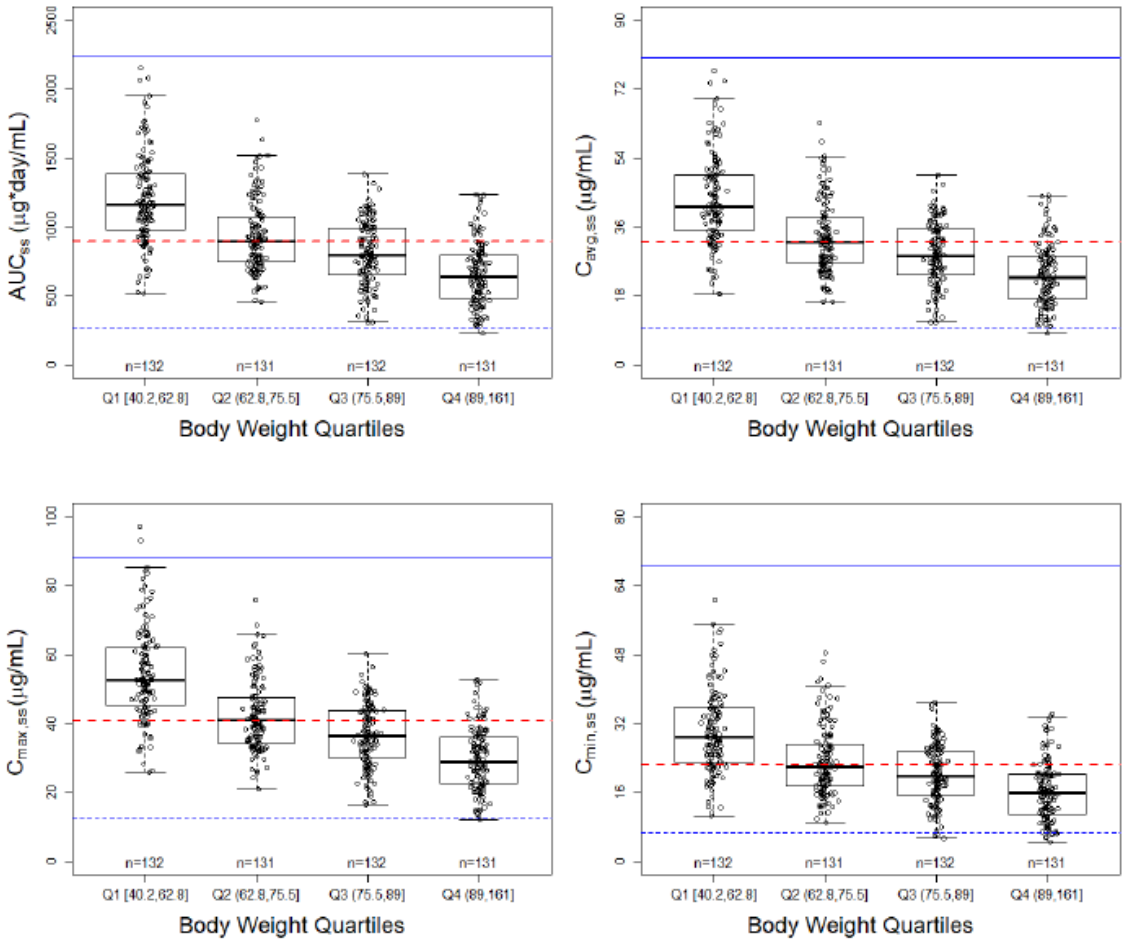
Body weight was identified as the most significant covariate on the CL, Vc, Q, and Vp of tezepelumab in the final popPK model. Increased body weight was associated with increased CL, Vc, Q, and Vp values. Therefore, subjects with higher body weight were predicted to have lower exposure. Simulations based on the final model were conducted by the Applicant to predict the steady state exposures following 210 mg SC Q4W dosing for subjects in the NAVIGATOR study stratified by body weight quartiles (Table 81 and Figure 42).

Table 81. Mean (SD) Simulated Steady State Exposure of Tezepelumab by Body Weight Quartiles following 210 mg SC Q4W dosing

Characteristics		Body Weight Quartiles			
		Q1	Q2	Q3	Q4
Number of subjects (%)		132 (25.1)	131 (24.9)	132 (25.1)	131 (24.9)
AUC_{ss} (µg*day/mL)	mean (SD)	1200 (324)	933 (256)	812 (226)	656 (226)
	% difference [a]	33.4	3.55	-9.90	-27.2
$C_{avg,ss}$ (µg/mL)	mean (SD)	42.9 (11.6)	33.3 (9.16)	29 (8.07)	23.4 (8.07)
	% difference [a]	33.4	3.55	-9.90	-27.2
$C_{max,ss}$ (µg/mL)	mean (SD)	54.6 (13.4)	42.3 (10.2)	36.7 (9.16)	29.8 (9.16)
	% difference [a]	33.6	3.50	-10.2	-27.1
$C_{min,ss}$ (µg/mL)	mean (SD)	30.1 (9.58)	23.3 (7.94)	20.3 (6.69)	16.2 (6.73)
	% difference [a]	33.8	3.66	-9.78	-27.9
Body weight (kg) [min, median, max]		[40.2; 55; 62.8]	[62.9; 69; 75.5]	[75.6; 82.2; 89]	[89.1; 100; 161]

a. % difference from the mean simulated exposures of the overall NAVIGATOR population
Abbreviations: AUCss, Area under curve at steady state (over 4 weeks); Cavg,ss, Average concentration at steady state; Cmax,ss, Maximum concentration at steady state; Cmin,ss, Trough concentration at steady state; max, Maximum; min, Minimum; Q1/2/3/4, First/second/third/fourth quartile; Q4W, Every 4 weeks; SC, Subcutaneous; SD,
Standard deviation.
Source: Table 11 of the Applicant's Population PK report.

Figure 42. Simulated Steady State Exposures of Tezepelumab by Body Weight Quartiles following 210 mg SC Q4W dosing



Circles are the simulated steady state tezepelumab exposure in individual subjects. The boxes represent the 25th to 75th percentiles (the interquartile range). The solid black horizontal line in the middle of each box represents the median. The whiskers represent the range of data points within 1.5 times the interquartile range. The dashed red horizontal line represents the mean of the overall NAVIGATOR population. The blue solid and dotted horizontal lines represent the mean of the simulated exposure at 280 mg SC Q2W and 70 mg SC Q4W in PATHWAY study, respectively.
Abbreviations: AUCss, Area under curve at steady state (over 4 weeks); Cavg,ss, Average concentration at steady state; Cmax,ss, Maximum concentration at steady state; Cmin,ss, Trough concentration at steady state; Q1/2/3/4, First/second/third/fourth quartile; Q2W, Every 2 weeks; Q4W, Every 4 weeks; SC, Subcutaneous.
Source: Figure 19 of the Applicant's Population PK report

Reviewer's comments: *In general, the Applicant's population PK analysis is considered acceptable to support the labeling claims in Section 12.3 of the prescribing information. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.*

Bodyweight is a major factor that influences the exposure of tezepelumab. Based on population pharmacokinetic analysis, higher body weight was associated with lower exposure: patients with body weight of 49 kg and 114 kg (the 5th and 95th percentiles of NAVIGATOR) were expected to have 45% higher and 40% lower steady state exposure, respectively, compared with a typical subject with body weight of 70 kg. Due to the flat exposue/dose-response relationship for efficacy and safety, no expected safety concerns or loss of efficacy was expected in subjects

