Clinical Study Protocol	
Study Intervention	Tezepelumab
Study Code	D5180C00031
Version	3.0
Date	22 Feb 2022

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Tezepelumab on the Humoral Immune Response to Seasonal Quadrivalent Influenza Vaccination in Adolescent and Young Adult Participants with Moderate to Severe Asthma (VECTOR)

Sponsor Name: AstraZeneca AB

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IND number: 103031

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D5180C00031

Amendment Number: 2.0
Study Intervention: Tezepelumab
Study Phase: 3b

Short Title: Tezepelumab Humoral Immune Response to Influenza Vaccine Study

Acronym: VECTOR

Parexel Medical Monitor Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 1.0	02 Jun 2021
Amendment 1, Version 2.0	07 Sep 2021
Amendment 2, Version 3.0	22 Feb 2022

The Protocol Amendment Summary of Changes table is provided below for the current amendment.

Amendment 2 (22 Feb 2022)

Overall Rationale for the Amendment:

The primary rationale for this amendment is to introduce a primary database lock after the end of treatment at Visit 7 (Week 16) and to update safety information based on the most recent Investigator's Brochure, Version 5.0, dated 21 Oct 2021. Additional changes include APFS device malfunction, medical device deficiencies, and Appendix F Medical Device Adverse Events (AEs) to align with International Organisation for Standardisation 14155 and European Medical Device Regulation. In addition, the vaccine immunogenicity analysis set definition was updated to exclude patients who experience influenza infection prior to Visit 7 (Week 16). Other minor changes included clarification of Schedule of Assessments for participants who prematurely discontinue study intervention. In addition, minor formatting and editorial administrative revisions were made throughout the protocol for clarification purposes.

The Clinical Study Protocol (CSP), Version 2.0, dated 07 Sep 2021, was updated with the following changes:

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Synopsis, Safety Endpoints; Section 6.3.4 Ensuring Blinding; Section 6.3.5 Methods of Unblinding; Section 9.3 Populations for Analyses, Table 10; Section 9.4 Statistical Analyses; Section 9.4.1 General Considerations; Section 9.4.3.1 Safety Endpoint(s); Section 9.5 Interim Analyses	Language relating to primary and final database locks was added.	To add primary analysis of data at Visit 7 (Week 16).	Substantial
Section 1.3 Schedule of Activities, Table 2;	Footnote 'b' was added explaining procedures which are to occur at the investigational product discontinuation (IPD) visit.	To clarify that if the IPD or follow-up safety visit were to occur at the scheduled Visit 6 (Week 12) or Visit 7 (Week 16), that participants should have the flu vaccine and antibody assessments per Visit 6 (Week 12) and Visit 7 (Week 16).	Substantial
Section 2.2 Background	Updated to reflect new information based on Investigator's Brochure (IB) V 5.0	IB V5.0 has been updated to reflect new data from Phase 2 and Phase 3 asthma studies which have been reported.	Substantial
Section 2.2 Background; Section 11 References	CINQAERO Summary of Product Characteristics (SmPc) reference was updated to the current version.	The SmPc was updated in 2021.	Non-Substantial
Section 6.1.3 Medical Devices	Added section regarding sponsor manufactured medical device use in this study and all medical device deficiencies should be documented and reported by the investigator throughout the study	To align with International Organization for Standardization 14155 and European Medical Device Regulation	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.2.3 Reporting Product Complaints	Added section regarding any defects with IP that must be reported immediately to the AstraZeneca representative as per the Parexel study-specific Investigator Manual and defects will be investigated further with AstraZeneca.	To align with Parexel study-specific Investigator Manual.	Non-substantial
Section 6.2.4 Reporting Product Defects	Added section regarding product defects that should be reported to the AstraZeneca representative as per the study-specific Investigator Manual.	To align with Parexel study-specific Investigator Manual.	Non-substantial
Section 6.2.5 Single Use APFS device malfunction	Added section regarding Device malfunctions that should be reported using appropriate form as per the Parexel study-specific Investigator Manual.	To align with Parexel study-specific Investigator Manual.	Non-substantial
Section 7.1 Discontinuation of study Intervention	Language was added explaining procedures which are to occur at the investigational product discontinuation (IPD) visit.	To clarify that if the IPD or follow-up safety visit were to occur at the scheduled Visit 6 (Week 12) or Visit 7 (Week 16), that participants should have the flu vaccine and antibody assessments per Visit 6 (Week 12) or Visit 7 (Week 16).	Substantial
Section 7.1 Discontinuation of study Intervention	Language was added explaining procedures to be followed if the follow-up visit occurs on the same date as the scheduled Visit 7 (Week 16).	To clarify the procedures to be followed at the Follow-up visit.	Substantial
Section 8.1.2.5 Reversibility Test and Post-BD FEV1 Assessment	Second post-BD spirometry was updated to third post-BD spirometry.	Correction of an error.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.3.12 Medical Device Deficiencies	Added Section 8.3.12 definitions of medical device deficiency and requirements to fulfil regulatory reporting obligations worldwide and investigator's responsibility for detection and documentation of events meeting the definition of device deficiency occur during the study.	To align with International Organization for Standardization 14155 and European Medical Device Regulation.	Substantial
Section 9.3 Populations for Analyses Table 10 and Table 11	Vaccine immunogenicity analysis set population updated to exclude participants who experience an influenza infection prior to Visit 7 (Week 16) assessments.	To reduce the potential to interfere with the generation or interpretation of an antibody response.	Substantial
Section 9.4 Statistical Analyses	Added wording to indicate selected safety objectives will be performed based on the primary database lock data.	To allow for review of selected safety outputs at primary database lock.	Non-substantial
Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law	Investigational Medicinal Product was updated to study intervention.	To align with other sections.	Non-substantial
Appendix F Medical Device AEs, ADEs, SAEs, SADEs, US ADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up	Added Appendix F Medical Device AEs, ADEs, SAEs, SADEs, US ADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up.	To align with International Organization for Standardization 14155 and European Medical Device Regulation.	Substantial
Appendix H Maintenance Therapy Equivalence Table	Reference to GINA 2018 was updated to GINA 2021.	Correction of footnote to align with the current version.	Non-substantial
Appendix I Abbreviations	New abbreviations were added.	To include all abbreviations in the document.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix J Protocol Amendment History	Appendix J was added.	Appendix was added to include previous amendments summaries of changes.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Tezepelumab on the Humoral Immune Response to Seasonal Quadrivalent Influenza Vaccination in Adolescent and Young Adult Participants with Moderate to Severe Asthma (VECTOR)

Short Title: Tezepelumab Humoral Immune Response to Influenza Vaccine Study

Rationale: The epithelial cell-derived cytokine, thymic stromal lymphopoietin (TSLP), is produced in response to proinflammatory stimuli and drives allergic inflammatory responses, primarily through its activity on type 2 innate lymphoid cells (ILC-2), dendritic and mast cells. Human TSLP expression is reported to be increased in asthmatic airways correlating with disease severity.

Owing to its immunomodulating effect, it is important to determine if tezepelumab affects functioning of the immune system. In this study, a functional response of the immune system will be assessed by measuring antibody responses to the influenza vaccine in adolescents and young adults with moderate to severe asthma.

The rationale for selecting this population is based on precedence from a similar study with anti-IL5 biologic drug benralizumab, in which humoral immune response was assessed in adolescents and young adults (12 to 21 years old) with severe asthma. In that study, the humoral antibody responses induced by seasonal influenza virus vaccination do not appear to be affected by benralizumab treatment.

Objectives and Endpoints

Please note: If influenza vaccine administration is delayed, some participants' assessments at Visit 6 (Week 12) and Visit 7 (Week 16) may be performed at later timepoints.

Objectives	Endpoints
Primary	
• To evaluate the effect of tezepelumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult participants with moderate to severe asthma	• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific serum HAI antibody geometric mean titers (GMTs) obtained at Week 16 (EOT) • Post-dose strain-specific serum MN antibody GMTs obtained at Week 16 (EOT) • Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in HAI antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in MN antibody titer from Week 12 (pre-antibody measure) to Week 16 (EOT) • Post-dose strain-specific HAI antibody titer ≥ 40 at Week 16 (EOT) • Post-dose strain-specific MN antibody titer ≥ 40 at Week 16 (EOT)
Secondary	
• To assess the PK and immunogenicity	• Serum trough tezepelumab concentrations • Anti-drug antibodies
Safety	
• To assess the safety and tolerability of tezepelumab	• AEs and SAEs • Laboratory variables • Vital signs

For Exploratory objectives and endpoints, see Section 3 of the CSP.

Overall Design

This is a Phase 3b, multicenter, randomized, double-blind, parallel group, placebo-controlled study designed to investigate the potential effect of tezepelumab (210 mg SC Q4W) on antibody responses following seasonal quadrivalent influenza virus vaccination in the fall/winter 2021-2022 in the USA.

Disclosure Statement: This is a parallel group treatment study with 2 arms that is participant and investigator blinded.**Number of Participants:**

Approximately 135 participants aged 12 to 21 years with moderate to severe asthma will be enrolled into screening to provide a target sample size of approximately 100 randomized participants for the study.

Intervention Groups and Duration:

Participants with moderate to severe asthma will be randomized 1:1 to receive tezepelumab 210 mg or placebo SC Q4W, administered at Weeks 0, 4, 8 and 12. Enrollment into screening will be monitored to ensure at least 50% of the randomized participants are between the ages of 12 to 17 years. Treatment allocation will be stratified by age at the time of informed consent/assent (12 to 17 years, and 18 to 21 years) to ensure equitable distribution of tezepelumab and placebo treatment in each age group.

Please note: If influenza vaccine administration is delayed, the treatment period may be extended and therefore participants may be given an additional 1 to 2 study intervention doses (as needed) every 4 weeks for a longer period than initially planned.

Data Monitoring Committee: No

Statistical Methods

Primary Endpoints

For the analysis of the anti-influenza antibody response endpoints, GMFRs and GMTs for HAI and MN antibody measurements will be summarized by treatment group and by strain, and the least square geometric mean ratio of GMFRs and GMTs between treatment groups (influenza vaccine divided by tezepelumab and influenza vaccine) will be calculated via an ANCOVA model on the log-transformed variable, adjusting for treatment group and age stratum (adolescents aged 12 to 17 or young adults aged 18 to 21). The least square geometric mean ratio will be provided with associated 90% CI.

The antibody response to the quadrivalent influenza vaccine strain is defined as a $\geq$ 4-fold rise in HAI or a $\geq$ 4-fold rise in MN from pre-dose antibody measure to post-dose antibody measure. The proportion of participants who experience a post-dose antibody response at Week 16 (EOT) for HAI and the proportion of participants who experience a post-dose antibody response at Week 16 (EOT) for MN and corresponding 90% Clopper-Pearson exact CIs will be summarized by treatment group and by strain.

The proportion of participants who achieve a post-dose HAI antibody titer $\geq$ 40 and the proportion of participants who achieve a post-dose MN antibody titer $\geq$ 40 at Week 16 (EOT) and corresponding 90% Clopper-Pearson exact CIs will be summarized by treatment group and by strain.

Secondary Endpoints

Tezepelumab serum concentrations will be summarized using descriptive statistics at each visit. ADA to tezepelumab will be summarized using descriptive statistics at each visit.

Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in force at the primary database lock. The definition of on-treatment and on-study for AE analyses will be given in the statistical analysis plan.

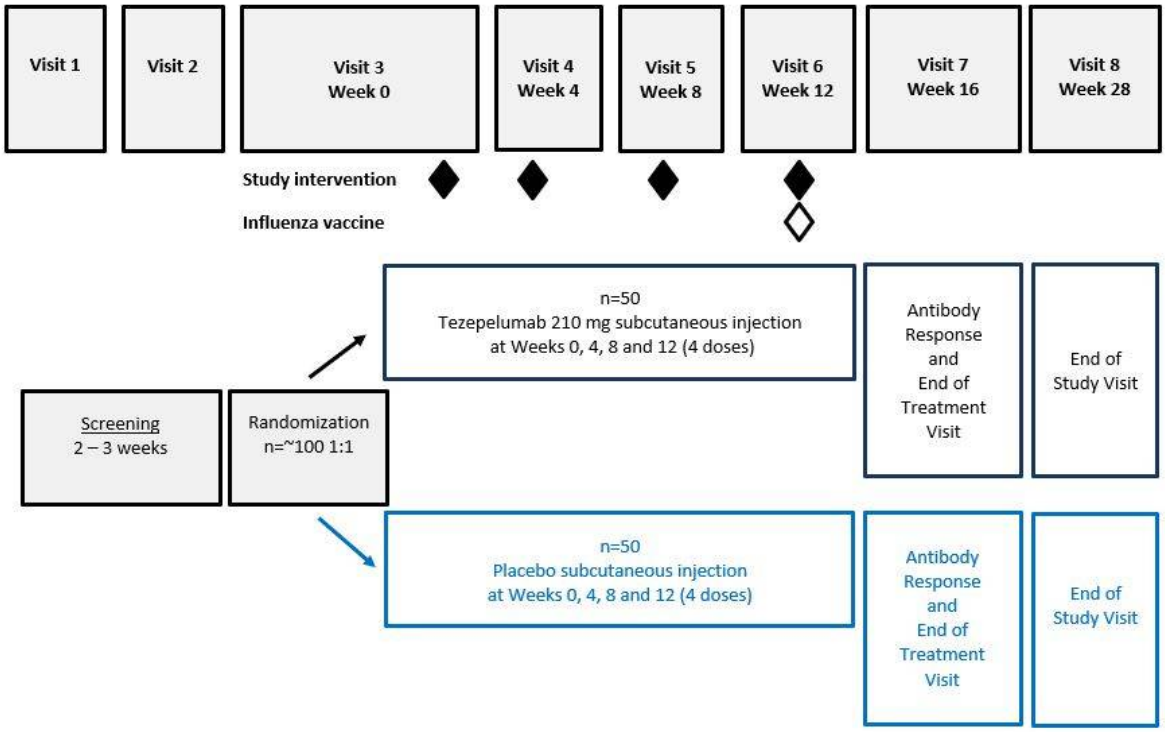
The number and percentage of participants with on-treatment and on-study AEs will be tabulated separately by preferred term and system organ class. An event that occurred one or more times during a period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all participants in the safety population. On-treatment AEs will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator).

