Clinical Study Protocol	
Study Intervention	Tezepelumab
Study Code	D5180C00025
Version	4.0
Date	06 January 2022

A Phase I, Open Label Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Mild, Moderate, or Severe Asthma (TRAILHEAD)

Sponsor Name: AstraZeneca

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s):
2020-000554-97 (EudraCT)

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: D5180C00025

Amendment Number: 3

Study Intervention: Tezepelumab

Study Phase: Phase I

Short Title: A Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Asthma

Medical Monitor Name and Contact Information will be provided separately

National Co-ordinating Investigator:
PPD
United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3 (Version 4.0)	06 Jan 2022
Amendment 2 (Version 3.0)	13 May 2021
Amendment 1 (Version 2.0)	21 July 2020
Original Protocol (Version 1.0)	25 February 2020

Amendment 3 (06 January 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 3:

The rationale for this amendment is to update safety information based on the most recent Investigator's Brochure, Version 5.0, dated 21 Oct 2021 and to include additional changes to update inclusion and exclusion criteria to be more reflective of the clinical characteristics of paediatric subjects with mild, moderate, or severe asthma who would be appropriately suited for a pharmacokinetic (PK) study, whilst minimising risks to the participant and to the study integrity, and maintaining compliance with Good Clinical Practice (GCP).

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Version 4.0, 06 Jan 2022 Changes to the protocol are summarised below.			
Section 1.1 Synopsis	Updated location where TRAILHEAD will be conducted to include approximately 10 study sites globally.	Additional sites to participate in TRAILHEAD in order to increase enrolment.	Substantial
Section 2.2 Background Section 2.3.2 Benefit Assessment	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 were completed since the last IB update.	Substantial
Section 4.1: Overall Design	Updated location where TRAILHEAD will be conducted to include approximately 10 study sites globally	Additional sites to participate in TRAILHEAD in order to increase enrolment.	Substantial
Section 5.1 Inclusion Criteria Appendix F	Removed inclusion (Inclusion Criterion #12) for body mass index for age at both Screening and Day 1 that is between 5th and 95th percentile and associated Appendix F	By allowing the full span of growth percentiles, this will aid in PK predictions that span across BMI ranges in this age group. This approach ensures a study population appropriate for a PK study.	Substantial
Section 5.2 Exclusion Criteria	Changed exclusion (Exclusion Criterion #2) for history of a deterioration in asthma or asthma exacerbation that required a burst of systemic glucocorticosteroids within 3 months prior to Visit 1, up	As systemic corticosteroid use does not impact tezepelumab PK levels and TRAILHEAD is not an efficacy study, prohibiting use of systemic corticosteroids for 3 months prior to V1 is not required. This approach ensures a study population appropriate for a PK study.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	to and including Visit 2 (Day 1) to decrease time restriction from 3 months to 6 weeks.		
Section 5.2 Exclusion Criteria	Changed exclusion (Exclusion Criterion #4) for history of hospitalisation (overnight admission) for asthma within 6 months of Visit 1, up to and including Visit 2 (Day 1) to decrease time restriction from 6 months to 3 months.	To align with changes to other exclusion criteria while still ensuring safety and a study population appropriate for a PK study.	Substantial
Section 5.2 Exclusion Criteria	Changed exclusion (Exclusion Criterion #6) for systemic corticosteroid use for the maintenance treatment of asthma within 3 months of Visit 1, up to and including Visit 2 (Day 1) and discouraged until EOS to decrease time restriction from 3 months to 6 weeks.	To align with changes to other exclusion criteria while still ensuring safety and a study population appropriate for a PK study.	Substantial
Section 5.2 Exclusion Criteria	Addition of Exclusion Criterion (#33) Receipt of any COVID-19 vaccine 28 days prior to Visit 2 (Day 1).	To provide guidance to Investigators regarding permitted timing for COVID-19 vaccination.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Table 1 Schedule of Activities Section 2.3.1.3 COVID-19 Risk Mitigations Section 5.2 Exclusion Criteria Table 8 Volume of Blood to be Drawn from each Subject Table 9 Laboratory Safety Variables Section 8.2.5.2 COVID- 19 Testing	Updated to reflect Coronavirus Disease 2019 (COVID-19) antibody testing will no longer be required (Exclusion Criterion #23) and added additional criteria (Exclusion Criteria #31 and #32) to exclude participants who have had a confirmed COVID-19 infection and have not fully recovered for at least 8 weeks prior to Visit 1 and those participants with a history of severe COVID-19 infection requiring hospitalization.	COVID-19 antibody testing has been removed, as vaccine development in this age group is moving forward, making antibody testing for exclusion criteria clinically irrelevant and additional information is available regarding MIS-C. New exclusion criterion to confirm absence of COVID-19 infection in recent past. This approach will ensure participant safety and simplify procedures for study participants and sites.	Substantial
Table 5 Restricted Medications	COVID-19 vaccination added to allow administration during study conduct (within 28 days before and 14 days after IP administration/Visit 2)	To provide guidance to Investigators regarding permitted timing for COVID-19 vaccination	
Section 8.6 Human Biological Sample Biomarkers	Updated to reflect that serum samples will be collected to be analysed for total immunoglobulin E.	Updated to correct an omission.	