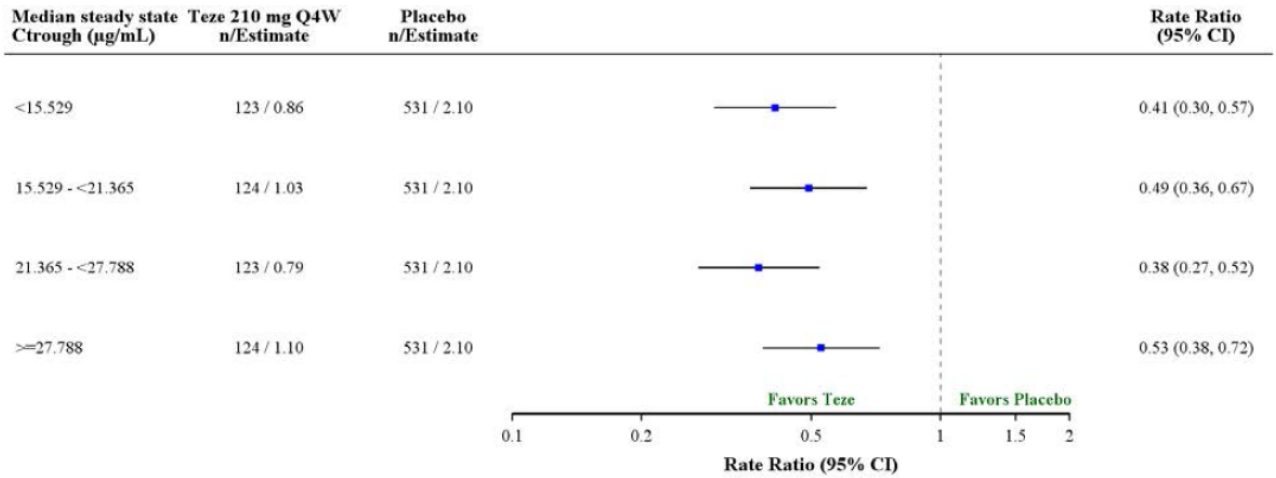
with low body weight or high body weight, respectively, therefore, no dose adjustment is recommended.

16.2.1.2. Exposure–Response Analysis

Exposure– Response Relationship for effectiveness

The exposure-response (E-R) relationship for the primary efficacy endpoint (asthma exacerbation rate) is flat based on analysis using data from the Phase 3 study NAVIGATOR as shown in Figure 43. This is consistent with the flatness of dose-response observed in dose-ranging Study PATHWAY (Table 82).

Figure 43 Forest Plot of Annualised Asthma Exacerbation Rate Ratio Over 52 Weeks by Observed Median Steady State Trough Concentration Quartiles in Study NAVIGATOR, Planned Treatment (Full Analysis Set)



The marginal ratio is presented. The rate ratio is displayed on the log scale. The dotted line represents no treatment difference.
Model: a negative binomial regression analysis with concentration quartiles (5 groups: Q1, Q2, Q3, Q4, and placebo), region, age group, and history of exacerbations as covariates.
The logarithm of each subject's corresponding time at risk was used as an offset variable in the model.
The median $C_{trough,ss}$ for each subject was calculated as the median of the observed tezepelumab concentrations at Week 24 (pre-dose), Week 36 (pre-dose), and Week 52.
$C_{trough,ss}$, Steady state trough concentration; CI, Confidence interval; n, number of subjects in analysis; Q, quartile; Q4W, Every 4 weeks; Teze, Tezepelumab.
Source: Figure 2 in the Exposure-Response analysis report in Module 5.3.4.2.

Table 82 Summary of Annual Asthma Exacerbation Rate Through Week 52 (ITT Population) in Study PATHWAY

Parameters	Placebo N = 138	Tezepelumab		
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137
Rate [a]	0.72	0.27	0.20	0.23
95% CI of rate [a]	(0.59, 0.88)	(0.19, 0.38)	(0.13, 0.30)	(0.16, 0.34)
Rate ratio [b]	---	0.38	0.29	0.34
95% CI of rate ratio [b]	---	(0.23, 0.63)	(0.16, 0.51)	(0.20, 0.58)
p-value [c]	---	< 0.001	< 0.001	< 0.001

CI = confidence interval; ITT = intent to treat; Q2W = every 2 weeks; Q4W = every 4 weeks

[a] Rate = total number of asthma exacerbations in each group/total person-year follow-up in each group; 95% CI for rate was based on the exact 95% Poisson CI.

[b] Rate ratio, and 95% CI for rate ratio were estimated from negative binomial regression with treatment group, and the stratification factors- baseline blood eosinophil count (≥ or < 250 cells/μL) and baseline ICS dose level (medium or high) as the covariates.

[c] Nominal p-value was from the negative binomial regression based on pairwise comparisons against the placebo group

Source: Table 11.4.1-1 in the CSR for Study PATHWAY

Exposure– Response Relationship for safety

No formal exposure-response relationship of safety was evaluated. No apparent dose-response relationship was observed for drug-related adverse events from Study PATHWAY. Adverse events in the SOCs of Infections and Infestations, Respiratory, Thoracic and Mediastinal Disorders, Musculoskeletal and Connective Tissue Disorders, and Gastrointestinal Disorders were the most frequent (incidence ≥10% in the tezepelumab total group) and occurred at similar frequencies across the tezepelumab and placebo treatment groups (Table 83).

Table 83 Summary of TEAEs, Regardless of Causality, by System Organ Class, As-treated Population

SOC [a] (MedDRA Version 19.1)	Placebo N = 138	Tezepelumab			
		70 mg Q4W N = 138	210 mg Q4W N = 137	280 mg Q2W N = 137	Total N = 412
Total subjects with ≥ 1 TEAE	91 (65.9%)	93 (67.4%)	90 (65.7%)	89 (65.0%)	272 (66.0%)
Infections and infestations	56 (40.6%)	60 (43.5%)	56 (40.9%)	54 (39.4%)	170 (41.3%)
Respiratory, thoracic and mediastinal disorders	54 (39.1%)	44 (31.9%)	34 (24.8%)	44 (32.1%)	122 (29.6%)
Musculoskeletal and connective tissue disorders	17 (12.3%)	15 (10.9%)	18 (13.1%)	14 (10.2%)	47 (11.4%)
Gastrointestinal disorders	11 (8.0%)	14 (10.1%)	14 (10.2%)	17 (12.4%)	45 (10.9%)
Nervous system disorders	11 (8.0%)	10 (7.2%)	19 (13.9%)	8 (5.8%)	37 (9.0%)

Injury, poisoning and procedural complications	11 (8.0%)	8 (5.8%)	9 (6.6%)	10 (7.3%)	27 (6.6%)
Skin and subcutaneous tissue disorders	9 (6.5%)	8 (5.8%)	8 (5.8%)	11 (8.0%)	27 (6.6%)
Vascular disorders	8 (5.8%)	11 (8.0%)	6 (4.4%)	7 (5.1%)	24 (5.8%)
General disorders and administration site conditions	12 (8.7%)	8 (5.8%)	9 (6.6%)	6 (4.4%)	23 (5.6%)
Cardiac disorders	5 (3.6%)	4 (2.9%)	6 (4.4%)	4 (2.9%)	14 (3.4%)
Reproductive system and breast disorders	2 (1.4%)	4 (2.9%)	3 (2.2%)	4 (2.9%)	11 (2.7%)
Ear and labyrinth disorders	1 (0.7%)	3 (2.2%)	3 (2.2%)	3 (2.2%)	9 (2.2%)
Immune system disorders	4 (2.9%)	2 (1.4%)	2 (1.5%)	5 (3.6%)	9 (2.2%)
Investigations	3 (2.2%)	4 (2.9%)	2 (1.5%)	3 (2.2%)	9 (2.2%)
Metabolism and nutrition disorders	0	3 (2.2%)	5 (3.6%)	1 (0.7%)	9 (2.2%)
Psychiatric disorders	3 (2.2%)	2 (1.4%)	3 (2.2%)	4 (2.9%)	9 (2.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.4%)	2 (1.4%)	4 (2.9%)	2 (1.5%)	8 (1.9%)
Renal and urinary disorders	4 (2.9%)	1 (0.7%)	3 (2.2%)	3 (2.2%)	7 (1.7%)
Endocrine disorders	0	4 (2.9%)	1 (0.7%)	1 (0.7%)	6 (1.5%)
Eye disorders	2 (1.4%)	4 (2.9%)	0	2 (1.5%)	6 (1.5%)
Hepatobiliary disorders	2 (1.4%)	3 (2.2%)	0	3 (2.2%)	6 (1.5%)
Blood and lymphatic system disorders	1 (0.7%)	2 (1.4%)	1 (0.7%)	1 (0.7%)	4 (1.0%)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.7%)	1 (0.7%)	2 (0.5%)
Social circumstances	1 (0.7%)	0	0	0	0

incl = including; MedDRA = Medical Dictionary for Regulatory Activities; Q2W = every 2 weeks; Q4W = every 4 weeks; SOC = System Organ Class;
TEAE = treatment-emergent adverse event.
a Subjects were counted once for each SOC regardless of the number of events.
Source: Table 12.2.3.1-1 in the CSR for Study PATHWAY