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarized.

Vital signs data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital signs abnormalities will be summarized.

1.2 Schema

Figure 1 Study Design



Abbreviations: n=number of participants.

1.3 Schedule of Activities

Table 1 Schedule of Activities (Screening)

Assessment/activity	Screening		Details in CSP Section or Appendix
Visit	**V1 (Week -2 to -3)**	**V2[a] (V1 plus maximum 7 days)**	
Informed consent/assent	X		Section 5.1
Inclusion and exclusion criteria	X	X	Sections 5.1 and 5.2
Demography	X		Section 5.1
Medical and asthma history[b]	X		Section 5.1
Complete physical examination	X		Section 8.2.1
Weight, height, and BMI	X		Section 8.2.5.2
Vital signs	X	X	Section 8.2.2
Local 12-lead ECG	X		Section 8.2.3
Serum chemistry	X		Section 8.2.4
Hematology	X		Section 8.2.4
Local urinalysis	X		Section 8.2.4
Serum concentration (theophylline)[c]	X		Section 8.2.4
Serology (hepatitis B, C; HIV-1; HIV-2)	X		Section 8.2.5.3
Local SARS-CoV-2 viral diagnostic test[d]	X		Section 8.2.5.4
Serum pregnancy test[e]	X		Section 8.2.5.1
Pre-bronchodilator FEV_1[f]	X	X	Section 8.1.2.2
Post-bronchodilator FEV_1[f]	X	X	Section 8.1.2.3
Adverse Events	X	X	Section 8.3

Assessment/activity	Screening		Details in CSP Section or Appendix
Visit	**V1 (Week -2 to -3)**	**V2[a] (V1 plus maximum 7 days)**	
Concomitant medication	X	X	Section 6.5

[a] Visit 1 and Visit 2 can be combined if the participant has the time and they have not taken SABAs for 6 hours or their long-acting bronchodilator-containing therapy for 12-24 hours. If spirometry/reversibility procedures are actually planned at Visit 1 as a convenience, then the ICF/assent must be signed prior to Visit 1 and prior to instructing the participant to withhold any medication.

[b] To include influenza vaccination history.

[c] For participants on theophylline, the serum concentration testing will be performed locally.

[d] SARS-CoV-2 viral diagnostic test to be performed locally (local COVID-19 viral test).

[e] For women of childbearing potential only.

[f] Pre and post-bronchodilator spirometry can be done at Visit 1 OR Visit 2. If participants do not demonstrate airway reversibility at either Visit 1 or Visit 2 and this is needed to qualify the participant for randomization, the site should screen fail the participant.

Abbreviations: AE=adverse event; BMI=body mass index; CSP=clinical study protocol; COVID-19=Coronavirus disease 2019; ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; HIV=human immunodeficiency virus; ICF=informed consent form; SABA=short-acting β-agonist; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; V=visit.

Table 2 Schedule of Activities (Randomization, Treatment, and Follow-up)

Assessment/activity	Treatment				Antibody response evaluation / EOT [a]	IPD [b]	FU / End of Study Visit	Unsch	Details in CSP Section or Appendix
Visit	V3	V4	V5	V6	V7		V8		
	W0	W4	W8	W12	W16		W28		
	Visit window (days) [c]								
	± 0	± 3	± 3	± 3	± 3	± 3	± 3		
Inclusion and exclusion criteria	X								Sections 5.1 and 5.2
Randomization	X								Section 6.3.1
Complete physical examination	X				X	X	X		Section 8.2.1
Brief physical examination		X	X	X				X	Section 8.2.1
Vital signs	X	X	X	X	X	X	X	X	Section 8.2.2
CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serum chemistry	X				X	X	X		Section 8.2.4
Hematology [d]	X				X	X	X		Section 8.2.4
Local urinalysis	X				X	X	X		Section 8.2.4
Urine pregnancy test (dipstick) [e]	X	X	X	X	X	X	X		Section 8.2.5.1
PK	X [f]			X [f]	X	X	X		Section 8.5.1
ADA	X [f]				X	X	X		Section 8.5.2
Serum antibodies to influenza virus				X [g]	X				
Administration of influenza vaccine [h]				X					Section 6.2.1.3
Administration of study intervention	X	X	X	X				X [i]	Section 6.2.1.3

Assessment/activity	Treatment				Antibody response evaluation / EOT [a]	IPD [b]	FU / End of Study Visit	Unsch	Details in CSP Section or Appendix
Visit	V3	V4	V5	V6	V7		V8		
	W0	W4	W8	W12	W16		W28		
	Visit window (days) [c]								
	± 0	± 3	± 3	± 3	± 3	± 3	± 3		
Adverse Events	X	X	X	X	X	X	X	X	Section 8.3
Concomitant medication	X	X	X	X	X	X	X	X	Section 6.5

[a] If influenza vaccine administration is delayed, unscheduled study intervention visits may occur prior to Visit 6 until the influenza vaccine is available at study sites. EOT assessments should be performed 4 weeks after last dose of study intervention.

[b] If IPD visit occurs at the same time as the scheduled Visit 6 (Week 12), participants should perform all assessments, including influenza antibodies followed by influenza vaccination. Participants should then return to the study site for Visit 7 (Week 16) and perform all assessments, including influenza antibodies. Refer to CSP Section 7.1 for additional information.

[c] All visits are to be scheduled from the date of randomization, not from the date of previous visit, except in the case of early discontinuation from study intervention (see Section 7.1 for details).

[d] Eosinophils, basophil, and monocyte counts will be redacted from the central laboratory reports except at Visit 3 prior to study intervention administration.

[e] For women of childbearing potential only, urine HCG test to be completed at study site on each study visit (before study intervention administration on Visit 3 to Visit 6).

[f] PK and ADA to be collected PRIOR to study intervention dose at Visit 3 and PK to be collected PRIOR to influenza vaccination at Visit 6.

[g] Blood draw for serum antibodies to influenza vaccine should occur prior to administration of influenza vaccine. If influenza vaccine administration is delayed from Visit 6 (Week 12), pre-influenza vaccine blood draw for serum antibodies should only occur on the week of influenza vaccine administration.

[h] Influenza vaccine is to be administered at a different site than study intervention and site of injection noted. Participant is to be observed for 15 minutes after injection and before administering study intervention. Influenza vaccine is to be administered after scheduled blood samples are taken and prior to study intervention administration.

[i] If influenza vaccine administration is delayed, an additional 1 to 2 unscheduled study intervention visits may occur prior to Visit 6, until the influenza vaccine is available at study sites. All assessments during the unscheduled visit may not be necessarily completed.

Abbreviations: CCI [redacted] ADA=anti-drug antibodies; AE=adverse event; CSP=clinical study protocol; EOT=end of treatment; FU=follow-up; HCG=human chorionic gonadotropin; IPD=investigational product discontinuation; PK=pharmacokinetics; Unsch=unscheduled; V=visit; W=week.

2 INTRODUCTION

This is a Phase 3b, multicenter, randomized, double-blind, parallel group, placebo-controlled study investigating the potential effect of tezepelumab on antibody responses following seasonal quadrivalent influenza virus vaccination.

2.1 Study Rationale

The epithelial cell-derived cytokine, TSLP, is produced in response to proinflammatory stimuli and drives allergic inflammatory responses, primarily through its activity on ILC-2, dendritic (Gilliet et al 2003, Soumelis et al 2002, Reche et al 2001) and mast cells (Allakhverdi et al 2007). Human TSLP expression is reported to be increased in asthmatic airways correlating with disease severity (Ying et al 2005).

Tezepelumab is a human mAb IgG2λ directed against TSLP, expressed in a CHO CS-9 cell line. The molecule is a heterotetramer consisting of 2 heavy chains of the IgG2 subclass and 2 light chains of the lambda subclass, which are covalently linked through disulfide bonds. Tezepelumab binds with human TSLP and prevents its interaction with TSLP receptor complex. As a result, targeting TSLP may inhibit multiple biologic pathways involved in asthma (Gauvreau et al 2014).

In the Phase 3 NAVIGATOR and Phase 2b PATHWAY studies, tezepelumab reduced exacerbations compared with placebo in participants with moderate to severe, uncontrolled asthma, irrespective of baseline levels of T2 inflammatory biomarkers (blood eosinophil counts, fractional exhaled nitric oxide, and serum total IgE) (Corren et al 2017, Menzies-Gow et al 2021). In these studies, tezepelumab also improved lung function, asthma control and patient health-related quality of life in the overall population. In addition, in these studies, tezepelumab has been shown to decrease IgE levels; however, its administration did not affect IgG, IgM or IgA. In a preclinical toxicology study with cynomolgus monkeys the IgG response to keyhole limpet antigen was suppressed but only at doses much higher than used in human studies (50 mg/kg subcutaneously [SC] weekly) (Investigator's Brochure for tezepelumab).

Owing to its immunomodulating effect, it is important to determine if tezepelumab affects functioning of the immune system. In this study, a functional response of the immune system will be assessed by measuring antibody responses to the influenza vaccine in adolescents and young adults with moderate to severe asthma.

The influenza vaccine was chosen for this study as GINA Guidelines recommend yearly influenza vaccination for asthmatics, in particular those with moderate to severe disease. The Center for Disease Control also recommends yearly influenza vaccination for asthmatics (GINA , CDC Asthma 2021). Quadrivalent, inactive influenza vaccine containing 4 strains (2

for influenza A and 2 for influenza B) selected for the influenza season 2021/2022 for the northern hemisphere will be used (FDA 2021).

Immunogenicity will be assessed using 2 types of strain-specific assays (dual primary endpoint) detecting vaccine humoral response:

- Hemagglutinin inhibition (HAI) assay and microneutralization (MN) assay.

Hemagglutinin inhibition assay measures the ability of serum to block haemagglutination, which is the aggregation of red blood cells caused by influenza virus. The resulting haemagglutination inhibition antibodies titer is a correlate of protection for influenza virus that is accepted by many regulatory agencies. Microneutralization assay detect antibodies that directly neutralize virus (Hannoun et al 2004, Hobson et al 1972, Krammer 2019).

The dual primary endpoint includes seroconversion outcome measures (4-fold rise in titer and titer $\geq$ 1:40) provided as response rates, and central measures of tendency for the immune response (geometric mean fold rises [GMFR] and geometric mean titers [GMT]) for the HAI and MN assay results. For the Influenza A H3N2-strain, only the MN assay will be performed owing to the known low hemagglutination effect of the strain (Sicca et al 2020).

In this study, a functional response of the immune system to the influenza vaccine will be assessed in adolescents and young adults with moderate to severe asthma. The rationale for selecting this population is based on the previous similar study with anti-IL5 biologic drug benralizumab in which humoral immune response was assessed in adolescent and young adult (12 to 21 years old) severe asthmatics (Zeitlin et al 2018). A total of 103 participants were randomized and received benralizumab (n=51) or placebo (n=52). There were no consistent differences in HAI or MN antibody responses 4 weeks after the inactive quadrivalent influenza vaccine administration between participants receiving benralizumab or placebo.

Participant entry will be stratified by age (12 to 17-year age group and 18 to 21-year age group) to ensure equitable distribution of treatment allocation for analysis.

In addition to the immune response to vaccine, the tezepelumab impact on CCI number of exacerbations, serum trough tezepelumab concentrations, and anti-drug antibodies (ADAs) will be investigated.

2.2 Background

Asthma is a chronic inflammatory disorder of the airways caused by the interaction of genetic and environmental factors. It is characterized by widespread, variable, and reversible airflow obstruction, airway inflammation, excessive mucus production; and airway hyperresponsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (CSGA 1997). Progressive pathologic airway remodeling and scarring

may occur in persistent asthma resulting in partially reversible or irreversible airway obstruction (Pascual and Peters 2005).

The etiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise when a person becomes hypersensitive to allergens. Approximately 19 million adult patients and 5.5 million children under 18 years of age in the USA are thought to have asthma (Asthma and Allergy Foundation of America 2017). Worldwide, asthma currently affects approximately 339 million people (Global Asthma Network 2018); yearly asthma accounts for an estimated 9.8 million physician office visits, 1.6 million emergency room visits, and over 3500 deaths in the USA (Asthma and Allergy Foundation of America).

Tezepelumab is being developed for the treatment of moderate to severe, uncontrolled asthma. Approximately 5% to 10% of asthma patients have severe asthma (based on 2018 estimates [Global Asthma Network 2018]), which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al 2008). These patients are at risk of asthma exacerbations (Tough et al 1998, Turner et al 1998) and have the greatest medical need among the asthmatic population today. Patients with severe asthma represent the greatest economic cost (> 50% of total asthma-related health care costs; Antonicelli et al 2004, Serra-Batlles et al 1998, Barnes and Kuitert 1996).