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase I, Open Label Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Mild, Moderate, or Severe Asthma.

Short Title: A Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Asthma.

Rationale:

The primary aim of this study is to evaluate the pharmacokinetic (PK) profile following a single subcutaneous (SC) CCI dose of tezepelumab in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma (Global Initiative for Asthma [GINA] 2020 Step 2 to Step 4) requiring daily controller medications.

Additional aims are to evaluate the safety, tolerability, immunogenicity and pharmacodynamics (PD) of a single SC CCI dose of tezepelumab.

Objectives and Endpoints

Objectives	Outcome Measures
Primary	
• To describe the PK parameters following a single SC administration of tezepelumab CCI in children with mild, moderate, or severe asthma	• Maximum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) • Terminal phase elimination half-life ($t_{1/2}$) • Apparent clearance (CL/F) • Apparent steady-state volume of distribution (V_{ss}/F)
Secondary	
• To evaluate the immunogenicity of tezepelumab	• Presence of anti-drug antibodies (ADA)
Safety	
• To evaluate the safety and tolerability following a single SC administration of tezepelumab CCI	• Adverse events/serious adverse events • Vital signs • Laboratory parameters • Electrocardiogram (ECG)

PK Pharmacokinetic; SC Subcutaneous.
For the CCI and outcome measures, see Section 3 of the protocol.

Overall Design

This is a multicentre, open label study designed to evaluate the PK profile of tezepelumab following a single SC CCI dose in children ≥ 5 to 11 years of age with mild, moderate, or severe asthma.

The study will be conducted globally with approximately 10 study sites.

Approximately 24 subjects will be enrolled and approximately 14 paediatric subjects aged ≥ 5 to 11 years (inclusive) will receive a single SC CCI dose of tezepelumab in an attempt to have at least 12 paediatric subjects complete the study. At least 4 subjects will have body weight < 25 kg and a minimum of 3 subjects will have body weight ≥ 25 kg to < 40 kg.

The 99-day study consists of:

- A consent/screening period of up to 14 days
- Treatment and follow-up period of 85 days.

This is an open label non-randomised study. Subjects will be allocated to receive tezepelumab if they fulfil the eligibility criteria.

Disclosure Statement: This is an open label single arm study.

Number of Subjects:

Approximately 24 subjects will be enrolled and approximately 14 subjects will receive IP such that at least 12 subjects complete the study.

Note: 'Enrolled' means a subject's, and their legally acceptable representative's agreement to participate in a clinical study following completion of the informed consent process. Potential subjects who are screened for the purpose of determining eligibility for the study but are not assigned in the study, are considered 'screen failures', unless otherwise specified by the protocol.