16.2.2. Clinical Pharmacology Related Individual Study Review

Clinical pharmacology-related clinical studies

Table 84 Overview of Drug Administration, Dosing Regimen, and Pharmacokinetic Sampling Time Points by Protocol

Study number (abbreviation)	Route of administration and dosage regimen	Pharmacokinetic sampling time points
20070620 (Study 0620) Part A[a]	Single doses of 2.1, 7, 21, 70, 210, and 420 mg SC, 210 or 700 mg IV, or placebo SC/IV.	Day 1, pre-dose (within 30 minutes before dosing), at 15 minutes (IV cohorts only), 30 minutes (IV cohorts only), 1 hour (or at the time when infusion stopped for IV cohorts only), 4, 8, 24, 48, and 72 hours post-dose, and Days 5, 6, 7, 11, 15, 22, 29, 43, 57, 71, 85, and 113 (Cohorts 6, 7, and 8 only).

20080390 (Study 0390)	The study comprised 5 SC cohorts and 1 IV cohort of 8 healthy subjects each, randomised (3:1) to receive tezepelumab or placebo at 35 (Cohort 1), 105 (Cohort 2), or 210 mg (Cohort 3) SC Q4W (total of 3 doses), 210 mg SC Q2W (total of 6 doses) (Cohort 4), 210 mg SC QW (total of 12 doses) (Cohort 5), or 700 mg IV Q4W (total of 3 doses) (Cohort 6).	Cohorts 1 to 3: Day 1 (pre-dose, 4-hours post-dose), Days 4, 8, 15, 28, 36, 43, 56, 57 (4 hours post-dose), 60, 64, 71, 85, 113, and 169. Cohort 4: Day 1 (pre-dose, 4-hours post-dose), Days 4, 8, 15 (pre-dose), 29 (pre-dose), 43 (pre-dose), 57 (pre-dose and 4 hours post-dose), 71 (pre-dose and 4 hours post-dose), 74, 78, 85, 113, 141, and 169. Cohort 5: Day 1 (pre-dose and 4 hours post-dose), Days 4, 8 (pre-dose), 15 (pre-dose), 29 (pre-dose), 43 (pre-dose), 57 (pre-dose), 78 (pre-dose and 4 hours post-dose), 81, 85, 113, 141, and 169. Cohort 6: Day 1 (pre-dose and 1 and 4 hours post-dose), Days 4, 8, 15, 28, 36, 43, 56, 57 (1 and 4 hours post-dose), 60, 64, 71, 85, 113, and 169.
20101183 (Study 1183)	Tezepelumab 700 mg IV Q4W (total of 3 doses) or placebo IV.	Days 1 (pre-dose and 1 and 4 hours post-dose), 4, 8, 15, 29 (pre-dose), 36, 41, 42, 43, 57 (pre-dose and 1 and 4 hours post-dose), 60, 64, 71, 83, 84, 85, 113, and 169.
D5180C00002 (Study 0002)	Single dose tezepelumab 140 mg SC.	Day 1 (pre-dose), Days 2, 4, 7, 11, 15, 22, 29, 43, 57, and 85.
D5180C00003 (Japan Study 0003)	Single dose of tezepelumab 35, 105, or 280 mg SC, or placebo SC.	Day 1 (within 3 hours pre-dose, then 4 and 8 hours post-dose), Days 2, 3, 4, 5, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, and 113.
D5180C00012 (PATH-BRIDGE)	Single dose of tezepelumab 210 mg SC (randomised 1:1 to vial-and-syringe, APFS, or AI).	Day 1 (immediately pre-dose), Days 2, 4, 5, 6, 7, 8, 10, 12, 15, 22, 29, 43, 57, 71, 85, 99, and 113.
CD-RI-MEDI9929-1146/D5180C00001 (PATHWAY)	Tezepelumab 280 mg Q2W SC, 210 mg Q4W SC, 70 mg Q4W SC, or placebo Q2W SC for up to 52 weeks.	Day 1, Weeks 4, 12, 20, 28, 40, 52, and 64 (all pre-dose samples except Weeks 52 and 64).
D5180C00007 (NAVIGATOR)	Tezepelumab 210 mg SC or placebo for up to 52 weeks.	Day 1, Weeks 4, 12, 24, 36, 52, and 64 (all pre-dose samples, except Weeks 52 and 64).
D5180C00009 (SOURCE)	Tezepelumab 210 mg SC or placebo for up to 48 weeks.	Day 1, Weeks 4, 12, 24, 40, 48, and 60 (all pre-dose samples, except Weeks 48 and 60).
D5180C00013 (CASCADE)	Tezepelumab 210 mg Q4W SC or placebo for up to 28 weeks.	Day 1, Weeks 12, 28/EOT, and 40 (all pre-dose samples, except Weeks 28/EOT and 40).
D5180C00011 (PATH-HOME)	Tezepelumab 210 mg SC for up to 24 weeks (randomised 1:1 to APFS or AI).	Day 1 (pre-dose), Weeks 4 (pre-dose), 20 (pre-dose), 24, and 36.

a. For Study 0620, only healthy subject data (Study Part A) are considered in this document; data for subjects with atopic dermatitis (Study Part B) are not considered relevant to this application.

AI, Autoinjector; APFS, Accessorised pre-filled syringe; EOT, End of treatment; IV, Intravenous; QW, Weekly; Q2W, Every 2 weeks; Q4W, Every 4 weeks; SC, Subcutaneous.

Source: Revised from Table 15 in Summary of Clinical Pharmacology Studies (Module 2.7.2)

16.2.2.1. Phase 1 Studies

- *Study 0620*

Study Type: Phase 1 single dose-escalation study

Title: A Randomized, Double-blind, Placebo-controlled, Ascending Single Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 157 in Healthy Subjects and Subjects with Moderate to Severe Atopic Dermatitis

Objective:

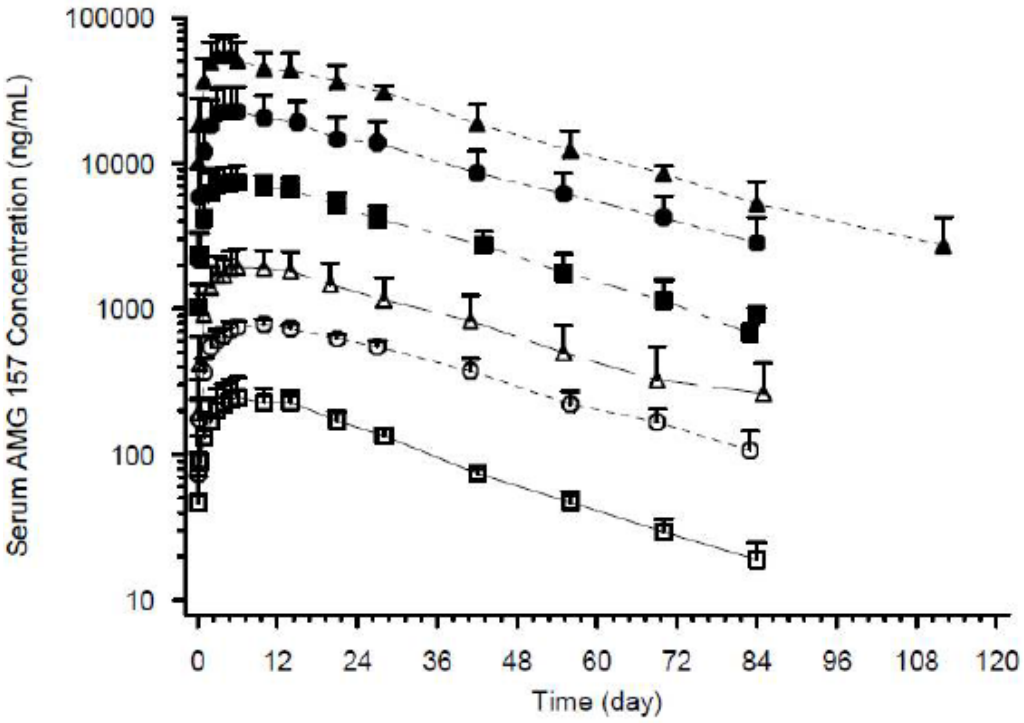
- The primary objective of the study was to evaluate the safety, tolerability, and immunogenicity of single-dose SC and IV administration of tezepelumab in healthy subjects (Part A) and subjects with moderate to severe atopic dermatitis (Part B). Part B of the study, conducted in subjects with atopic dermatitis, is not considered to be relevant to the current application and is not discussed further.
- Secondary and exploratory objectives included the following: to determine the PK profile of tezepelumab after single-dose SC and IV administration in healthy subjects.

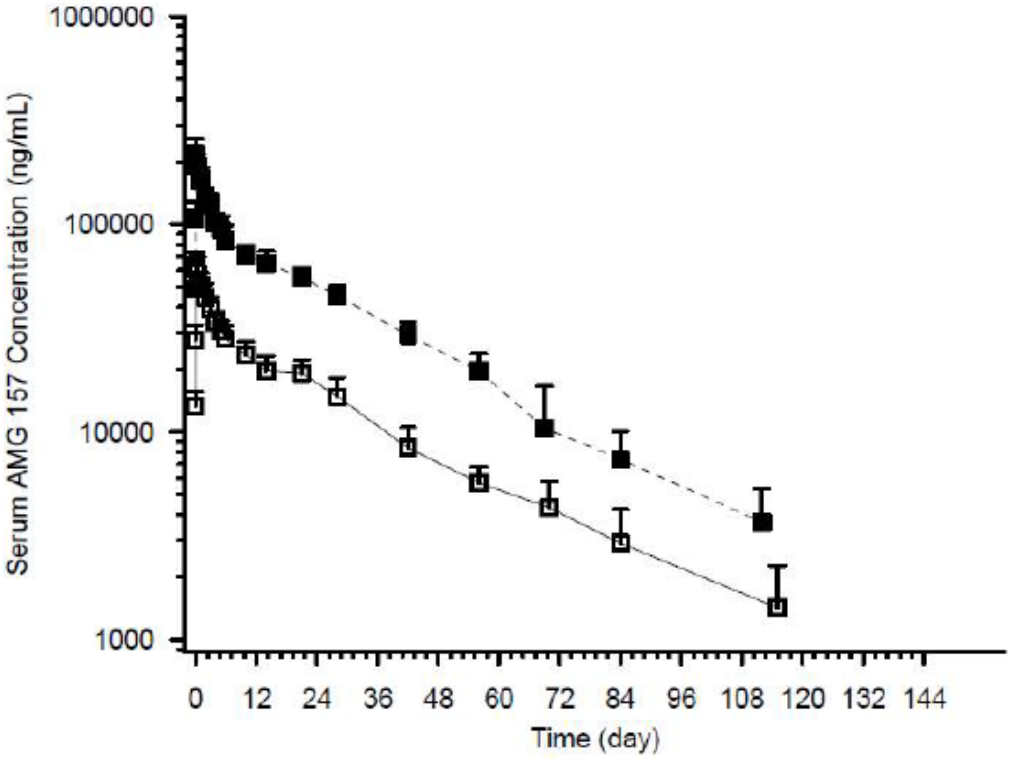
Study Design:
This was a first-time-in-human study, conducted in adult healthy subjects. The first 2 subjects enrolled in Cohort 1 were randomised 1:1 and subsequent subjects in this cohort were randomised in a 5:1 ratio to tezepelumab or placebo. In Cohorts 2 to 8, subjects were randomised 6:2 to tezepelumab or placebo. Subjects received single doses of Tezepelumab (2.1, 7, 21, 70, or 420 mg SC, or 210 or 700 mg IV). Intensive PK sampling was conducted up to Day 113.

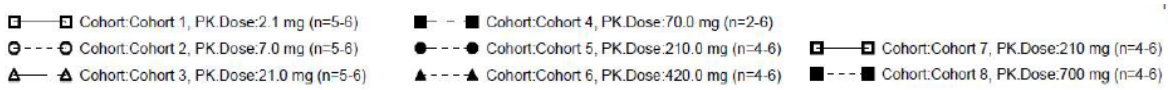
PK Results:
Single-dose IV and SC PK data were obtained from a total of 48 subjects who received tezepelumab. Tezepelumab serum concentration versus time profiles exhibited linear PK, as indicated by dose-proportional increases in serum exposure across all doses tested (Figure 44). The time to maximum observed serum concentration (tmax) across doses ranged from 81 to 237 hours (approximately 3 to 10 days) after a single SC administration. Absolute bioavailability was estimated to be 81% based on comparison of the mean area under the serum concentration-time curve to infinity (AUCinf) after a single SC 210 mg dose compared with the same dose administered IV. Mean estimates of the elimination half-life during terminal phase (t1/2,z) after SC and IV administration across all dose groups ranged from 19.9 to 25.7 days.

Immunogenicity:
None of the subjects (0/48) who received tezepelumab tested positive for ADA. In the placebo group, 13% (2/15) of subjects tested positive for ADA; one subject was positive at baseline and post-baseline and the other subject was positive post-baseline only; both tested negative for nAbs at all time points.

Figure 44 Mean (+SD) Serum Concentration-time Profiles (Semi-log) in Healthy Subjects Following Single Doses of Tezepelumab – Subcutaneous [left panel] and Intravenous [right panel] – Study 0620







Source: Figures 10-1 and 10-2 in Study 0620 CSR in Module 5.3.3.1.

- *Study 0390*

Study Type: Phase 1 multiple dose escalation study

Title: A Randomized, Double-blind, Placebo-controlled, Ascending Multiple Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of AMG 157 in Healthy Subjects