Study D5180C00007 (NAVIGATOR) was a Phase 3, multicenter, global, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 210 mg tezepelumab administered SC Q4W for 52 weeks. The population of interest was adults and adolescents with severe, uncontrolled asthma between the ages of 12 and 80 years and both overall and across a broad spectrum of asthma phenotypes as determined by participants with blood eosinophils above and below 300 cells/µL, FeNO above and below 25 ppb, as well as allergic and non-allergic status. A total of 1061 participants were randomized in a 1:1 ratio to tezepelumab or placebo and 1059 participants (including 82 adolescents) received at least one dose of study intervention. Tezepelumab treatment resulted in a statistically significant and clinically meaningful reduction in annualised asthma exacerbation rate (AAER) by 56% ($p < 0.001$) compared with placebo in the overall population and by 41% compared with placebo in participants with baseline blood eosinophils <300 cells/µL ($p < 0.001$). The mean serum trough concentration of tezepelumab increased over time and approached steady state by 12 weeks. Treatment-emergent ADAs were detected at any time during the study in 4.9% (26) of participants treated with tezepelumab. Neutralizing antibodies to tezepelumab were detected in only one (0.2%) of the participants treated with tezepelumab. On-treatment AEs were similar between the placebo (80.8%) and the total tezepelumab (77.1%) dose groups and the majority of participants had on-treatment AEs that were mild or moderate in severity and not related to the study intervention. The percentage of participants who discontinued the trial regimen was 6.8% in the tezepelumab group and 10.7% in the placebo group. On-treatment

AEs that resulted in permanent discontinuation of study intervention was 2.1% in the tezepelumab group and 3.6% in the placebo group. Overall, tezepelumab was well tolerated with an acceptable safety profile and no safety signals in both adult and adolescent participants with severe, uncontrolled asthma (Menzies-Gow et al 2021, TEZSPIRE FDA Prescribing Information 2021).

For moderate to severe asthma patients who are uncontrolled on ICS, LABA and other controllers, biologic therapies may provide benefit. Omalizumab may be suitable for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum IgE levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2019, XOLAIR SmPC 2019). Four additional biologics, mepolizumab, reslizumab, benralizumab, and dupilumab, have been approved for severe asthma with an eosinophilic phenotype and/or those requiring oral corticosteroid (OCS) therapy (NUCALA SmPC 2019, NUCALA US PI 2019, CINQAERO SmPC 2021, CINQAIR US PI 2020, FASENRA SmPC 2019, FASENRA US PI 2019, DUPIXENT SmPC 2020, DUPIXENT US PI 2019).

Biologics targeting IL-4, IL-5, and IgE are now included in international treatment guidelines (GINA) as add-on treatments to patients whose asthma remains uncontrolled with LABA/ICS treatment. However, even when using currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2016, Froidure et al 2016, Swedin et al 2017). Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among patients with moderate to severe asthma, independently of IgE status or eosinophil level, who are unable to gain asthma control using currently available therapies.

Both GINA and CDC recommend annual influenza vaccines for children and adults with asthma because they are at high risk of developing serious flu complications, even if their asthma is mild or their symptoms are well-controlled by medication. Influenza can result in airway and lung inflammation which can contribute to acute asthma exacerbations. Asthma is the most common medical condition among children hospitalized with influenza and one of the more common medical conditions among hospitalized adults (CDC Asthma 2021). Recent systematic review and meta-analysis that included observational studies designs suggested that influenza vaccination reduced the risk of asthma exacerbations (GINA 2021).

Tezepelumab is currently being developed as a potential treatment option for the management of moderate to severe, uncontrolled asthma in adolescent and adult patients. By blocking TSLP, tezepelumab has been shown to have a broader impact on the inflammatory responses seen in asthma than other biologics.

Additional studies with tezepelumab have been completed. These include a mechanistic study (D5180C00013; CASCADE) conducted in adults with inadequately controlled asthma, an OCS sparing study (D5180C00009; SOURCE) conducted in adults with OCS-dependent asthma, an

at-home use study in adults and adolescents with severe asthma study (D5180C00011; PATH-HOME), and a Japanese long-term safety study in participants with inadequately controlled asthma (D5180C00019; NOZOMI).

A detailed description of the above-mentioned additional studies and chemistry, pharmacology, efficacy, and safety of tezepelumab is provided in the current Investigator's Brochure.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Tezepelumab has been well-tolerated with no identified risks in the completed clinical studies to date. No serious allergic reactions or anaphylactic reactions causally related to tezepelumab were reported in the Phase 2 and Phase 3 studies. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host defense against certain infections, there is no clear preclinical or clinical evidence supporting such a role, and no safety signals related to infections have been detected in the tezepelumab program.

Mild problems following inactivated influenza vaccine may include soreness, redness, or swelling where the injection was given, as well as headache (low grade), fever, muscle aches, nausea, and fatigue (CDC Influenza 2021). Very rarely, as with all vaccines, anaphylaxis may occur.

2.3.1.1 Important Identified Risks

To date there are no important identified risks in the tezepelumab clinical development program.

2.3.1.2 Important Potential Risks

The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to infection.

Severe infections

Severe infections are defined as infections that are SAEs, require treatment with systemic antiviral medications, intravenous antibiotics or medications for helminth parasitic infection, or require permanent discontinuation of study intervention.

To mitigate the potential risk of severe infections eligibility criteria will exclude vulnerable participants, and included participants will be monitored for infection with complete blood counts, including differential white cell count throughout the study; and through standard AE/SAE reporting. Participants using immunosuppressive medication within 3 months prior to screening; who have a history of a known immunosuppressive disorder; who have a history

of clinically significant infection prior to screening; and who have known active or suspected tuberculosis either treated or untreated, will be excluded.

Parasitic infestation/infections

Tezepelumab may decrease the protective response to helminth infection by blockade of TSLP.

To decrease the risk of parasitic infestation or infection, participants who have a history of clinically significant infection prior to screening and at screening, and participants with untreated systemic helminth parasitic infections or those at significant increased risk of systemic helminth parasitic infestations will all be excluded.

Serious hypersensitivity/allergic reactions (including immune complex disease)

As with any large molecule therapeutics, administration of tezepelumab may result in systematic and/or local reactions. Systemic reactions to large molecule therapeutics can be IgE or non-IgE-mediated and are generally characterized by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnea, wheezing, bronchospasm, nausea/vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can all be severe or life-threatening. Effects typically occur during or within several hours after study intervention, but may be delayed.

To mitigate the potential risk of serious hypersensitivity reactions, during and after administration of tezepelumab, specific requirements for observing participants for AEs/SAEs and for monitoring vital signs before, during, and after administration of tezepelumab are included in the CSP. In addition, medical equipment to treat acute anaphylactic reactions will be immediately available and site staff will be trained to recognize and treat anaphylaxis.

The administration of a mAb can result in the formation of ADA. The occurrence of ADA could result in immune complex disease (Type 3 hypersensitivity reactions) with manifestations such as serum sickness, nephritis, and vasculitis, or altered tezepelumab levels or activity.

To mitigate the potential risk of immune complex disease participants will be monitored for the presence of ADA and confirmed immune complex disease through routine monitoring of AEs/SAEs. Participants with a prior history of immune complex disease will be excluded.

More detailed information about the known and expected benefits and potential risks of tezepelumab may be found in the current Investigator’s Brochure.

2.3.2 Benefit Assessment

Benefits for tezepelumab over placebo include a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics (Corren et al 2017).

Participants in this study may benefit from the continuous monitoring of all AEs arising during the clinical study, related or not related to the study intervention. In addition, participants will be contributing to the development of new therapies for moderate to severe asthma.

Benefits of seasonal influenza vaccination would include probable protection against developing influenza in the upcoming influenza season. GINA Guidelines recommend patients with moderate and severe asthma receive influenza vaccination every year to decrease risk of influenza and potential asthma exacerbation.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants enrolling in this study (see Section 2.3.1.2), the potential risks identified in association with tezepelumab are justified by the anticipated benefits that may be afforded to participants with moderate to severe asthma.

3 OBJECTIVES AND ENDPOINTS

Please note: If influenza vaccine administration is delayed, some participants' assessments at Visit 6 (Week 12) and Visit 7 (Week 16) may be performed at later timepoints.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of tezepelumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult participants with moderate to severe asthma	• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific serum HAI antibody geometric mean titers (GMTs) obtained at Week 16 (EOT) • Post-dose strain-specific serum MN antibody GMTs obtained at Week 16 (EOT) • Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a $\geq$ 4-fold rise in HAI antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a $\geq$ 4-fold rise in MN antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific HAI antibody titer $\geq$ 40 at Week 16 (EOT) • Post-dose strain-specific MN antibody titer $\geq$ 40 at Week 16 (EOT)
Secondary	
• To assess the PK and immunogenicity	• Serum trough tezepelumab concentrations • Anti-drug antibodies
Safety	
• To assess the safety and tolerability of tezepelumab	• AEs and SAEs • Laboratory variables • Vital signs

Table 3 Objectives and Endpoints

Objectives	Endpoints
CCI	

Abbreviations: CCI AEs=adverse events; PK=pharmacokinetic; SAE=serious adverse events.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3b, multicenter, randomized, double-blind, parallel group, placebo-controlled study designed to investigate the potential effect of tezepelumab (210 mg SC Q4W) on antibody responses following seasonal quadrivalent influenza virus vaccination in the fall/winter 2021-2022 in the USA.

Approximately 135 participants aged 12 to 21 years with moderate to severe asthma will be enrolled into screening to provide a target sample size of approximately 100 randomized participants for the study. Participants will be randomized 1:1 to receive tezepelumab 210 mg or placebo SC Q4W, administered at Weeks 0, 4, 8 and 12. Randomization will be monitored to ensure at least 50% of the enrolled participants are between the ages of 12 to 17 years. Treatment allocation will be stratified by age at the time of informed consent/assent (12 to 17 years, and 18 to 21 years) to ensure equitable distribution of tezepelumab and placebo treatment in the 2 age groups. To ensure that at least 50% of the enrolled participants are 12 to 17 years old, the IWRS/IVRS will be set up with a 50% cap on the 18 to 21-year age group. Once this cap is reached, no more participants will be enrolled into the 18 to 21-year age group. Once an age group is closed, participants in the screening period in the closed age group will not be allowed to be randomized and will be considered a screen failure.

After enrollment and confirmation of entry criteria, participants will enter the screening period of a minimum of 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated before being randomized. Participants who meet the eligibility criteria will be randomized at Visit 3 [Week 0] and will receive either tezepelumab 210 mg or placebo by SC injection at intervals of 4 weeks, ie doses of study intervention will be administered at Weeks 0, 4, 8 and 12. The study schema is presented in Figure 1.

Participants will receive a single dose of inactivated quadrivalent seasonal influenza vaccine IM at Week 12, prior to the fourth dose of study intervention. Steady-state of tezepelumab is achieved at Week 12. Serum samples for evaluation of antibody response will be drawn at Week 12 (pre-vaccination) and at Week 16 (4 weeks post-vaccination) when humoral response to the vaccination is expected to be fully developed.

The EOT Visit will be conducted at Week 16 and a final Follow-up Visit and the End of Study Visit will be conducted at Week 28.

Please note: If influenza vaccine administration is delayed, the treatment period may be extended and therefore participants may be given an additional 1 to 2 study intervention doses (as needed) every 4 weeks for a longer period than initially planned.

Participants will be maintained on their currently prescribed ICS-LABA therapies without

change from enrollment throughout the screening and treatment period. If asthma exacerbations occur during the treatment period, participants can be treated with oral or other systemic corticosteroids or other asthma therapies according to standard practice.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Re-screening: One additional re-screening to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated Parexel Medical Monitor.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV only during safety follow-up (after Visit 7).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls and virtual or video visits only during safety follow-up (after Visit 7).

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix B.

4.2 Scientific Rationale for Study Design

This study is designed to investigate the potential effect of tezepelumab on the antibody response to the quadrivalent seasonal influenza virus vaccine in participants 12 to 21 years of

age with moderate to severe asthma (see Section 2.1).

4.3 Justification for Dose

The selection of the 210 mg SC Q4W dose was based on efficacy and safety results from the Phase 2b PATHWAY study. In PATHWAY, 210 mg tezepelumab Q4W led to numerically improved efficacy compared with 70 mg Q4W, whereas the 280 mg Q2W dose did not increase efficacy further with the 210 mg Q4W dose. Tezepelumab was well-tolerated at all 3 doses and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship to AEs. Efficacy and safety of the 210 mg SC Q4W dose was further confirmed in the Phase 3 NAVIGATOR study in adults and adolescents with severe asthma.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all visits of the study including the End of Study Visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study.

5 STUDY POPULATION

Prospective approval of CSP deviations to recruitment and enrollment criteria, also known as CSP waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

5.1.1 Study Eligibility

Participants are eligible to be included in the study only if **all** of the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent/assent as described in Appendix C which includes compliance with the requirements and restrictions listed in the ICF/assent and in this CSP.

Age

2 Participant must be 12 to 21 years of age inclusive, at the time of signing the ICF/assent.

Type of Participant and Disease Characteristics

3 Documented physician-diagnosed asthma for at least 12 months prior to Visit 1.

4 Evidence of asthma as documented by either:

- Post-bronchodilator airway reversibility ($FEV_1 \geq 12\%$ and ≥ 200 mL) demonstrated at Visit 1 or Visit 2 using the Maximum Post-bronchodilator Procedure.

OR

– Airway reversibility documented in the previous 12 months prior to Visit 1.

Note: All participants must have reversibility testing performed before randomization to establish a baseline characteristic even if historical documentation is used to meet this criterion.

5 Documented history of stable treatment with ICS and LABA for at least 30 days prior to Visit 1.

– The ICS and LABA can be parts of a combination product or given by separate inhalers. For ICS/LABA combination preparations, both the mid and high-strength maintenance doses approved in the USA will meet this ICS criterion.

– The ICS dose must be > 250 µg fluticasone propionate dry powder inhaler or equivalent daily. Equivalent ICS doses as detailed in Appendix H.

– Additional asthma controller medications (eg, LTRAs, short and long-acting anti-muscarinics, theophylline, oral corticosteroids, etc) that have been used for at least 30 days prior to Visit 1 are allowed.

6 Morning pre-bronchodilator FEV_1 of > 50% predicted normal value at Visit 1 or Visit 2.

Weight

7 Body weight ≥ 40 kg.

Sex

8 Male and female participants.

Contraceptive use by women of childbearing potential should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see Section 5.3.4).