Intervention Groups and Duration:

This is a 99-day study. Screening assessments should be completed within 14 days (Day -14 to Day -1). Subjects who meet eligibility criteria will receive a single SC CCI dose of tezepelumab on Day 1. The subjects will then return for Follow-up visits on Days 3, 7, 11, 15, 29, 57 and 85 (End of Study [EOS]). The study will be completed after the EOS visit on Day 85.

Data Monitoring Committee: No

Statistical methods

All data will be presented using descriptive statistics. No formal statistical hypothesis tests will be made.

Individual tezepelumab serum concentration data will be tabulated along with descriptive statistics. The following PK parameters will be estimated by noncompartmental analysis: area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time zero to the time of the last measured concentration ($AUC_{0\text{-}last}$), maximum concentration (C_{max}), time to C_{max} (t_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F) and apparent steady-state volume of distribution (V_{ss}/F). Additional PK parameters may be reported if appropriate.

Safety will be assessed by summarising adverse events (AEs) and serious AEs (SAEs). Other

variables used for the safety assessments include but are not limited to electrocardiograms (ECGs), vital signs and routine laboratory assessments. These variables as well as their changes from baseline will be summarised descriptively.

The incidence of positive serum antibodies to tezepelumab will be reported.

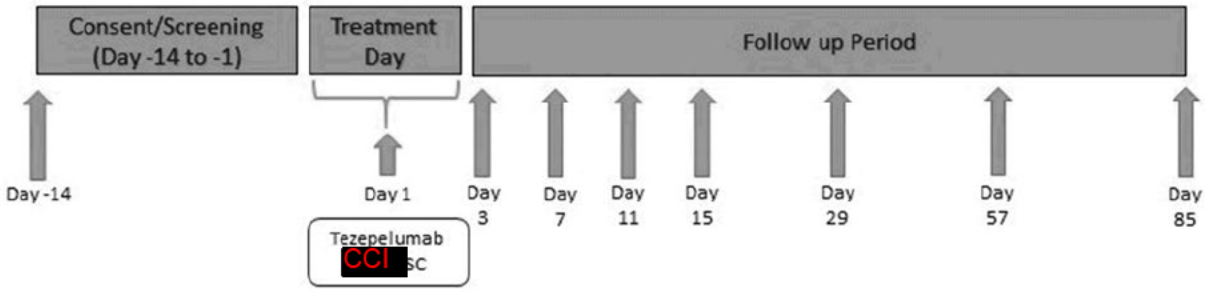
All PK summaries will be based on the PK analysis set. Anti-drug antibodies (ADA) and PD parameter summaries and safety presentations will be based on the safety analysis set.

No formal sample size calculation was conducted for this study. The number of subjects was based on the desire to obtain adequate PK and safety data while exposing as few paediatric subjects as possible to tezepelumab and study procedures. A total of 12 subjects is considered sufficient to provide adequate data to characterise PK of tezepelumab in children ≥ 5 to 11 years of age. Approximately 14 subjects will receive tezepelumab in an attempt to have at least 12 subjects complete the study.

1.2 Schema

The study design is shown in Figure 1.

Figure 1 Study design



SC Subcutaneous.

1.3 Schedule of Activities

The schedule of activities (SoA) is presented in Table 1.

Table 1 Schedule of Activities

	Consent/ Screening	Treatment Day	Follow-up period							Details in CSP Section or Appendix
Visit number	**V1***	**V2****	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Study day Procedure	**Day -14 to -1**	**Day 1**	**Day 3**	**Day 7 (± 1)**	**Day 11 (± 1)**	**Day 15 (± 1)**	**Day 29 (± 2)**	**Day 57 (± 2)**	**Day 85/EOS (± 3)**	
Written informed consent and assent	X									Section 5.1, Appendix A 3
Assignment of SID number	X									Section 6.3
Verify eligibility criteria	X	X								Sections 5.1, 5.2
Demography	X									Section 5.1
Medical history	X									Section 5.1
Physical examination	X [a]	X [a]		X [b]			X [b]	X [b]	X [a]	Section 8.2.1
Weight	X	X					X		X	Sections 5.1, 8.2.1.1, Appendix F
Height		X							X	Section 8.2.1.1
12-lead ECG	X	X					X		X	Section 8.2.3
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of COVID-19 signs and symptoms [n]	X	X	X	X	X	X	X	X	X	Section 2.3.1.3
Concomitant medications	X	X	X	X	X	X	X	X	X	Section 6.5