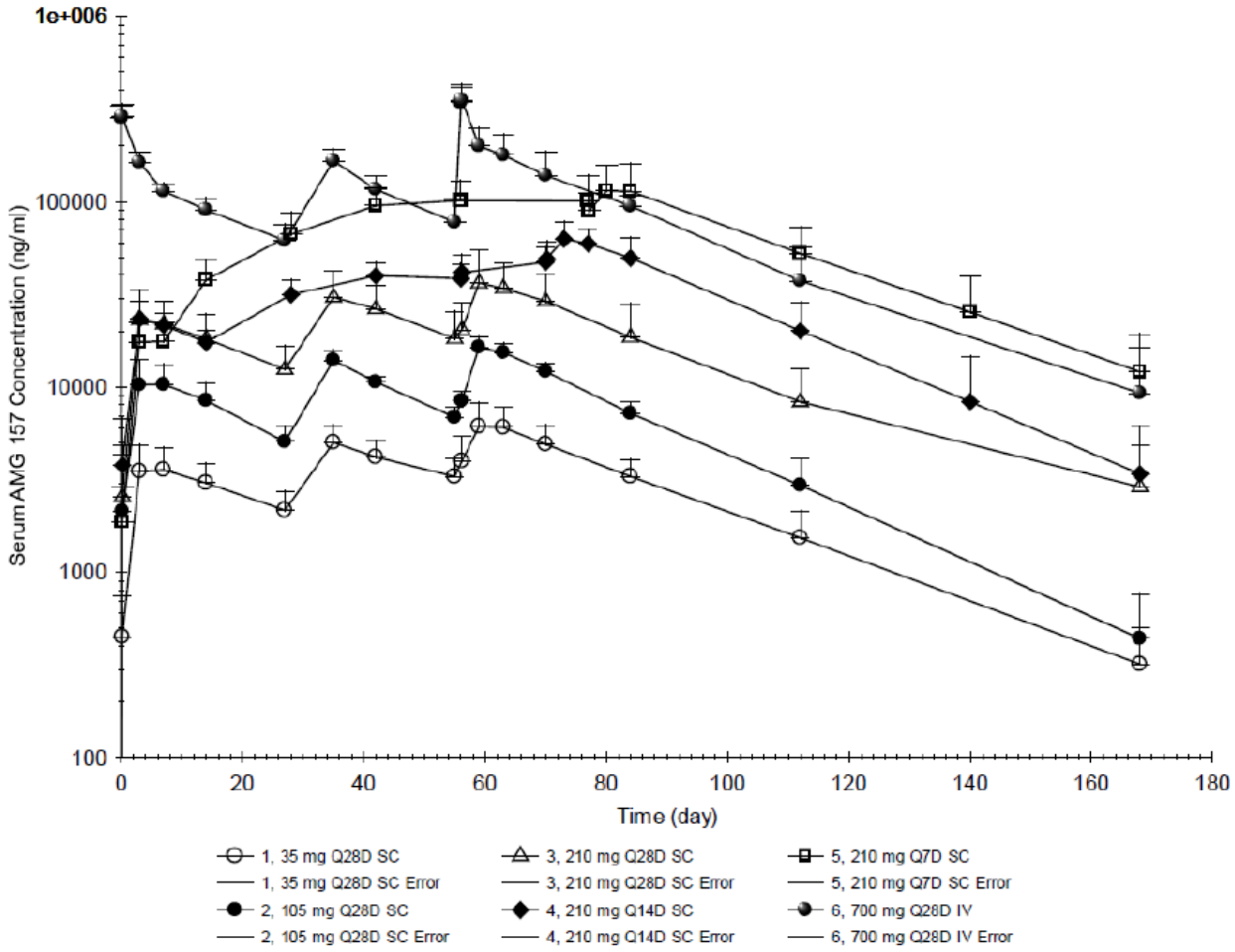
Objective:
- The primary objective of the study was to evaluate the safety, tolerability, and immunogenicity of multiple-dose administration of tezepelumab in healthy subjects.
- Secondary and exploratory objectives included the following: To determine the PK profile of tezepelumab after multiple-dose administration in healthy subjects.

Study Design:
The study consisted of 5 SC cohorts and 1 IV cohort of 8 healthy subjects each, randomised (3:1) to receive tezepelumab or placebo at 35, 105, or 210 mg SC Q4W for a total of 3 doses; 210 mg SC Q2W for a total of 6 doses; 210 mg SC weekly (QW) for a total of 12 doses; or 700 mg IV Q4W for a total of 3 doses. Dose escalation proceeded when the previous dose regimen was judged safe and well tolerated by a Dose Level Review Team.
Subjects were followed-up to Day 169. Intensive PK sampling was conducted up to Day 169.

PK Results:
Multiple-dose IV and SC PK data were evaluable for 37 healthy subjects who received tezepelumab. Multiple doses of tezepelumab exhibited linear PK in good agreement with single-dose data after IV administration at 700 mg and SC administration ranging from 35 to 210 mg. Mean accumulation ratios measured by AUC over the dosing interval (AUCtau) ranged from 1.36 to 1.72 for the Q4W dose cohorts. Mean accumulation ratios measured by Cmax were 1.58, 2.68, and 6.50 for the Q4W, Q2W, and QW 210 mg SC dose groups, respectively.

Immunogenicity:
Out of the 37 subjects who received tezepelumab, one subject (3%)
(who received tezepelumab 210 mg Q2W) tested positive for ADA at baseline; the subject tested negative at all subsequent time points. No subjects (0/12) in the placebo group tested positive for ADA. All 49 subjects tested negative for ADA at post-baseline time points. No subjects tested positive for nAbs during the study.

Figure 45 Mean (+SD) Serum Tezepelumab Concentration-time Profiles (Semi-log) in Healthy Subjects – Study 0390



Source: Figure 10-1 in the Study 0390 CSR in Module 5.3.3.1.

- *Study D5180C00003*

Study Type: Phase 1 single dose escalation study in Japanese adult male healthy subjects

Title: A Phase 1, Single Centre, Single-blind, Randomized, Placebo-controlled Parallel-group Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Immunogenicity of Tezepelumab after Administration of Single Ascending Doses in Healthy Male Japanese Subjects

Objective:
The primary objective of the study was to assess the safety and tolerability of single ascending SC doses of tezepelumab in healthy male Japanese subjects.
Secondary and exploratory objectives included the following:

- To characterize the PK of tezepelumab in healthy male Japanese subjects.
- To evaluate the immunogenicity of tezepelumab in healthy male Japanese subjects.

Study Design:
Healthy male Japanese subjects aged 20 to 45 years were randomised to Tezepelumab or placebo. The study design allowed a gradual escalation of dose with intensive safety monitoring to ensure the safety of the subjects. There were to be a maximum of 3 cohorts, each containing up to 8 subjects. Subjects were randomised in a 3:1 ratio to Tezepelumab (single SC doses of 35, 105, and 280 mg) or placebo. Each subject participated in only one cohort in the study. Subjects received a single dose of tezepelumab or placebo SC on Day 1 followed by safety monitoring and serial collection of blood samples for PK evaluation throughout the study period. The follow-up period after the dosing was 84 days (for Cohorts 1 or 2) or 112 days (for Cohort 3). Pharmacokinetic sampling was conducted on Days 1 (within 3 hours pre-dose, then 4 and 8 hours post-dose), 2, 3, 4, 5, 6, 8, 11, 15, 22, 29, 43, 57, 71, 85, and 113.

PK Results:
PK data were evaluable in 18 subjects who received tezepelumab, 6 in each treatment group. One subject in the 280 mg cohort exhibited an atypical 5-fold lower PK exposure, which was considered an outlier given the interindividual variability in tezepelumab exposure. This subject was excluded from the PK summary presented here.
Serum tezepelumab concentrations increased dose-proportionally following a single SC dose from 35 to 280 mg. Pharmacokinetic parameters in Japanese subjects were similar to other IgG antibodies with median tmax of 7 to 10 days, mean CL/F of 150 to 175 mL/day, apparent volume of distribution during terminal phase (Vz/F) of 5.5 to 6.0 L, and t1/2,z of 24 to 26 days. Compared with non-Japanese subjects in previous human studies, Japanese subjects had 30% to 60% higher dose-normalized Cmax and AUC, due to lower body weight in Japanese subjects.

Immunogenicity:
None of the subjects tested positive for ADA at any time point in either the tezepelumab (0/18) or placebo (0/6) groups.

- *Study D5180C00002*

Study Type: Phase 1 open label PK study in adolescent subjects with mild to moderate asthma

Title: A Phase 1, Open-label Study to Evaluate the Pharmacokinetics of MEDI9929 in Adolescents with Mild to Moderate Asthma

Objective:
The primary objective of the study was to evaluate the PK profile of a single dose of 140 mg SC administration of tezepelumab in adolescent subjects with mild to moderate asthma.
Secondary and exploratory objectives included the following:
- To evaluate the immunogenicity of tezepelumab.