5.1.2 At Randomization

Participants are eligible to be randomized if all of the following criteria apply:

1 For women of childbearing potential, a negative urine pregnancy test is required prior to administration of study intervention at Visit 3 (randomization).

2 Must have 'not well-controlled' asthma as documented by either:

– CCI [redacted]

or

– A peak expiratory flow of 60-80% predicted.

or

– An exacerbation, one or more, that required oral corticosteroids in the previous 12 months.

or

- Any one of the following assessed by a participant recall over the previous 2-4 weeks:
  - Asthma symptoms > 2 days/week.
  - Night-time awakenings once or more per week.
  - SABA use for symptom control (not for the prevention of exercise-induced asthma) > 2 days/week.

NOTE: A participant's verbal history suggestive of asthma symptoms, but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

5.2 Exclusion Criteria

5.2.1 Study Eligibility

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Clinically important pulmonary disease other than asthma (eg, active lung infection, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangitis (EGPA), hypereosinophilic syndrome), or prior history of immune complex disease.

2 Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
   - Affect the safety of the participant throughout the study.
   - Influence the findings of the studies or their interpretations.
   - Impede the participant's ability to complete the entire duration of study.

3 Life-threatening asthma defined as episodes requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episodes.

4 History of cancer
   - Participants who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the participant is in remission and have had their curative therapy completed at least 12 months prior to Visit 1.

- Participants who have had other malignancies are eligible provided that the participant is in remission and have had their curative therapy completed at least 5 years prior to Visit 1.

5 Allergy to eggs, if egg based influenza vaccine will be administered.

6 History of anaphylaxis to any biologic therapy.

7 History of Guillain-Barré syndrome.

8 Known or suspected active tuberculosis either treated or untreated.

9 A helminth parasitic infection diagnosed within 24 weeks prior to Visit 1 that has not been treated with, or has failed to respond to standard of care therapy.

10 Current smokers or participants with smoking history ≥ 10 pack-years and participants using vaping products, including electronic cigarettes. Former smokers with a smoking history of < 10 pack-years and users of vaping or e-cigarette products must have stopped for at least 6 months prior to Visit 1 to be eligible.

11 History of alcohol or drug abuse within 12 months prior to the date of informed consent.

12 Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures during the conduct of the study.

Prior/Concomitant Therapy

13 If on allergen immunotherapy, participants must be on a stable maintenance dose and schedule for at least 30 days prior to Visit 1 with no anticipated change in therapy during the conduct of the study.

14 Use of immunosuppressive medication (including but not limited to methotrexate, troleandomycin, cyclosporine, azathioprine, tacrolimus, mycofenolate mofetil, intramuscular long-acting depot corticosteroid, or any experimental anti-inflammatory therapy) within 3 months prior to Visit 1.

15 Receipt of immunoglobulin or blood products within 30 days prior to Visit 1.

16 Receipt of live attenuated vaccines 30 days prior to the date of randomization.

17 Receipt of influenza vaccine for season 2021/22 prior to Visit 1.

18 COVID-19 vaccination within 6 days prior to randomization.

Prior/Concurrent Clinical Study Experience

19 Participants with a known history of allergy or reaction to the study intervention formulations or influenza vaccine.

20 Receipt of any marketed or investigational biologic within 16 weeks or 5 half-lives prior to Visit 1, whichever is longer.

21 Receipt of any non-biologic investigational medication within 30 days or 5 half-lives prior to randomization, whichever is longer.

22 Previously received tezepelumab.

23 Concurrent enrollment in another drug-related interventional clinical trial.

Diagnostic Assessments

24 Any clinically significant abnormal findings in physical examination, vital signs, baseline ECG, hematology, clinical chemistry, or urinalysis during screening period, which in the opinion of the investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete entire duration of the study.

25 Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Participants with a history of hepatitis B vaccination without history of hepatitis B are allowed to enroll.

26 A history of known immunodeficiency disorder including a positive HIV test at V1, or the participant is taking antiretroviral medications as determined by medical history and/or participant’s verbal report.

27 Positive SARS-Cov2 test during the screening period.

28 ALT or AST level ≥ 2 times the ULN confirmed during screening period.

Other Exclusions

29 For women only - currently pregnant (confirmed with positive pregnancy test), breastfeeding, or lactating women.

30 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

31 Employees of the study center or any other individuals involved with the conduct of the study or immediate family members of such individuals.

32 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

5.2.2 At Randomization

Participants are excluded from randomization if any of the following criteria apply:

1 Asthma exacerbation during the screening period that requires treatment with oral corticosteroids or a hospitalization/emergency room visit for the treatment of asthma.

2 Acute illness or evidence of significant active infection (eg COVID-19) or known influenza infection during the current influenza season.

5.3 Lifestyle Considerations

Participants must abstain from donating blood and plasma from the time of informed consent/assent, and for 16 weeks (5 half-lives) after last dose of study intervention.

5.3.1 Meals and Dietary Restrictions

- Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the study site.

5.3.2 Caffeine, Alcohol, and Tobacco

- Chronic alcohol or drug abuse within 12 months is restricted prior to Visit 1 and throughout the conduct of the study.
- Smoking is not allowed throughout the course of the study.
- The use of e-cigarettes is also not allowed during the course of the study.

5.3.3 Activity

- Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the study site.

5.3.4 Contraception

Female participants:

- Female participants of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception from screening, and must agree to continue using such precautions for 16 weeks after the final dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Highly effective forms of birth control include: true sexual abstinence, a vasectomised sexual partner, Implanon™, female sterilization by tubal occlusion, any effective intrauterine device/system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™ or Nuvaring™.

Adolescent specific information:

- If participant is female and has reached menarche, or has reached Tanner Stage 3 breast development (even if not having reached menarche), the participant will be considered a female of childbearing potential.

5.4 Screen Failures

Screen failures are defined as participants who complete informed consent/assent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

These participants should have the reason for study withdrawal recorded as 'Screen Failure' (ie, participant does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures, and not randomized participants.

Re-screening is allowed only once under the following circumstances:

- If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), participants may potentially be re-screened. These cases should be discussed with the Parexel Medical Monitor and documented in the investigator study file.
- Any re-screened participant will be re-enrolled and reassigned their originally assigned enrollment number after signing a new informed consent/assent form, and after all Visit 1 assessments have been performed as listed in Table 1 (with the exception of testing for HIV-1 and HIV-2, hepatitis B and C). If the timeframe between screening and re-screening is more than 30 days, then all Visit 1 assessments should be repeated.
- Participants who experience an asthma exacerbation during the screening/run-in period will be screen failed and may be re-screened after 14 days of complete resolution of the asthma exacerbation, and when the subjects return to baseline, at Investigator's discretion (the extension of the screening period beyond 14 days should be discussed with Parexel Medical Monitor).

Re-screened participants should be assigned the same enrollment number as for the initial screening.

However, re-screening should be documented so that its effect on study results, if any, can be assessed.

Re-screening of a participant for any other reason will be allowed only upon approval of the Parexel Medical Monitor. A documented approval for re-screening should be filed in the investigator study file.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to a study participant according to the CSP.

In this study, administration of the inactivated quadrivalent influenza vaccine is considered a background intervention, not a study intervention.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 4 Investigational Medicinal Products

Intervention name	Tezepelumab	Placebo
Type	Biologic	Placebo
Dose formulation	CCI [redacted]	CCI [redacted]
Unit dose strength(s)	210 mg	N/A
Dosage level(s)	210 mg Q4W	Placebo Q4W
Route of administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor.	Provided centrally by the sponsor.
Packaging and labelling	Study Intervention will be provided in APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP.	Study Intervention will be provided in APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP.

Abbreviations: APFS=accessorized pre-filled syringe; IMP=investigational medicinal product; N/A=not applicable; NIMP=non investigational medicinal product; SC=subcutaneous; Q4W=every 4 weeks; USA=United States of America.

The Accessorized Pre-Filled Syringe (APFS) is a single use, disposable system that is

designed to deliver the labelled dose to the SC space during one injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system. The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 2.25 mL syringe barrel - pre-filled to 1.91 mL with a 1/2-inch 27-gauge thin wall staked in needle, rigid needle shield, plunger stopper) and safety device.

6.1.1.1 Management of Study Intervention Related Reactions

Appropriate drugs (eg, epinephrine, H_1 and H_2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available. Site staff must be trained to recognize and treat anaphylaxis (Kroger et al 2011, Lieberman et al 2010). Management of anaphylaxis must be in accordance with current standard of care and clinical guidelines. Details on anaphylaxis management are provided in Appendix A.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Simpson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise or b) reduced blood pressure or symptoms of end-organ dysfunction.
2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms.
3 Reduced blood pressure after exposure.

At Visits 3 and 4, participants will have a pre-assessment (ie, vital signs) prior to study intervention administration) and should be observed after study intervention administration for a minimum of 2 hours for the appearance of any acute drug reactions. For the remaining visits involving study intervention administration, participants will be observed for a minimum of 1 hour after study intervention administration for any such reaction.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn as close as possible to the event for possible additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator.

6.1.2 Non-Investigational Product

Table 5	**Non-Investigational Medicinal Product**
Intervention name	Inactivated Quadrivalent influenza vaccine
Type	Vaccine

Dose formulation	Pre-filled syringe
Unit dose strength(s)	Background intervention
Dosage level(s)	0.5 mL once
Route of administration	IM injection
Use	Background intervention
IMP and NIMP	NIMP
Sourcing	Provided centrally by the sponsor.
Packaging and labelling	Provided as per manufacturer's packaging

Abbreviations: IM=intramuscular; IMP=investigational medicinal product; NIMP=non investigational medicinal product.

6.1.3 Medical Devices

The Sponsor-manufactured medical device, which forms part of the combination product and is referred to as a device constituent part, provided for use in this study is:

- Accessorised pre-filled syringe (APFS)

Instructions for medical device use are provided in study intervention Handling Instructions.

All medical device deficiencies (including malfunction, use error and inadequate labelling) should be documented and reported by the investigator throughout the study (see Section 8.3.12) and appropriately managed by the manufacturer.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Tezepelumab

6.2.1.1 Preparation and Handling

Blinded study intervention will be supplied to the site in a kit containing APFS tezepelumab or matching placebo. The kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the APFS within the carton).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

The study intervention is to be stored at the study center in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log while study intervention is stored at the study center. The study intervention must be kept in the original outer container and under

conditions specified on the label (between 36 °F to 46 °F [2 °C to 8 °C], protected from light).

In the following cases neither the center staff should use the affected study intervention and should immediately contact a Parexel representative for further guidance:

- Temperature excursion upon receipt or during storage at the study center
- Storage conditions were not met (eg, frozen) or cannot be confirmed
- Damaged kit upon receipt
- Damaged APFS device
- Security seal on the carton has been broken
- The expiration date has passed
- Other reason(s) that may have affected the study intervention

Damaged study intervention should be documented via IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

6.2.1.2 Dose Preparation

Prior to each study intervention administration at the study site:

- Investigator/authorized delegate will assess injection site as per standards of medical care.
- For women of childbearing potential, urine pregnancy test will be done; study intervention will be administered only when the result of the test is negative (see Section 8.2.5.1).

The APFS should be visually inspected prior to dose preparation. The study intervention will be provided to the study sites as a clear to slightly opalescent, colorless to light yellow liquid, practically free from particles contained in a pre-filled syringe to be stored between 36 °F to 46 °F (2 °C to 8 °C) until used.

If defects are noted with the study intervention, the investigator and site monitor should be notified immediately. Preparation of the study intervention must be performed by a qualified person (eg, pharmacist, investigator or nurse) at the site.

The study intervention does not contain preservatives and any unused portion must be discarded. Total in-use storage time from removal of the study intervention from the refrigerator to start of administration must not exceed 8 hours. If storage time exceeds this limit, a new dose must be prepared with a new study intervention kit.

To prepare the participant's dose, a study intervention kit will be selected for administration according to the kit identification number assigned by IWRS/IVRS.

Dose preparation steps:

1 Allow the study intervention to equilibrate to room temperature 68 °F to 77 °F (20 °C to 25 °C) for at least 60 minutes prior to dose administration. Ensure that the APFS is adequately protected from light during the warming process.

2 To prepare the study intervention for administration, remove the syringe from the carton by holding the middle of the syringe body.

3 Unwrap, but do not detach, the wrap-around label attached to syringe body to view the syringe contents.

4 Look at the liquid through the viewing window. The liquid should be clear to slightly opalescent, colorless to light yellow liquid, practically free from particles. Do not inject the study intervention if the liquid is cloudy, discolored, or contains large particles.

5 Re-wrap the label around the syringe body.

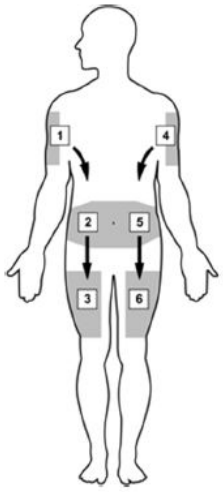
Unused product in opened and dispensed study intervention kits should not be used for subsequent dosing and should be stored for study intervention accountability. If the opened and dispensed APFS must be discarded immediately after dose preparation as per the site's standard operating procedures, the kit boxes must be retained for study intervention accountability.

6.2.1.3 Dose Administration

The administration of all study intervention should be recorded in the appropriate sections of the eCRF. The study intervention will be administered at the study center. The study intervention will be administered by the investigator/authorized delegate or qualified healthcare professional (eg, pharmacist or study nurse) as specified in the SoA (Section 1.3). Each participant will receive tezepelumab 210 mg (one 1.91 mL injection) or matching placebo administered SC Q4W for 4 doses in the abdomen, thigh, or upper arm by APFS.