Table 1 Schedule of Activities

	Consent/ Screening	Treatment Day	Follow-up period							Details in CSP Section or Appendix
Visit number	**V1***	**V2****	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Study day Procedure	**Day -14 to -1**	**Day 1**	**Day 3**	**Day 7 (± 1)**	**Day 11 (± 1)**	**Day 15 (± 1)**	**Day 29 (± 2)**	**Day 57 (± 2)**	**Day 85/EOS (± 3)**	
CCI										Section 8.1.3
Vital signs	X	X[c]	X	X	X	X	X	X	X	Section 8.2.2
Serum chemistry and haematology [d]	X	X				X	X		X	Sections 8.2.4, 8.5.3
CCI										Section 8
Urinalysis [m]	X	X				X	X		X	Section 8.2.4
Pregnancy test (serum β-HCG)	X[e]									Section 8.2.4.1
Urine pregnancy test (dipstick)	X[e]	X[e]							X[e]	Section 8.2.4.1
Urine drug screen		X								Section 8.2.4
Virology: HBsAg, HCAb; HIV-1, HIV-2	X									Section 8.2.5.1
COVID-19 viral rapid test via local laboratory	X	X[m]								Section 8.2.5.2
Blood sample for PK analysis [f]		X[g]	X	X	X	X	X	X	X	Section 8.5.1
Serum for immunogenicity analysis [h, i]		X[j]					X		X	Section 8.5.2
CCI										Section 8.1.1
CCI										Section 8.1.2

Table 1 Schedule of Activities

	Consent/ Screening	Treatment Day	Follow-up period							Details in CSP Section or Appendix
Visit number	**V1***	**V2****	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Study day Procedure	**Day -14 to -1**	**Day 1**	**Day 3**	**Day 7 (± 1)**	**Day 11 (± 1)**	**Day 15 (± 1)**	**Day 29 (± 2)**	**Day 57 (± 2)**	**Day 85/EOS (± 3)**	
IP Administration		X[k]								Section 6.2.2

* Visit 1 local COVID-19 viral rapid test results must be negative prior to spirometry at V1.

** Visit 1 and Visit 2 local COVID-19 viral rapid test results must be negative prior to spirometry, CCI , and IP administration at V2.

[a] Complete physical examination to be performed.

[b] Brief physical examination to be performed.

[c] Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be assessed within 1 hour prior to and at 1 hour and 2 hours post-IP administration.

[d] CCI (Section 8.5.3).

[e] Pregnancy tests (serum and urine) to be performed for females of childbearing potential.

[f] Serum sample for PK analysis will be collected within ± 1 hour of the time the baseline Day 1 sample was collected, on Days 3, 7, 11, 15, 29, 57 and 85/EOS.

[g] Serum sample for PK analysis to be taken within 1 hour prior to IP administration on Day 1.

[h] Serum sample for determination of ADA; if positive for ADA, may be analysed for nAb (Section 8.5.2). In the event of suspected immunologically-related AE, an unscheduled ADA sample will be collected.

[i] Serum sample for immunogenicity analysis will be collected within ± 1 hour of the time the baseline Day 1 sample was collected, on Day 29 and Day 85/EOS.

[j] Serum sample for immunogenicity analysis to be taken within 1 hour prior to IP administration on Day 1.

[k] Local COVID-19 viral rapid test must be available and negative prior to IP administration at V2.

[l] Urinalysis will be performed at site via dipstick. If any parameter is abnormal, the urine sample will be sent to the central laboratory for further microscopy and culture analysis.