Study Design:
The study recruited adolescent subjects (≥ 12 to < 18 years of age) with mild to moderate asthma requiring the daily use of controller medications. All subjects received a single SC dose of 140 mg tezepelumab, with 12-week PK and safety follow-up. Pharmacokinetic sampling was conducted on Days 1 (pre-dose), 2, 4, 7, 11, 15, 22, 29, 43, 57, and 85.

PK Results:
PK data were evaluable from 21 adolescent subjects. Tezepelumab was absorbed slowly following SC administration with tmax ranging from approximately 4 to 6 days post-dose and a mean Cmax of 24.0 ± 6.59 µg/mL. The apparent clearance (CL/F) was 0.159 ± 0.0443 L/day and the t1/2,z was estimated to be 25.3 ± 4.70 days. Serum concentrations of tezepelumab were slightly higher for the 12 to 14 years (inclusive) age group (Cohort 1) compared with the 15 to 17 years (inclusive) age group (Cohort 2) at Day 28 and beyond. Body weight differences may have contributed, at least partially, to the observed difference in exposure. Overall, the differences observed in PK parameter values between age groups were small.

Immunogenicity:
One out of 21 (5%) subjects who received tezepelumab tested ADA positive at baseline and remained persistently ADA positive post-baseline; no nAbs were detected for this subject. The PK in the ADA positive subject was similar to that in the other (ADA negative) subjects, indicating no impact of ADA on PK.

- *Study D5180C00012 (PATH-BRIDGE)*

Study Type: Phase 1 single dose, open label PK comparability study following SC administration with APFS, AI, and vial-and-syringe in adult healthy subjects

Title: An Open-label, Randomized, Parallel-group Study to Evaluate the Pharmacokinetics of Tezepelumab Administered Subcutaneously via an Accessorized Pre-filled Syringe (APFS) or Autoinjector (AI) Compared with Vial-and-Syringe in Healthy Adult Subjects

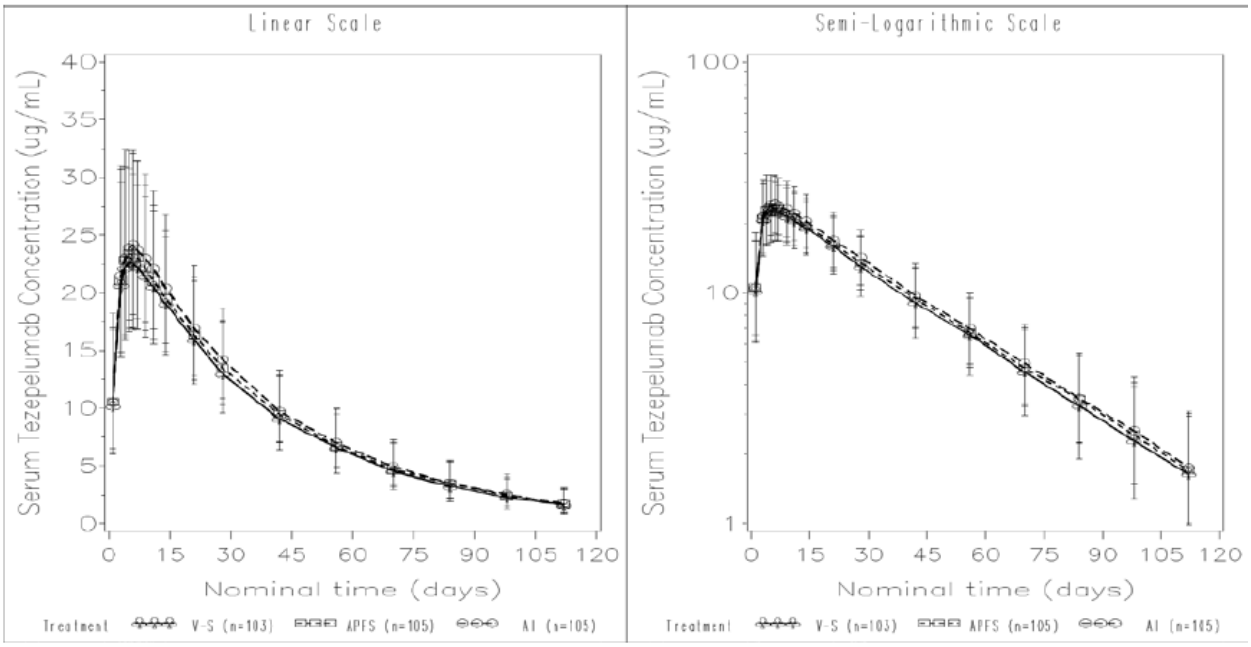
Objective:
The objectives of the study were to compare the PK exposure and immunogenicity following single-dose SC administration of tezepelumab 210 mg using vial-and-syringe versus an APFS and versus an AI presentation.

Study Design:
The study recruited healthy adult subjects. Subjects received a single dose of 210 mg tezepelumab administered SC using vial-and-syringe, APFS, or AI injected into the abdomen, thigh, or upper arm. Within each of 3 weight categories (50 to < 70 kg, 70 to < 80 kg, and 80 to 90 kg), subjects were randomised 1:1:1:1:1:1:1:1:1 into one of 9 combinations of treatment (vial-and-syringe, APFS, or AI) with different injection sites (abdomen, thigh, and upper arm). Pharmacokinetic sampling was conducted on Days 1 (immediately pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 15, 22, 29, 43, 57, 71, 85, 99, and 113.

PK Results:
A total of 315 subjects were randomised, including 313 evaluable for PK, 103 in the vial-and-syringe group, 105 in the APFS group, and 105 in the AI group. Following a single-dose SC administration of 210 mg tezepelumab using vial-and-syringe, APFS, or AI, serum tezepelumab concentrations reached C_{max} at a median tmax of 5 to 6 days post-dose and then decreased exponentially with a mean half-life of approximately 29 days. The PK of tezepelumab was comparable between treatment groups (vial-and-syringe, APFS, and AI) as assessed by the bioequivalence criteria (for C_{max}, AUC_{inf}, and AUC up to the last measurable concentration

[AUC_{last}]). Similar serum concentration profiles and PK parameters were observed across treatment groups, regardless of body weight categories or injection site.

Figure 46 Geometric Mean Serum Concentration (µg/mL) of 210 mg Tezepelumab Over Time by Treatment (Device) Linear and Semilogarithmic Scale



AI = autoinjector; APFS = accessorized pre-filled syringe, V-S = vial-and-syringe.
'n' denotes the number of subjects exposed to each treatment included in the figure.
PK samples with >10% deviation from the nominal time were excluded from the figure.
Source: Figure 11-1 in the CSR for PATH-BRIDGE

Immunogenicity: Treatment-emergent ADAs were detected in 3/103 (2.9%) subjects in the vial-and-syringe group, 1/105 (1.0%) subjects in the APFS group, and 0/105 (0%) subjects in the AI group. No apparent impact of ADA on PK was observed, and no injection site reactions were reported in ADA-positive subjects.

- *Study 1183*

Study Type: Phase 1 multiple dose allergen challenge study in adult subjects with mild atopic asthma

Title: Randomized, Double-blind, Placebo-controlled, Parallel Design, Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 157 in Subjects With Mild Atopic Asthma

Objective:
The primary objective of the study was to evaluate the late asthmatic response after an allergen inhalation challenge in subjects with mild atopic asthma who received multiple doses of tezepelumab.
Secondary and exploratory objectives included the following:

- To determine the PK profile of tezepelumab after multiple-dose administration in subjects with mild atopic asthma.
- To evaluate the safety, tolerability, and immunogenicity of multiple-dose administration of tezepelumab in subjects with mild atopic asthma.
- To evaluate the early asthmatic response after an allergen inhalation challenge in subjects with mild atopic asthma who received multiple doses of tezepelumab.