The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be fully inserted at a 45-degree angle approximately into the SC tissue. The injection site should not be rubbed after each injection. It is suggested that the site of injection of study intervention be rotated such that the participant receives study intervention at a different anatomical site each time. Suggested injection site rotation sequence is presented below (see Figure 2). In cases when rotation of the injection site is not favorable for the participant and/or investigator, the reason should be recorded in the source documents. The injection site must be recorded in the source documents and the eCRF at each treatment visit.

Figure 2 Suggested Schema of Rotation of Injection Sites



Further details on study intervention administration are provided in the study intervention handling instructions. Study intervention administration must be carried out in line with the instructions provided.

At Visits 3 and 4 (Weeks 0 and 4), participants should be observed by the qualified healthcare professional for a minimum of 2 hours after study intervention administration for the appearance of any acute drug reactions. For the remaining visits involving study intervention administration, participants will be observed by the qualified healthcare professional for a minimum of 1 hour after study intervention administration for the appearance of any such reaction.

If any of the following occur, the investigator should reschedule the visit and the study intervention should not be administered until the rescheduled visit:

- The participant received allergen immunotherapy injection on the same day as scheduled study intervention administration.
- The participant has an intercurrent illness that in the opinion of the investigator may compromise the safety of the participant in the study (eg, viral illnesses).
- The participant was febrile (≥ 100.4 °F; ≥ 38 °C) within 72 hours prior to study intervention administration.
- The participant is confirmed to have an active COVID-19 infection based on positive SARS-CoV-2 test results.
- The participant is suspected to have an active COVID-19 infection based on assessment of COVID-19 symptoms.

The visit should be rescheduled within the allowed visit window and study intervention should

be administered at that rescheduled visit.

If the participant is suspected to have an active COVID-19 infection or fever (≥ 100.4 °F; ≥ 38 °C) suspected due to COVID-19 infection, the visit should be rescheduled (and study intervention administration deferred) and participant should be re-assessed for symptoms of COVID-19 prior to re-scheduled visit.

The Parexel Medical Monitor should be contacted to discuss further participation in the following situations:

- The participant has been diagnosed with an active COVID-19 infection.
- The participant skips 2 consecutive study intervention administrations.

If the participant reports an injection site reaction, the investigator or qualified designee will complete the AE eCRF page and an additional eCRF page with questions about the injection site reaction.

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure facility with limited access.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions are provided in the investigator instructions document.

6.2.2 Influenza vaccine

6.2.2.1 Preparation and Handling

Inactivated quadrivalent influenza vaccine will be provided to the study sites in the manufacturer's packaging and will be in Pre-Filled Syringes. Influenza vaccine will be stored in the refrigerator at 35 °F to 46 °F (2 °C to 8 °C).

6.2.2.2 Dose Administration

The influenza vaccine will be administered by a qualified healthcare professional at the site at Week 12. The influenza vaccine should be injected IM, in the deltoid muscle and should be administered prior to study intervention. After influenza vaccine administration, the participant should be observed for a minimum of 15 minutes for the appearance of any acute

drug reaction and prior to administration of study intervention. A different injection site should be used for SC injection of study intervention on that day (ie, not the same upper arm). The injection sites must be recorded in the source documents and the eCRF.

6.2.3 Reporting Product Complaints

Any defects with the study intervention must be reported immediately to the Site Monitor. All defects will be communicated to the Sponsor and investigated further with the AstraZeneca Supply Chain Group.

During the investigation of the product complaint, all study intervention must be stored at labelled conditions 2°C to 8°C (36°F to 46°F), separated from other study intervention kits, unless otherwise instructed.

6.2.4 Reporting Product Defects

Product defects may be related to component, product, or packaging and labelling issues prior to or during use. Product defects should be reported to the Study Monitor. The list below includes the 3 categories of product complaints that should be reported as defects. Descriptions of product complaints in these 3 categories include, but are not limited to:

- **Component Issue:** Defect in the container or dosing mechanism of the study intervention. The component may be damaged, missing, or broken. For the APFS, component examples include syringes and the accessory housing the syringe.
- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description in the Parexel study-specific Investigator Manual.
- **Packaging/Labelling Issue**: Defect in the packaging or labelling of the product. The packaging (eg, carton, thermo-fitted tray, or tamper-evident seal) or labelling may be damaged or unreadable, or the label may be missing.

6.2.5 Single Use APFS Device Malfunction

An APFS malfunction is when the APFS appeared normal during verification of shipment and then does not work during administration, eg, the safety feature activated prematurely, part of the device (finger flange, plunger rod, etc.) came off or broke, the needle shield could not be removed, only a partial dose was administered, the needle guard safety feature did not activate, needle bent or broke upon use.

Device malfunctions should be reported using the “Defect Malfunction Return Form” and the Study Monitor should be notified.

If a device malfunction is identified:

- Before study intervention administration has started, another kit (replacement) should be dispensed to perform study intervention administration;
- After study intervention administration has started and participant has been administered partial dose of study intervention, another kit must not be dispensed, and the participant must not be administered with another study intervention kit. The Parexel Medical Monitor and Study Monitor should be notified.

The return address and attention for malfunctioning device is available in the Device Malfunction Return Instructions.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Participant Enrollment and Randomization

The investigator(s) will:

1 Obtain signed informed consent/assent from the potential participant, or their guardian/legal representative, before any study specific procedures are performed.
2 Assign the potential participant a unique enrollment number via the IWRS/IVRS.
3 Determine participant eligibility.
4 Assign the eligible participant unique randomization code via the IWRS/IVRS.
5 Participants will be allocated to receive tezepelumab or placebo in a 1:1 ratio and according to the stratification factor listed in Section 4.1. Randomization numbers will be grouped in blocks. If a participant withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn participants will not be replaced.

Specific information concerning the use of the IWRS/IVRS will be provided in a separate manual.

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study intervention. There can be no exceptions to this rule. Participants who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study. These participants are defined as screen failures.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the Parexel Medical Monitor

immediately, and a discussion should occur between the Parexel Medical Monitor and the investigator regarding whether to continue or discontinue the participant from treatment. Study intervention must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the participant and the Parexel Medical Monitor must ensure the decision is appropriately documented. Participants that are discontinued from treatment should be followed up according to the options described in Section 7.1.

In those cases where continuation of the study intervention is judged not to present a concern related to safety and disease management, the rationale for continuing study intervention must be clearly documented.

6.3.3 Methods for Assigning Treatment Groups

Randomization codes will be assigned strictly sequentially in each stratum as participants become eligible for randomization.

The randomization code will be assigned from a randomization list prepared by a computerized system provided by CALYX on behalf of AstraZeneca in accordance with the AZRand process. All participants will be stratified at randomization by age group at the time of informed consent/assent (12 to 17 years and 18 to 21 years). The randomization will be set up to ensure that at least 50% of enrolled participants are in the 12 to 17-year age group. This will be accomplished by placing a 50% cap on the 18 to 21-year age group in the IWRS/IVRS such that enrollment in this age group stops once this cap is reached.

6.3.4 Ensuring Blinding

This is a double-blind study in which tezepelumab and placebo are not visually distinct from each other. All packaging and labelling of study intervention will be done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the participant nor any of the investigators or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the treatment received. Since tezepelumab and placebo are not visually distinct, study intervention will be handled by a qualified person (eg, pharmacist or study nurse) at the site.

A Parexel site monitor will perform study intervention accountability. In the event that the treatment allocation for a participant becomes known to the investigator or other study staff involved in the management of study participants, or needs to be known to treat an individual participant for an AE, the sponsor must be notified immediately by the investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list:

- Those carrying out the packaging and labelling of study intervention

- Those generating the randomization list (CALYX)
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- Bioanalytical lab analyst performing the PK sample analysis

No other member of the extended study team at AstraZeneca, or any contract research organization (CRO) handling data, will have access to the randomization scheme during the conduct of the study until after the planned unblinding at the primary database lock after the last participant (enrolled in the 2021/2022 flu season) completes Visit 7 (Week 16).

The information in the randomization list will be kept from other personnel involved in the conduct of the study and in a secure location until the end of the study.

Maintaining the blind to the participant's blood eosinophil counts

While not entirely specific, participants on active tezepelumab treatment are expected to have lower blood eosinophil counts than participants on placebo. Procedures to mitigate unblinding on this basis include:

- From Week 4 onward, eosinophil, monocyte, and basophil counts will be redacted from central laboratory reports to prevent the investigator/designee from possibly deducing the eosinophil contribution to the complete blood count.
- If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a hemoglobin is desired, the investigator should avoid ordering a complete blood cell count with differential.
- Handling of labs obtained during the treatment period but ordered outside of the clinical trial. Site staff who are directly involved in the participant's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside laboratory reports. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in participant management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the participant's management and prior to filing as a source document. Similarly, eosinophil, monocyte, and basophil results must be redacted from all communications with the sponsor.
- In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

6.3.5 Methods for Unblinding

Individual treatment codes, indicating the treatment randomization for each randomized

participant, will be available to the investigator(s) and delegate(s) at the study sites from the IWRS/IVRS. Routines for this will be described in the IWRS/IVRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator should document and report the action to Parexel, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and until the primary database lock - after the last participant has completed Visit 7 (Week 16) - has been documented.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

To satisfy inclusion criterion 5, a history of treatment with medium or high-dose ICS plus LABA and a history of treatment with additional asthma controller medications for at least 30 days prior to Visit 1 should be documented in source and recorded in the eCRF, along with reason for treatment, prior to the date of randomization. Changes are discouraged to background asthma medications throughout the duration of the study except during the treatment of an asthma exacerbation. All other medications taken for conditions other than asthma in the 30 days prior to Visit 1 must be recorded in the eCRF along with reason for treatment by the investigator/authorized delegate at each visit (as shown in SoA Section 1.3).

As theophylline has a narrow therapeutic window, please note that participants on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented before Visit 1. If this is not documented before signing the informed consent/assent, it can be obtained after informed consent/assent has been given or as part of the Visit 1 procedures. The sample can be analyzed at the local lab as applicable. The investigator can use their clinical judgment about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Treatment for any exacerbation that occurred within 12 months prior to Visit 1 should be recorded
- Dosage information including dose and frequency for asthma medications

The Parexel Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Table 6 Permitted Medications

Type of medication/treatment	Usage
The ICS and LABA can be parts of a combination product or given by separate inhalers.	The ICS dose must be > 250 µg fluticasone propionate dry powder inhaler or equivalent daily.
Additional asthma controller medications (eg, LTRAs, short and long-acting anti-muscarinics, theophylline, oral corticosteroids, etc).	These must have been used for at least 30 days prior to Visit 1.
Background controller regimen.	Changes are discouraged throughout the study unless judged medically necessary by the investigator or the participant's health care practitioner.
Oral or other systemic corticosteroids or other asthma therapies.	Asthma exacerbations can be treated according to standard practice.

Abbreviations: ICS=inhaled corticosteroids; LABA=long-acting β2 agonist; LTRA=leukotriene receptor antagonist.

Table 7 Restricted Medications

Type of medication/treatment	Usage
Allergen therapy.	These should not be administered within 7 days of study intervention administration.
Medication with narrow therapeutic range.	The level of theophylline or other drugs with a narrow therapeutic range should not exceed the upper limit of therapeutic range at the time of enrollment.

Table 7 Restricted Medications

Type of medication/treatment	Usage
Scheduled inactivated/killed vaccines, including the COVID-19 vaccination	These are allowed, provided they are not administered within 6 days before or after study intervention administration. Scheduled influenza vaccination at Visit 6 is not allowed within 6 days after the COVID-19 vaccination. Administration timing of COVID-19 vaccination should be discussed with Parexel Medical Monitor.

Abbreviations: COVID-19= Coronavirus disease 2019; OCS=oral corticosteroids.

Table 8 Prohibited Medications

Type of medication/treatment	Usage
Influenza vaccine.	Not allowed for the fall/winter 2021/22 season prior to randomization or throughout study period (except for the influenza vaccine given at Visit 6 per CSP).
Any immunomodulators or immunosuppressives.	Not allowed 3 months prior to Visit 1, throughout the treatment period or until the End of Study Visit at Week 28 is complete.
Live attenuated vaccines.	Not permitted 30 days prior to randomization, throughout the treatment period or until the End of Study Visit at Week 28 is complete.
Any marketed or investigational biologic product.	Not allowed 16 weeks or 5 half-lives prior to Visit 1, throughout the treatment period or until the End of Study Visit at Week 28 is complete.
Other investigational products (including investigational use of an approved drug).	Not allowed 30 days, or 5 half-lives (whichever is longer), prior to Visit 1, or throughout the treatment period.
Blood products or immunoglobulin therapy.	Not allowed 30 days prior to date of Visit 1 and throughout the treatment period.
Regular use of SABA	Regular scheduled use of SABA is not allowed from Visit 1 and throughout the study intervention treatment and preferably 4 weeks after the last dose of study intervention, PRN use is allowed if needed; however, attention should be paid to the following restrictions. SABA should be withheld for at least 6 hours prior to scheduled spirometry at site with the exception of any unscheduled visits due to asthma worsening.

Abbreviations: CSP=clinical study protocol; SABA=short-acting β2 agonists.

6.5.1 Rescue Medicine

Short-acting bronchodilators may be used as rescue medication during the study in the event of a worsening of asthma symptoms.

6.5.2 Asthma Medication Restrictions

- **Changes to the participant's background controller regimen are discouraged during the study** unless judged medically necessary by the investigator or the participant's HCP; ideally such changes should be discussed with the Parexel Medical Monitor. All changes in the participant's background medication should be documented in source along with rational for change and recorded in the eCRF.

  Asthma exacerbations can be treated with oral or other systemic corticosteroids or other asthma therapies according to standard practice.
- **Asthma medication restrictions on the days of scheduled spirometry visits**

  Pre and/or post-dose spirometry assessments will be performed at the study center at scheduled visits (see SoA, Section 1.3). Restrictions to the participant's background medication are required prior to the spirometry as described below (also see Section 8.1.2).

  Screening Visit 1 or 2: Participants will be asked to withhold their usual bronchodilator medications on the morning of scheduled spirometry measurements (see Section 8.1.2.1).

  The participant's usual asthma medications may be administered following completion of the screening lung function procedures.

6.6 Dose Modification

If influenza vaccine administration is delayed, an additional 1 to 2 unscheduled study intervention visits may occur prior to Visit 6 until the influenza vaccine is available at study sites.

6.7 Intervention After the End of the Study

Participants who complete Week 28 should continue to receive standard of care asthma medication at the discretion of the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive any further study intervention in the following situations.

- Participant decision. The participant is at any time free to discontinue study intervention, without prejudice to further treatment.

- An AE considered to jeopardize the safety of a participant in the study.
- Pregnancy.
- Severe noncompliance with the CSP.
- Development of any study specific criteria for discontinuation, including:
  - An anaphylactic reaction to the study intervention requiring administration of epinephrine.
  - A helminth parasitic infestation requiring hospitalization.
  - An asthma-related event requiring intubation.
  - Any malignancy except participants who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins.
- Development of one or more of the following:
  - Confirmed ALT or AST increase of ≥ 8 × ULN.
  - Confirmed ALT or AST increase of ≥ 5 × ULN for more than 2 weeks.
  - Confirmed ALT or AST increase of ≥ 3 × ULN and total bilirubin of ≥ 2 × ULN.
  - ALT or AST of ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%).

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

Participants who discontinue study intervention should return to the study center and complete the procedures described for the IPD visit (refer to Section 1.3, SoA, IPD visit) at 4 weeks (±3 days) post last study intervention administration. If the IPD visit occurs on the same date as the scheduled Visit 6 (Week 12), all IPD assessments should be performed, in addition to influenza antibodies and influenza vaccine administration. The participant should then return for the scheduled Visit 7 (Week 16) visit and have all scheduled assessments performed, including the influenza antibodies, as per the SoA.

All participants who discontinue study intervention should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments.

The participant should return for a Follow-up Visit 16 weeks (± 3 days) post last study intervention administration (refer to Section 1.3, SoA, V8 – Week 28). If the follow-up visit occurs on the same date as the scheduled Visit 7 (Week 16), all follow-up assessments should be performed, in addition to influenza antibodies.

See the SoA for data to be collected and for any further evaluations that need to be completed in case of discontinuation from study intervention.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own (parent or legal guardian) request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an IPD Visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant (parent or legal guardian) withdraws informed consent/assent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of informed consent/assent.
- If a participant withdraws from the study, it should be confirmed if he/she (parent or legal guardian) still agrees for existing samples to be used in line with the original informed consent/assent. If he/she (parent or legal guardian) requests withdrawal of informed consent/assent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent/assent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix C.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent/assent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 150 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Humoral Response to Influenza Vaccine

Serum HAI and MN antibody testing for antibody responses will be performed on blood samples taken at Week 12 (pre-dose antibody measure) and at Week 16 (EOT) from all study participants. Methods for these analyses will be described in the Laboratory Manual.

8.1.2 Spirometry

8.1.2.1 General requirements

Lung function (reversibility, FEV_1 and FVC) at the study center will be measured by spirometry using the sites own equipment. Spirometry should be performed by the investigator

or authorized delegate according to ATS/ERS or local guideline recommendations.

The PI/authorized delegate is responsible for assuring that the spirometer is in good working condition, calibrated and meets the ATS/ERS or local guidelines recommendations, and that the study center personnel who will perform the test are properly certified.

IMPORTANT: Participants should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below:

- SABAs or SAMAs should be withheld at least 6 hours prior to scheduled spirometry at site.
- Twice daily LABA or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at site.
- Once daily LABA or LAMA-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at site.
- LTRA should be restricted for at least 24 hours prior to scheduled spirometry at site.
- Twice daily theophylline should be withheld for at least 12 hours prior to scheduled spirometry at site.
- Once daily theophylline should be withheld for at least 24 hours prior to scheduled spirometry at site.

If Visits 1 and 2 are combined, bronchodilator therapy(ies) with or without ICS should be withheld for 12 to 24 hours depending on whether the participant is using twice or once daily bronchodilator-containing therapy.

Options for handling participants who have inadvertently taken their asthma medication within the restricted window are described in Section 6.5.2.

8.1.2.2 Spirometry Technique

Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Participants should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the center. Forced expiratory maneuvers should be performed with the participant seated in an upright position. If this is not comfortable for the participant, standing is permitted. The same position should be used by the participant for each forced expiratory maneuver. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence, tight clothing should be loosened. A nose-clip should be used for the maneuver. Mouthpieces of the same dimension and shape should be used by the participant.

The forced expiratory maneuver (FEV_1 and FVC) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds. It is

important to encourage the participant to continue the expiration to be fast and forceful throughout the maneuver. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the American Thoracic Society/European Respiratory Society acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1.

The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value will be recorded using the local spirometer at the site with predicted values derived from the reference value of choice, eg, NHANES III 2010, Quanjer et al 2012, etc. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

8.1.2.3 Post-bronchodilator Spirometry

All participants must meet inclusion criterion 3 either by having documented historical reversibility or by demonstrating reversibility either at Visit 1 or Visit 2. Even if documented historical reversibility is available, the post-BD spirometry procedures must be performed at Visit 1 to categorize participants (establish baseline characteristic) prior to randomization. The documented historical reversibility must be recorded in the eCRF/spirometer prior to randomization.

The post-BD spirometry procedure should commence within 30 ± 15 minutes according to the regimen for reversibility testing outlined in Section 8.1.2.5 and Figure 3.

8.1.2.4 Order of Administration

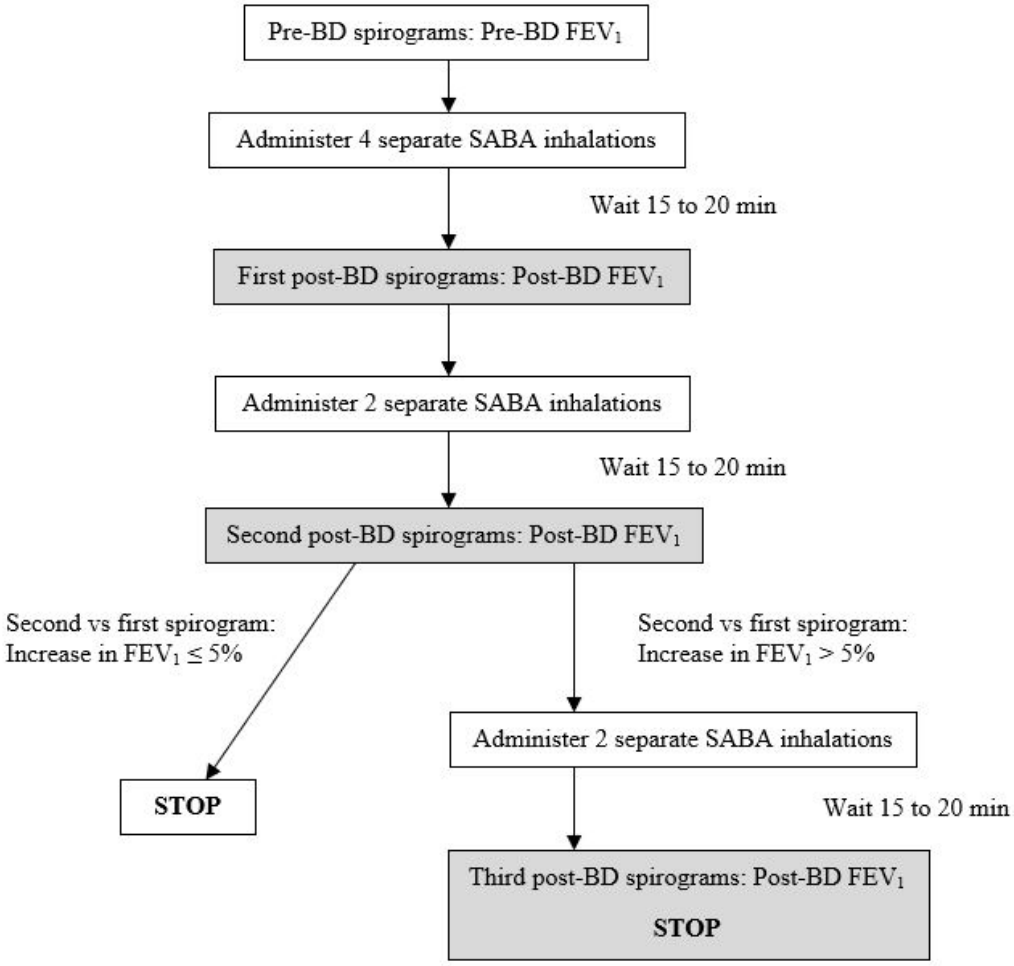
Order of administration of usual asthma controller medication and study intervention relative to scheduled pre and post-bronchodilator spirograms.

The participant's usual morning asthma controller therapy must not be given until after the initial pre-medication, pre-BD spirogram is complete for the reasons discussed above; usual asthma controller may be given after the post-BD spirogram.

8.1.2.5 Reversibility Test and Post-BD FEV_1 Assessment

The procedure described in this section refers to the reversibility testing at Visit 1 or Visit 2. Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 8 inhalations. It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 3.

Figure 3 Reversibility Testing Algorithm



Abbreviations: BD=bronchodilator; FEV_1=forced expiratory volume in 1 second; SABA=short-acting β2 agonists.

1 Verify with the participant that the medication restrictions to allow the reversibility assessment have been met (Section 6.5.2).

2 After a gentle and complete expiration, albuterol, salbutamol or levalbuterol is inhaled in one breath to total lung capacity from a spacer device. The breath is then held for 5 to 10 seconds before the participant exhales. Four separate inhalations are delivered at approximately 30 second intervals. Post-BD spirometry should be performed 15 to 20 minutes later.

3 If the participant has not met reversibility criteria, an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 6 inhalations). Second post-BD spirometry should be performed 15 to 20 minutes later.

4 If the participant still has not met reversibility criteria, an additional 2 inhalations of albuterol, salbutamol, or levalbuterol can be administered as single inhalations, 30 seconds apart (for a total of 8 inhalations). Third post-BD spirometry should be performed 15 to 20 minutes later.

A lower total dose, eg, 2 inhalations instead of 4 in the first round of puffs can be used if there is a concern about any effect on the participant's heart rate, tremor, or safety. The bronchodilator algorithm can be stopped at any time once a participant has met reversibility criteria.

The highest pre and post-BD FEV_1 should be used to determine reversibility.

Reversibility is calculated as follows:

$$\% \text{ Reversibility} = \frac{(\text{post-BD } FEV_1 - \text{pre BD } FEV_1) \times 100}{\text{pre-BD } FEV_1}$$

8.1.2.6 Record Keeping

A signed and dated copy of the pre- and post- BD printout must be kept at the study center for source data verification. The printout must be marked with the study code, enrollment code, date and time of measurement, and visit number.

CCI

CCI

[redacted]

CCI

[redacted]

8.2 Safety Assessments

8.2.1 Physical Examinations

Physical examination will be performed at timepoints as specified in the SoA (Section 1.3).

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.3.

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems.

- A brief physical examination will include, at a minimum, assessments of the general appearance, abdomen, cardiovascular, and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

8.2.2 Vital Signs

Pre-dose vital signs (pulse, blood pressure, respiration rate, and body temperature) are to be obtained in accordance with the SoA (Section 1.3).

Body temperature is to be recorded in degrees Fahrenheit/Celsius.

8.2.3 Local Electrocardiograms

An ECG will be performed at Visit 1 as specified in the SoA (Section 1.3).

A single 12-lead ECG will be taken in supine position, after the participant has been resting for at least 5 minutes. The assessment should be performed before interventions with the participant (eg, spirometry). Measurements will be performed on site supplied equipment.

A standard ECG with a recommended paper speed of 25 or 50 mm/second covering at least 6 sequential beats will be used. The investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the investigator's interpretation and that provided by the ECG machine (if applicable), the investigator's interpretation takes precedence and should be noted on the printout and recorded in the eCRF. Two identical copies of the ECG will be produced, quality checked, and kept in case of further need for re-evaluation. The ECG printouts will be signed and dated by the investigator and stored at the study center.

ECG data and evaluation will be recorded in the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

All CSP-required laboratory assessments, as defined in Table 9 for the determination of clinical chemistry, hematology, and urinalysis, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3). Fasting before blood draw is recommended but not mandatory.

Additional safety samples (repeated or scheduled) may be collected if clinically indicated at the discretion of the investigator.

The clinical chemistry and hematology will be performed at a central laboratory. Urinalysis, theophylline level, and SARS-CoV-2 viral diagnostic test will be performed at a local laboratory at the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables.

The following laboratory variables listed in Table 9 will be measured.

Table 9 Laboratory Safety Variables

Hematology / Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Hemaglobin	S-ALP
B-Leukocyte count	S-ALT
B-Leukocyte differential count (absolute count)[a]	S-AST
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-BUN
B-MCV	S-Calcium, total
B-RBC count	S-Chloride
Urinalysis (dipstick) – local laboratory	S-Creatinine
U- Hemaglobin/Erythrocytes/Blood	S-Creatinine kinase (CK)
U-Protein/Albumin	S-CRP
U-Glucose	S-GGT
	S-Glucose
U-Microscopy and culture as required[b]	S-Phosphorus
	S-Potassium
SARS-Cov-2 (swab) – local laboratory	S-Sodium
SARS-CoV-2 viral test	S-Total cholesterol
	S-Uric acid
	S- Theophylline level (local laboratory)[c]

[a] Eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except for Visit 1 and Visit 3 (see Section 6.3.4).
[b] Urine samples will be analyzed locally and sent to the central laboratory only for analysis when a positive dipstick result for any parameter is observed.
[c] For participants on theophylline see Section 6.5.
Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyl transpeptidase; HPF=high power field; MCV=mean corpuscular volume; RBC=red blood cell; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WBC=white blood cell

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN please refer to Appendix D. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Pregnancy Test

The following tests are applicable to female participants only and will be conducted at the timepoints specified in the SoA (Section 1.3).