Study Design:
The study recruited nonsmoking adult subjects with mild atopic asthma on asthma therapy limited to short-acting beta agonists taken less than Q2W. Subjects were randomised 1:1 to receive 700 mg IV tezepelumab or placebo Q4W for a total of 3 doses. Subjects were challenged with nebulized methacholine and an inhaled allergen at specified time points throughout the study. Intensive PK sampling was conducted up to Day 169.

PK Results:
PK data were evaluable for 16 subjects who were treated with tezepelumab. The mean (standard deviation [SD]) Cmax for the first and third doses were 262 (73) µg/mL and 325 (81) µg/mL, respectively. The mean (SD) for the AUCtau for the first and third doses were 2730 (700) and 4420 (1250) day*µg/mL, respectively. Mean (SD) estimate of t1/2,z after the third dose was 28.0 (4.2) days. Mean accumulation ratios were 1.31 for Cmax and 1.64 for AUCtau. The PK results were consistent with the results from the previous multiple dose (Study 0390) and single dose (Study 0620) studies with respect to the 700 mg IV cohorts.

Immunogenicity:
None of the subjects (0/16) who received tezepelumab tested positive for ADA. In the placebo group, 1/15 (7%) subjects tested positive for ADA post-baseline; in this subject, ADA-positive status was transient and non-neutralizing in nature.

PD Results:
Administration of tezepelumab to subjects with mild atopic asthma attenuated the late asthmatic response (between 3 and 7 hours post allergen inhalation challenge) and early asthmatic response (between 0 and 2 hours post allergen inhalation challenge), as measured by AUC for the maximum percent fall in FEV1 on Days 42 and 84 following the allergen challenge. In addition, tezepelumab suppressed the inhaled allergen-induced increase in blood and sputum eosinophils and FeNO relative to placebo.

16.2.2.2. Phase 2 Studies

- *Study D5180C00013 (CASCADE)*

Study Type: Phase 2 efficacy, and safety trial in adult subjects with inadequately controlled asthma on ICS and at least one additional asthma controller

Title: A Phase 2, Randomized, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults with Inadequately Controlled Asthma on Inhaled Corticosteroids and at Least One Additional Asthma Controller

Objective:

The primary objective of the study was to explore the airway anti-inflammatory effect of tezepelumab.
Secondary and exploratory objectives included the following:

- To evaluate the PK, PD, and immunogenicity of tezepelumab.

Study Design:
Subjects had a background asthma therapy of medium- or high-dose ICSs plus at least one additional asthma controller medication, with or without maintenance OCS. Subjects were randomised 1:1 to receive tezepelumab 210 mg Q4W or placebo, and entered a 4-week screening/run-in period, followed by a 28-week treatment period (with an optional 4-week to 24-week extension because of the coronavirus disease 2019 [COVID-19] pandemic), and a 12-week follow-up period. Pharmacokinetic sampling was conducted on Day 1 and Weeks 12, 28/EOT, and at Week 40/the end of follow-up (all pre-dose samples, except Weeks 28/EOT and 40/end of follow-up).

PK Results:
A total of 59 subjects were treated with tezepelumab and had evaluable PK data. The mean serum trough concentrations of tezepelumab were similar at Week 12 (22.5 μg/mL) and EOT (24.5 μg/mL).

Immunogenicity:
No (0/59) subjects on tezepelumab and 2/55 (3.6%) subjects on placebo tested positive for treatment-emergent ADAs.

PD Results:
The primary outcome variable of the study was change from baseline to EOT, expressed as a ratio, in the number of airway submucosal inflammatory cells/mm2 (eosinophils, neutrophils, T cells, and mast cells) from bronchial biopsies.
Tezepelumab 210 mg SC Q4W reduced airway inflammation over the course of treatment compared with placebo, as demonstrated by an 89% reduction in bronchial submucosal eosinophils (ratio for change from baseline to EOT of 0.11; 90% CI 0.06 to 0.21) in the tezepelumab group compared with a 25% reduction (ratio for change from baseline to EOT of 0.75; 90% CI 0.41 to 1.38) in the placebo group. This equated to a 6.7-fold reduction in bronchial submucosal eosinophils from baseline to EOT compared with placebo (ratio of geometric least squares mean of 0.15; 90% CI 0.06 to 0.35). Tezepelumab had no detectable effect on bronchial submucosal neutrophil, CD3+ and CD4+ T-cell, or tryptase+ and chymase+ mast cells counts, RBM thickness, or % airway epithelial integrity.
The decrease in bronchial submucosal eosinophils was seen irrespective of baseline levels of blood eosinophils, FeNO, total serum IgE, allergic/non-allergic status (defined by a positive serum IgE result specific to a panel of perennial aeroallergens in the fluorescent enzyme immunoassay [FEIA] versus negative results for all perennial aeroallergens in the panel), serum IL-5, and serum IL-13. Treatment with tezepelumab also resulted in reduced levels of blood eosinophils, FeNO, total serum IgE, serum IL-5, serum IL-13, and plasma EDN (an eosinophil activation marker).

- *Study CD-RIMEDI9929-1146 (PATHWAY)*

Study Type: Phase 2b efficacy, and safety trial in adult subjects with severe, inadequately controlled asthma

Title: A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

Objective:
The primary objective of the study was to evaluate the effect of 3 dose levels of tezepelumab on asthma exacerbations in adult subjects with inadequately controlled, severe asthma.
Secondary and exploratory objectives included the following:

- To determine the optimal dose and regimen of tezepelumab to be used in later studies.
- To describe the PK and immunogenicity of tezepelumab.
- To assess the PD effect of tezepelumab on biomarkers.

Study Design:
The study recruited adult subjects with inadequately controlled severe asthma on medium-dose or high-dose inhaled corticosteroids (ICS) and at least one additional controller. Subjects were randomised 1:1:1:1 to receive one of 3 dose levels of SC Tezepelumab (70 mg Q4W, 210 mg Q4W, or 280 mg Q2W) or placebo Q2W, and entered a 5-week screening/run-in period, followed by a 52-week treatment period, and a 12-week follow-up period. Pharmacokinetic sampling was conducted on Day 1 and Weeks 4, 12, 20, 28, 40, 52, and 64 (all pre-dose samples, except for Weeks 52 and 64).
Thirty-four subjects from one site in the United States were excluded from all populations (including the evaluable for PK population) due to suspected non-compliance with Good Clinical Practice. Exclusion of the 34 subjects did not alter study conclusions.

PK Results:
A total of 550 subjects randomised (138, 137, 137, and 138 subjects in the 70 mg Q4W tezepelumab, 210 mg Q4W tezepelumab, 280 mg Q2W tezepelumab, and placebo groups, respectively) were included in analyses. Pharmacokinetic data were evaluable in a total of 393 subjects who received tezepelumab (133, 128, and 132 subjects in the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W groups, respectively**).**
After repeated SC administration of tezepelumab 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W, the mean serum trough concentration increased over time and achieved steady state by Week 12. Tezepelumab exhibited linear PK across the 3 doses. The mean accumulation ratios were 1.65 to 1.8, based on ratio between the trough concentrations at Week 52 and Week 4.

Immunogenicity:
Thirteen out of 138 (9.4%), 5/137 (3.6%), 1/132 (0.8%), and 3/133 (2.3%) subjects tested positive for ADA post-baseline in the placebo, 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W groups, respectively. There were no nAbs detected for the ADA-positive samples. The presence of ADA did not appear to impact tezepelumab PK in the subjects with ADA.

PD Results:
In exploratory biomarker analyses, treatment with tezepelumab resulted in substantial and persistent reductions in the levels of peripheral blood eosinophils and FeNO and a progressive

decrease in total serum IgE levels. The reductions in blood eosinophils and FeNO were seen as early as Week 4 (first time point assessed) and were maintained throughout the 52-week treatment period.

16.2.2.3. Phase 3 Studies

- *Study D5180C00007 (*NAVIGATOR*)*

Study Type: Phase 3 efficacy and safety trial in adult and adolescent subjects with severe uncontrolled asthma

Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma

Objective:
The primary objective of the study was to assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo.
Secondary and exploratory objectives included the following:

- To evaluate the PK and immunogenicity of tezepelumab.
- To assess the PD effect of 210 mg of tezepelumab SC Q4W on biomarkers.

Study Design:
The study recruited adult (≥ 18 years of age) and adolescent subjects (≥ 12 to < 18 years of age) with a history of asthma exacerbations and severe asthma receiving medium- or high-dose ICS plus at least one additional asthma controller medication with or without OCS. Subjects were randomised to tezepelumab 210 mg SC Q4W or placebo for up to 52 weeks. Pharmacokinetic sampling was conducted on Day 1 and Weeks 4, 12, 24, 36, 52, and 64 (all pre-dose samples, except for Weeks 52 and 64).

PK Results:
The PK analysis set contained a total of 526 subjects who were treated with tezepelumab and had at least one PK sample post first dose with quantifiable serum concentrations of tezepelumab. After administration of tezepelumab 210 mg SC Q4W, the mean serum trough concentration increased over time, approaching steady state by Week 12. At Weeks 4, 12, 24, 36, and 52 (EOT), mean serum trough concentrations were 11.5, 20.7, 22.5, 21.9, and 22.6 μg/mL, respectively. The mean serum trough concentrations were higher in adolescent subjects (age 12 to < 18 years) than in adults, due to the lower average body weight in the adolescents, and similar between adults of age 18 to < 65 years and those ≥ 65 years of age. At Week 52, the mean serum trough concentrations were 27.9, 21.8, and 23.8 μg/mL in adolescents, adults 18 to < 65 years and ≥ 65 years of age, respectively.

Immunogenicity:
The incidence (ie, the proportion of subjects who were treatment emergent ADA positive) of ADAs was low. In the overall population, 10/522 (1.9%) subjects on tezepelumab and 20/523 (3.8%) subjects on placebo tested positive for treatment-emergent ADAs. One subject on tezepelumab and one subject on placebo had nAbs. In total, 26 subjects treated with tezepelumab

were ADA positive at any time, of whom 15 were ADA positive at baseline only, 7 were transiently positive, and 4 were classified as persistently positive.
In both the tezepelumab and placebo treatment groups, the median of the maximum ADA titers were low (67.20 in the tezepelumab group and 134.40 in the placebo group; the limit of detection for the ADA assay was 67.20) throughout the course of the study. The median of the maximum ADA titre of the treatment-emergent ADA positive subjects was 100.80 in each treatment group. No adolescent subjects in either treatment group tested positive for treatment-emergent ADAs or nAbs.
There was no apparent effect of ADA on PK, PD, efficacy, or safety.

PD Results:
Tezepelumab 210 mg SC Q4W reduced biomarkers and cytokines associated with inflammation from baseline versus placebo, with an onset of effect by 2 weeks and sustained reduction to 52 weeks for blood eosinophil counts, FeNO, serum IL-5, and serum IL--13. Tezepelumab also caused a progressive reduction in total serum IgE, with levels continuing to decrease throughout 52 weeks of treatment.

- *Study D5180C00009 (SOURCE)*

Study Type: Phase 3 efficacy and safety trial in adult subjects with OCS-dependent asthma

Title: A Multicenter, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Objective:
The primary objective of the study was to evaluate the effect of Tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in subjects with asthma requiring chronic treatment with maintenance OCS in addition to high-dose ICS plus a long-acting β2 agonist (LABA).
Secondary and exploratory objectives included the following:
- To evaluate the PK and immunogenicity of tezepelumab
- To assess the PD effect of tezepelumab on biomarkers.

Study Design:
The study recruited adult subjects with asthma requiring treatment with maintenance OCS in combination with ICS + a LABA with or without other asthma controller therapy. Subjects were randomised to tezepelumab 210 mg SC Q4W or placebo and entered a 2-week screening/run-in period, followed by an up to 8-week OCS optimization phase, a 48-week treatment period (including an OCS-reduction phase), and a 12-week follow-up period. Pharmacokinetic sampling was conducted on Day 1 and Weeks 4, 12, 24, 40, 48, and 60 (all pre-dose samples, except Weeks 48 and 60).

PK Results:
The PK analysis set contained a total of 73 subjects who were treated with tezepelumab and provided at least one PK sample post first dose that contained quantifiable serum concentrations of tezepelumab. After administration of tezepelumab 210 mg SC Q4W, the mean serum trough

concentration increased over time, approaching steady state by Week 12. At Weeks 4, 12, 24, 40, and 48, the mean serum trough concentrations of tezepelumab were 11.2, 20.0, 21.3, 21.8, and 20.2 μg/mL, respectively.

Immunogenicity:
The incidence of ADAs was low; 1/73 (1.4%) subjects on tezepelumab and 0/76 (0%) subjects on placebo tested positive for treatment-emergent ADAs. No subjects in either treatment group tested positive for nAbs. Anti-drug antibodies had no apparent effect on PK or safety.

PD Results:
Tezepelumab 210 mg SC Q4W reduced biomarkers and cytokines associated with inflammation from baseline versus placebo with an onset of effect by 4 weeks and sustained reduction to 48 weeks for blood eosinophil counts, FeNO, serum IL-5, and serum IL-13. Tezepelumab caused a progressive reduction in total serum IgE, with levels continuing to decrease throughout 48 weeks of treatment.

- *Study D5180C00011 (PATH-HOME)*

Study Type: Phase 3 open label device functionality study (APFS & AI) in adult and adolescent subjects with severe asthma

Title: A Multicenter, Randomized, Open-label, Parallel-group, Functionality, and Performance Study of an Accessorized Pre-filled Syringe and Autoinjector with Home-administered Subcutaneous Tezepelumab in Adolescent and Adult Subjects with Severe Asthma

Objective:
The primary objective of the study was to assess the successful administration of tezepelumab 210 mg SC by injection with an APFS or AI in the clinic and at home.
Secondary and exploratory objectives included the following:

- To assess the functionality and performance of APFS and AI presentations.
- To assess the PK and immunogenicity of tezepelumab administered via APFS or AI in the clinic and at home.

Study Design:
The study recruited adult and adolescent subjects with severe asthma. All subjects received tezepelumab 210 mg SC Q4W delivered using the APFS or AI and entered a 2-week screening/run-in period, followed by a 24-week treatment period and a 12-week follow-up period. Pharmacokinetic sampling was conducted on Day 1 (pre-dose) and Weeks 4 (pre-dose), 20 (pre-dose), 24, and 36.

PK Results:
The PK analysis set contained a total of 216 subjects (111 from the APFS group and 105 from the AI group) who were treated with tezepelumab and had at least one post-treatment sample with quantifiable serum concentrations of tezepelumab. At all the post-dose time points the mean serum concentrations of tezepelumab were similar between the APFS and the AI groups. At Week 4, Week 20, Week 24 (EOT), and Week 36 (follow-up) the mean serum concentrations of tezepelumab were 12.0, 21.9, 22.2, and 2.65 μg/mL, respectively, in the APFS group, and 11.8, 23.0, 22.3, and 2.92 μg/mL, respectively, in the AI group.

Immunogenicity:
The incidence of ADAs was low following treatment with tezepelumab, with 1.8% (2/111) of subjects in the APFS group and 7.6% (8/105) of subjects in the AI group testing positive for treatment-emergent ADA. Overall, ADA titers to tezepelumab were low in both the APFS and AI groups. The median of the maximum ADA titre of the post-dose ADA-positive samples achieved in any subject through study completion was 67.20 (limit of detection of the ADA assay) both for subjects using the APFS device and for subjects using the AI device. The subject with the highest maximum titre (537.60) in the study was ADA positive at baseline only.

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