- Serum β-HCG: To be done at screening Visit 1 only, for women of childbearing potential (analyzed at central laboratory).
- Urine pregnancy test: To be performed at the study center for women of childbearing potential at each treatment visit (before study intervention administration on Visit 3 to Visit 6) using a dipstick. A positive urine test result must be confirmed with serum β-HCG (analyzed at central laboratory).

8.2.5.2 Weight and Height

Weight and height will be measured, and BMI calculated in accordance with the SoA (Section 1.3).

The participant's weight will be recorded in pounds/kg; height will be recorded in inches/meters.

8.2.5.3 Serology

- Hepatitis B surface antigen and hepatitis C antibody

  To be done at screening Visit 1 only (Section 1.3); test to be performed at central laboratory.
- HIV-1 and HIV-2 antibodies

  To be done at screening Visit 1 only (Section 1.3); test to be performed at central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the study centers.

8.2.5.4 SARS-CoV-2 Diagnostic Test

- Local viral testing to be performed at screening Visit 1 to confirm exclusion criterion 27 (Section 1.3).
- Results of local negative viral SARS-Cov-2 testing must be available and recorded in the eCRF before Visit 3.

Local COVID-19 viral test results must be recorded in the eCRF.

8.3 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix E.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF, throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing of the informed consent form.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

'The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix E to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in CSP mandated laboratory values, vital signs and

other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Adverse Events of Special Interest

An AESI is an event of scientific and medical interest towards improving the understanding of the study intervention. An AESI may be serious or non-serious. For this study, AESIs include:

- Anaphylactic reactions
- Immune complex disease (Type 3 hypersensitivity reactions)
- Malignancy
- Helminth infections
- Severe infections which are defined as:
  - SAEs or
  - Requiring treatment with systemic antiviral medications, intravenous antibiotics or medications for helminth parasitic infection or
  - Requiring a permanent discontinuation of study intervention
- Injection site reactions
- Opportunistic infections
- Guillain-Barré Syndrome

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases

of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Disease Under Study

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnea, breathlessness and phlegm, will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Appendix E 2.
- The participant discontinues the study due to the sign or symptom.
- The sign or symptom is new to the participant or not consistent with the participant's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

CCI should be recorded as an AE or SAE only if it fulfills any of the above criteria.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate Parexel representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Parexel representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Parexel representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Parexel representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate Parexel representative by telephone.

The Parexel representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix E 2 of the CSP.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate Parexel representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Parexel representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9 and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 16 weeks (5 half-lives) after the last administration of study intervention, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before

the Pregnancy Report Form is completed.

8.3.11 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate Parexel representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Parexel representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix E 4.

8.3.12 Medical Device Deficiencies

Device constituents of the combination product (APFS) are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with the device constituent of the study drug combination product.

The definition of a deficiency in the device constituent of a combination product (APFS) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and issues with information supplied by the manufacturer. For simplicity, the term medical device deficiency will be used for deficiency in the device constituent of a combination product.

NOTE: Additional guidance, including expanded definitions, can be found in Appendix F of the protocol.

The AstraZeneca Report Form will be used to collect the deficiency as per the Parexel study-specific Investigator Manual.

8.3.12.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device deficiency is provided in Appendix F and the Parexel study-specific Investigator Manual.

8.3.12.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.12.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Deficiencies associated with the device constituent part of the combination product should be reported to the Sponsor.
- Medical device deficiencies will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The AstraZeneca Report Form will be sent to the sponsor via email
  - Medical device deficiency with an associated adverse event
    - AEMailboxClinicalTrialTCS@astrazeneca.com
    - AstraZeneca complaint representative(s), as per the Parexel study-specific Investigator Manual

NOTE: For AEs and SAE's, the eCRF must also be populated - see Section 8.3.9.

  - Medical Device Deficiency without an associated adverse or serious adverse event
    - AstraZeneca complaint representative(s), as per the Investigator Manual
- The Sponsor will be the contact for the receipt of medical device deficiency reports.

8.3.12.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.
- For further guidance on the definitions, see Appendix F of the CSP.

8.4 Overdose

For this study, any dose of study intervention greater than 700 mg SC within a 2-week period will be considered an overdose.

There is currently no specific treatment in the event of overdose of study intervention and possible symptoms of an overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate Parexel representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Parexel representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix G.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of

the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

Serum samples will be collected for measurement of serum concentrations of tezepelumab as specified in the SoA (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Determination of Drug Concentration

Samples for determination of tezepelumab concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Drug concentration information that may/would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded (see Section 6.3.4 for maintaining the study blind).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum from both tezepelumab and placebo groups will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate Bioanalytical Report.

ADA samples may also be further tested for characterization of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Samples for the analysis of peripheral blood eosinophils will be performed in a central laboratory as part of the routine hematology assessment.

8.6 Human Biological Sample Biomarkers

Biomarker research is not applicable in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypotheses will be tested.

9.2 Sample Size Determination

The sample size justification is based on the desired precision of the estimate of the ratio of the GMTs (as $GMT_{vaccine}$ / $GMT_{tezepelumab+vaccine}$). With 50 participants per arm, the 90% CI for the GMT ratio would be 0.67 to 1.48, assuming an observed ratio of 1, and that the log (post-dose HAI antibody titer or post-dose MN antibody titer) is normally distributed with a standard deviation (SD) of 1.2 on the natural log scale (Langley et al 2013).

9.3 Populations for Analyses

Antibody endpoints to the influenza vaccine—strain-specific HAI and MN antibody GMFRs and GMTs—will be analyzed using the vaccine immunogenicity analysis set. All remaining efficacy analyses will be performed using an ITT approach based on the full analysis set. Demographic and baseline characteristics will be presented for both the full analysis set and the vaccine immunogenicity analysis set. Safety objectives and ADA will be analyzed based on the Safety analysis set. The population analysis sets are defined in Table 10.

Table 10 Populations for Analysis

Population/Analysis set	Description
All participant analysis set	All participants screened for the study will be included in the 'All participant analysis set' and will be used for reporting of disposition and screening failures.
Full (ITT) analysis set	All participants randomized and receiving any study intervention will be included in the 'Full analysis set', irrespective of their CSP adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Participants who withdraw informed consent/assent to participate in the study will be included up to the date of their study termination.
Vaccine immunogenicity analysis set	All randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre and post-dose HAI or MN antibody measurements, had no influenza infection prior to Visit 7

Table 10 Populations for Analysis

Population/Analysis set	Description
	(Week 16), and had no protocol deviation, judged to have the potential to interfere with the generation or interpretation of an antibody response, will be included in the 'vaccine immunogenicity analysis set'. The analyses conducted using this analysis set will be based on the actual treatment received. Protocol deviations will be reviewed by the study team before unblinding at the primary database lock (Visit 7 [Week 16]).
Safety analysis set	All participants who received at least 1 dose of study intervention will be included in the safety analysis set. Participants will be classified according to the treatment they actually received. A participant who has on one or several occasions received active treatment will be classified as active. All safety and ADA summaries will be based on this analysis set.
PK analysis set	All participants who received tezepelumab and from whom PK blood samples were obtained and assumed not to be affected by factors such as CSP deviations will be included in the 'PK analysis set'. Those participants who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

Abbreviations: ADA=anti-drug antibody; CSP=clinical study protocol; HAI=hemagglutination-inhibition; ITT=intent to treat; MN=microneutralization; PK=pharmacokinetic.

Primary Analyses Estimands

Table 11 provides the parameters to follow for each set of primary analyses. **Please note**: If influenza vaccine administration is delayed, some participants' assessments at Week 12 and Week 16 may be performed at later timepoints.

Table 11 Primary Analysis Estimands

Primary Endpoints	Parameters
• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific serum HAI antibody geometric mean titers (GMTs) obtained at Week 16 (EOT)	**Population:** Vaccine immunogenicity analysis set, defined as all randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre- and post-dose HAI or MN antibody measurements, had no influenza infection prior to Visit 7 (Week 16), and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an antibody response. **Intercurrent Events:** Treatment discontinuation: All data up to timepoint of post-dose antibody measurements will be included for participants in the vaccine immunogenicity analysis set.

Table 11 Primary Analysis Estimands

Primary Endpoints	Parameters
• Post-dose strain-specific serum MN antibody GMTs obtained at Week 16 (EOT)	Initiation of other medication: All data up to timepoint of post-dose antibody measurements will be included for participants in the vaccine immunogenicity analysis set. **Summary Measure:** Least square geometric mean ratio estimates for placebo vs. tezepelumab and corresponding 90% CIs.
• Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in HAI antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in MN antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT) • Post-dose strain-specific HAI antibody titer ≥ 40 at Week 16 (EOT) • Post-dose strain-specific MN antibody titer ≥ 40 at Week 16 (EOT)	**Population:** Vaccine immunogenicity analysis set, defined as all randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre- and post-dose HAI or MN antibody measurements, had no influenza infection prior to Visit 7 (Week 16), and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an antibody response. **Intercurrent Events:** Treatment discontinuation: All data up to timepoint of post-dose antibody measurements will be included for participants in the vaccine immunogenicity analysis set. Initiation of other medication: All data up to timepoint of post-dose antibody measurements will be included for participants in the vaccine immunogenicity analysis set. **Summary Measure:** Number and % of participants in each treatment group meeting the specified threshold and corresponding 90% CI.

9.4 Statistical Analyses

There will be two database locks in this study. The primary database lock and analysis will be conducted after the last participant (enrolled in the 2021/2022 flu season) completes Visit 7 (Week 16), and the final database lock and analysis will be conducted once all participants have completed the follow-up period, Visit 8 (Week 28). All analyses of the primary objectives and selected safety objectives will be performed based on the primary database lock data.

The SAP will be finalized and signed-off prior to the primary database lock. It will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1 General Considerations

All statistical analyses will be performed by Parexel International Biostatistics or other designated third-party providers, under the direction of the Biostatistics Group, AstraZeneca. Further details will be provided in the SAP. The SAP will be prepared prior to first participant randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data. All statistical analyses presented in the CSP will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher.

All personnel involved with the analysis and conduct of the study will remain blinded until the primary database lock and important protocol deviations have been identified. After the primary database lock, treatment allocation for participants during this study will become known to the sponsor staff and designated CRO. The blind will be maintained for the investigator, investigational site staff, and for the participant.

9.4.2 Efficacy

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomized study intervention at Week 0 and the conclusion of Week 16 (EOT) Visit, inclusive.

The tezepelumab versus placebo humoral immune responses following seasonal influenza virus vaccination will be assessed by the following endpoints.

9.4.2.1 Primary Endpoint(s)

- Post-dose strain-specific HAI antibody GMFRs from Week 12 (pre-dose antibody measure) to Week 16 (EOT).
- Post-dose strain-specific MN antibody GMFRs from Week 12 (pre-dose antibody measure) to Week 16 (EOT).

- Post-dose strain-specific serum HAI antibody GMTs obtained at Week 16 (EOT).
- Post-dose strain-specific serum MN antibody GMTs obtained at Week 16 (EOT).
- Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in HAI antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT).
- Post-dose strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in MN antibody titer from Week 12 (pre-dose antibody measure) to Week 16 (EOT).
- Post-dose strain-specific HAI antibody titer ≥ 40 at Week 16 (EOT).
- Post-dose strain-specific MN antibody titer ≥ 40 at Week 16 (EOT).

As the HAI assay may not work for one of the influenza virus strains (Influenza A H3N2), the corresponding MN result for that strain will only be used. Hence, both the HAI and MN results will serve as the dual primary endpoints for this study such that results from both assays can be used for the analyses of the primary objective. This dual endpoint approach allows for a broader characterization of the immune response and flexibility in case the results for either assay are missing.

Analysis Methods for Efficacy Variables

The analyses of the primary endpoints will use the vaccine immunogenicity analysis set. If informed consent/assent to the study was withdrawn, all data up until the date of withdrawn informed consent/assent will be included. The full analysis set will be used for the other non-primary efficacy analyses.

Analysis methods for antibody endpoints

Geometric mean fold rises for the HAI and MN antibody measurements are defined as:

$GMFR = \text{antilog}_z\ (\text{mean}\ [\log_e x])$

Where x is the post-dose (EOT) HAI or MN antibody titer fold rise from Week 12 (pre-dose antibody measure) and e is the natural logarithm.

Geometric mean titers for the HAI and MN antibody measurements are defined as:

$GMT = \text{antilog}_z\ (\text{mean}\ [\log_e y])$

Where y is the HAI or MN antibody titer and e is the natural logarithm.

The analysis of the anti-influenza antibody response endpoints–strain-specific GMFRs and GMTs–will be performed on the vaccine immunogenicity analysis set. Geometric mean fold

rises and GMTs will be summarized by treatment group and by strain, and the least square geometric mean ratio of GMFRs and GMTs between treatment groups (influenza vaccine divided by tezepelumab and influenza vaccine) will be calculated via an ANCOVA model on the log-transformed variable, adjusting for treatment group and age stratum (adolescents aged 12 to17 or young adults aged 18 to 21). The least square geometric mean ratio will be provided with associated 90% CI.

The antibody response to the quadrivalent influenza vaccine strain is defined as a ≥ 4-fold rise in HAI or a ≥ 4-fold rise in MN from Week 12 (pre-dose antibody measure) to Week 16 (EOT). The proportion of participants who experience a post-dose antibody response at Week 16 (EOT) for HAI and the proportion of participants who experience a post-dose antibody response at Week 16 (EOT) for MN and corresponding 90% Clopper-Pearson exact CIs will be summarized by treatment group and by strain.

The proportion of participants who achieve a post-dose HAI antibody titer ≥ 40 and the proportion of participants who achieve a post-dose MN antibody titer ≥ 40 at Week 16 (EOT) and corresponding 90% Clopper-Pearson exact CIs will be summarized by treatment group and by strain.

No interim blinded review is planned.

9.4.2.2 Secondary Endpoint(s)

Calculation or Derivation of PK Variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed serum trough concentrations.

Analysis Methods for PK Variables

The PK analyses will be performed by a third-party vendor under the guidance of AstraZeneca Research and Development.

Tezepelumab serum concentrations will be summarized using descriptive statistics at each visit.

Calculation or Derivation of Tezepelumab Immunogenicity Variables

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer).

Analysis Method for Tezepelumab Immunogenicity Variables

ADA to tezepelumab will be summarized using descriptive statistics at each visit by treatment group.

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[redacted]

9.4.3 Safety

9.4.3.1 Safety Endpoint(s)

Calculation or Derivation of Safety Variable(s)

The following safety data will be collected: vital signs, physical examination, hematology, serum chemistry, urinalysis, and reported AEs.

Change from baseline (Week 0) to each post-treatment visit where scheduled assessments were made will be calculated for relevant measurements. Adverse events will be summarized by means of descriptive statistics and qualitative summaries.

Analysis Methods for Safety Variables

Adverse events will be coded using the MedDRA version in force at the primary database lock. The definition of on-treatment and on-study for AE analyses will be given in the SAP.

The number and percentage of participants with on-treatment and on-study AEs will be tabulated separately by preferred term and system organ class. An event that occurred one or

more times during a period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all participants in the safety population. On-treatment AEs will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a participant report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the participant's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation from study intervention, and commonly occurring AEs will be summarized in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to discontinuation of study intervention will be summarized for each treatment group as applicable.

An overall summary of on-treatment AEs will be presented by treatment group.

AEs of special interest (AESIs), as defined in Section 8.3.6 will also be summarized descriptively by treatment group.

Laboratory data will be summarized by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarized.

Vital signs data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital signs abnormalities will be summarized.

9.5 Interim Analyses

There is neither an unblinded data review nor interim analysis planned for this study prior to primary database lock.

9.6 Data Monitoring Committee

Not Applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Anaphylaxis: Signs and Symptoms, Management

A 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex mediated]) and nonimmunologic (Johansson et al 2004). The clinical criteria for defining anaphylaxis for this study are listed in Appendix A 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix A 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample will be drawn from the participant as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

A 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongueuvula)

   AND AT LEAST ONE OF THE FOLLOWING

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   (b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).

   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

3 Reduced BP after exposure to known allergen for that subject (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that subject's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type 3 is evoked by the deposition of antigen-antibody or antigen-antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis is common.

A 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:
Itchy nose, eyes, pharynx, genitalia, palms, and soles

- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Light headedness
- Headache
- Uterine cramps
- Generalized warmth

A 4 Management of Acute Anaphylaxis

Immediate intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation

2 Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place participant in recumbent position and elevate lower extremities.

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H_1 and H_2 antihistamines.

(c) Consider nebulized β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (eg, dopamine).

(f) Consider glucagon for subject taking β-blocker.

(g) Consider atropine for symptomatic bradycardia.

(h) Consider transportation to an emergency department or an intensive care facility.

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: Kemp SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008;63(8):1061-70.

A 5 References

Johansson et al 2004
Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. A revised

nomenclature for allergy for global use: report of the nomenclature review committee of world allergy organization. J Allergy Clin Immunol. 2004;113:832-6.

Appendix B Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the Parexel Medical Monitor.

B 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on-site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections B 2 to B 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

B 2 Re-screening of Participants To Reconfirm Study Eligibility

One additional re-screening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated Parexel Medical Monitor.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 1.3 the participant will need to be re-screened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 5.1.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

B 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the participants home / or other remote location as per local standard of procedures, as applicable, only during safety follow-up (after Visit 7). Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

B 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls and virtual or video visits only during safety follow-up (after Visit 7).

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events, concomitant medication to be reported and documented.

B 5 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home / remote visits will be captured by the qualified HCP from the study site or TPV service, or by the participant themselves.

Appendix C Regulatory, Ethical, and Study Oversight Considerations

C 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with US-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

C 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

C 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her parent/legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their informed consent/assent at any time and for any reason during the study. Participants or their parent/legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written informed consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are re-screened are required to sign a new ICF.

C 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent/assent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

C 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by Parexel representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

C 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

C 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from

source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

C 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

C 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is when the first participant consents to take part in the study and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites may have the opportunity to be transferred to another site to continue the study.

C 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a co-ordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI) caused by the study intervention.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the

elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change* in the participant's condition.
- The Parexel Medical Monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Parexel Medical Monitor. This includes deciding which the tests available in the Hy's Law lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

*__A 'significant' change__ in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Parexel Medical Monitor if there is any uncertainty.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Parexel Medical Monitor contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the study intervention:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to study intervention and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Intervention

This section is applicable to participants who meet PHL criteria on study intervention, having previously met PHL criteria at a study visit prior to starting study intervention.

At the first on-study intervention occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participants' condition compared with the last visit where PHL criteria were met

- If there is no significant change no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section D 4.2

D 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study intervention and has already met PHL criteria at a previous on study intervention visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver?

If **No**: follow the process described in Section D 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change[#] follow the process described in Section D 4.2 for reporting PHL as an SAE

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D 8 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA[a] IgG anti-HCV HCV RNA[b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

[a]HBV DNA is only recommended when IgG anti-HBc is positive
[b]HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive

D 9 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation.

Appendix E Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

E 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

E 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study period (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse Events (AEs) for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'important medical event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix E 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix E 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix E 2.

E 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

E 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up

- This appendix supports the activities described in section 8.3.12
- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the Sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.
- For simplicity, medical device will be used to cover device constituent parts of combination products and standalone medical device whether investigational or approved.

F 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. A medical device AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

F 2 Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any medical device adverse event that:

a. Led to death.

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital anomaly or birth defect.

SADE definition

- A serious adverse device effect (SADE) is defined as an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE (eg, needle stick requiring surgical intervention or battery leakage chemical burn causing scaring).
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An unanticipated serious adverse device effect (USADE) (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

F 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

F 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure or Product Information in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.

  The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

Appendix G Handling of Human Biological Samples

G 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

G 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

G 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

Appendix H Maintenance Therapy Equivalence Table

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid[a]	**Medium**	**High**
Beclomethasone dipropionate (pMDI, standard particle, HFA)	>500-1000	>1000
Beclomethasone dipropionate (DPI or pMDI, extrafine particle, HFA)	>200-400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	>400-800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	>160-320	>320
Fluticasone furoate (DPI, eg Arnuity® Ellipta® Breo®)	100	200
Fluticasone propionate (DPI)	>250-500	>500
Fluticasone propionate (pMDI, standard particle, HFA)	>250-500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information	
Mometasone furoate (pMDI, standard particle, HFA)	>200-400	>400
Inhaled Corticosteroid in ICS/LABA combination[a]	**Medium**	**High**
Beclomethasone dipropionate (eg. Fostair®)	>200-400	>400
Fluticasone propionate HFA (eg. Seretide®, Advair®)	>250-500	>500
Fluticasone furoate (eg. Relvar® Ellipta®, Breo® Ellipta®)	92-100	184-200
Budesonide, if as delivered dose (eg. Symbicort®)	>400-640	>640
Mometasone Furoate (eg. Dulera®)	>220-400	>400

[a] The ICS doses were derived from GINA 2021 and the ICS/LABA combinations were derived from GINA 2017, 2018, and 2021 and using prescribing information.

Abbreviations: DPI=dry powder inhaler; HFA=hydrofluoroalkane propellant; ICS=inhaled corticosteroid; LABA=long-acting β2 agonist; pMDI=pressurized metered dose inhaler.

ICS by pMDI should preferably be used with a spacer.

Appendix I Abbreviations

Abbreviation or special term	Explanation
CCI	[redacted]
CCI	[redacted]
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
ANCOVA	analysis of covariance
APFS	Accessorized pre-filled syringe
AST	aspartate aminotransferase/transaminase
BALF	bronchoalveolar lavage fluid
BD	bronchodilator
BMI	body mass index
BUN	blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CHO	Chinese hamster ovary
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	coefficient of variation
DILI	Drug Induced Liver Injury
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	end of treatment
ER	emergency room
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma

Abbreviation or special term	Explanation
CCI [redacted]	[redacted]
GMFR	geometric mean fold rise
GMT	geometric mean titer
HAI	hemagglutination-inhibition
HCG	human chorionic gonadotropin
HCP	health care provider
HIV	human immunodeficiency viruses
HL	Hy's Law
HPF	high power field
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
ID	identification
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgG2λ	immunoglobulin G2λ
IgM	immunoglobulin M
IL-13	Interleukin-13
IL-4	Interleukin-4
IL-5	Interleukin-5
ILC-2	type 2 innate lymphoid cells
IM	intramuscular
IMP	Investigational Medicinal Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LABA	long-acting β2 agonist
LAMA	long-acting muscarinic antagonists
LPLV	last participant last visit

Abbreviation or special term	Explanation
CCI [redacted]	[redacted]
LTRA	leukotriene receptor antagonists
mAb	monoclonal antibody
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NIMP	non investigational medicinal product;
OCS	oral corticosteroids
PHL	potential Hy's Law
PI	principal investigator
PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
RBC	red blood cell
SABA	short-acting β2 agonist
SADE	serious adverse device effect
SAE	serious adverse events
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	Schedule of Activities
T2	type 2
TBL	total bilirubin
Th2	T helper type 2
TPV	third party vendor
TSLP	thymic stromal lymphopoietin
ULN	upper limit of normal
USA/US	United States of America/United States
USADE	unanticipated adverse device effect
WBC	white blood cell

Appendix J Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment, **Amendment 2**, is located directly before the Table of Contents.

Amendment 1 (07 Sep 2021)

Overall Rationale for the Amendment:

The Clinical Study Protocol (CSP), Version 1.0, dated 02 June 2021, was updated with the following changes:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Title Page	Text was deleted.	As Amgen is not a co-sponsor of study conduct, their name is not required in the protocol. This is consistent with other AZ run tezepelumab clinical studies.	Non-substantial
Synopsis; Section 9.4.2.1 Primary Endpoints	Analysis will be summarized by treatment group and by strain.	To add additional details.	Non-substantial
Synopsis; Section 9.4.2.1 Primary Endpoints	Text was updated.	To clarify that there are four strains of the influenza vaccine	Non-substantial
Section 1.3 Schedule of Activities, Table 2	Text related to serum antibody testing being done prior to influenza vaccination was deleted.	To add clarity that serum antibody testing is done not only prior to influenza vaccine, but also 4 weeks later.	Non-substantial
Section 1.3 Schedule of Activities, Table 2, footnote g	Text was updated.	To clarify that unscheduled study intervention visits may be done prior to V6, if needed.	Non-substantial
Section 1.3 Schedule of Activities, Table 2, footnote h; Section 6.6 Dose Modification	Text was updated.	To clarify that unscheduled study intervention visits may be done prior to V6, if needed.	Non-substantial
Section 3 Objectives and Endpoints	'Not controlled' was updated to 'not well-controlled'	Correction of 'not controlled' to 'not well-controlled' based on Juniper et al 2006 reference	Non-substantial
Section 5.2.1 Study Eligibility	Exclusion criterion #5 regarding allergy to eggs was updated.	To clarify that if cell based vaccine is used, this is not considered an exclusion criterion.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.2.1 Study Eligibility	Exclusion criterion #18 regarding COVID-19 vaccine was updated.	To accommodate changing environment with booster COVID-19 vaccines recommended for high-priority groups including people with underlying health conditions.	Non-substantial
Section 6.1.1.1 Management of Study Intervention Related Reactions	Lung function assessment was removed.	Correction of Error: Lung function assessments are not performed at V3 and V4.	Non-substantial
Section 6.5 Concomitant Therapy, Table 7	Scheduled inactivated/killed vaccines, including the COVID-19 vaccination, were added.	To ensure safety and well-being of participants and clarify that inactivated vaccines are permitted within specified timeframes.	Non-substantial
Section 6.5 Concomitant Therapy, Table 7	Contraception was removed from the table of restricted medications.	Clarification to indicate this is not a restriction as contraception must be used for women of child bearing potential throughout the study.	Non-substantial
Section 6.5 Concomitant Therapy, Table 8	COVID-19 vaccination was deleted from the table of restricted medications.	Ensure safety and well-being of participants and allow COVID-19 vaccination which is recommended for high-priority groups, including people with underlying health conditions.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Language regarding Investigational Product Discontinuation visit and End of Study visit was added.	To clarify that study participants should continue in the study even if study intervention is prematurely withdrawn.	Non-substantial
Section 7.2 Participant Withdrawal from the Study	'End of Treatment' visit was updated to 'Investigational Product Discontinuation' visit.	To clarify that upon withdrawal, an IPD visit needs to be conducted.	Non-substantial
Section 7.2 Participant Withdrawal from the Study	Follow-up was removed from the sentence on data to be collected at the time of study withdrawal.	Correction of error.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.2.2 Spirometry Technique	Language was removed to align with Schedule of Activities.	To adjust wording to protocol requirements - spirometry is performed only during screening.	Non-substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
Section 8.2.4 Clinical Safety Laboratory Assessments	Language regarding recording the date, time of collection, and results being recorded on the appropriate electronic case report form, was deleted.	Other than for severe infections, information regarding local laboratory tests done outside of the Schedule of Activities are not collected in the electronic case report form.	Non-substantial
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

In addition, minor formatting and editorial revisions were made throughout the protocol.

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