[m] The local COVID-19 viral rapid test should be able to provide results in less than 60 minutes. Refer to Section 8.2.5.2 for additional details

[n] Subjects/caregivers must be contacted by telephone for COVID-19 screening assessment within 24 hours prior to every study visit, regardless of on-site or remote

[o] CCI

ADA Anti-drug antibodies; AE Adverse event; BD Bronchodilator; β-HCG Beta-human chorionic gonadotrophin; COVID-19 Coronavirus Disease 2019; CSP Clinical Study Protocol; ECG Electrocardiogram; EOS End of Study; CCI ; HBsAg Hepatitis B surface antigen; HCAb Hepatitis C antibody; HIV-1/-2 Human immunodeficiency virus; IgE Immunoglobulin E; IP Investigational product; nAb Neutralising antibodies; CCI ; PD Pharmacodynamic; PK Pharmacokinetic; CCI ; SAE Serious adverse event; SID Subject identification; V Visit.

2 INTRODUCTION

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine that is produced in responses to proinflammatory stimuli. Tezepelumab is currently being developed as a potential treatment for severe asthma, moderate to severe atopic dermatitis and moderate to very severe chronic obstructive pulmonary disease.

2.1 Study Rationale

Tezepelumab is currently in Phase III development and a pivotal Phase III safety and efficacy study (D5180C00007) is being conducted in adolescents and adults with severe asthma (GINA Steps 4 and 5). The study is ongoing and has randomised/dosed approximately 80 adolescents aged 12 to 17 years, inclusive. To date, there are no identified risks and no safety data have been received that would negatively impact the benefit: risk of tezepelumab.

The primary aim of this study is to evaluate the PK profile following a single SC [CCI] dose of tezepelumab in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma (GINA 2020 Step 2 to Step 4) requiring daily controller medications. This is a necessary step before beginning safety and efficacy studies in children aged ≥ 5 to 11 years to determine the appropriate tezepelumab dosing.

Additional aims are to evaluate the safety, tolerability, immunogenicity and PD of a single SC [CCI] dose of tezepelumab.

2.2 Background

Biologic therapies have been shown to reduce the annualised asthma exacerbation rate (AAER) in subjects with severe asthma who are uncontrolled with medium to high-dose inhaled corticosteroids (ICS) and additional asthma controller medications. Omalizumab (XOLAIR®, Genentech, Inc) provided benefit for a subgroup of subjects with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with an ICS plus a long-acting β2-agonist (LABA) (Xolair US Prescribing Information 2019). Four additional biologics, mepolizumab (NUCALA®, GlaxoSmithKline), reslizumab (CINQAIR®, Teva Respiratory), benralizumab (FASENRA®, AstraZeneca AB) and dupilumab (DUPIXENT®, Regeneron Pharmaceuticals, Inc) have recently been approved for severe asthma with an eosinophilic phenotype (Cinqair US Prescribing Information 2016, Dupixent US Prescribing Information 2019, Fasenra US Prescribing Information 2017, Nucala US Prescribing Information 2019). Biologics targeting interleukin-5 and IgE are now included in international treatment guidelines (GINA 2020) as an add-on treatment to subjects uncontrolled with ICS/LABA treatment. However, even when using currently available biologics, substantial proportions of subjects continue to experience exacerbations and may benefit from agents that target different

molecular pathways (Froidure et al 2016, Son and Friedman 2021

Son MBF, Friedman K. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis. UpToDate April 2021

Swedin et al 2017, Wenzel 2016). Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among subjects with severe asthma, independently of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

Thymic stromal lymphopoietin is an epithelial cell-derived cytokine that is produced in responses to proinflammatory stimuli (eg, infectious, allergic and environmental stimuli) and trauma. Thymic stromal lymphopoietin has an upstream and central role in the initiation of immune responses and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells and basophils (Watson and Gauvreau 2014). Classically, TSLP may be a critical component in the initiation and perpetuation of the T helper 2 (Th2) response and the resulting cascade of cytokines associated with Th2 driven asthma (Kaur and Brightling 2012). Asthma is recognised as a heterogeneous disease, though, and there are subsets of subjects that do not exhibit Th2-associated disease (Wenzel 2012). Emerging data indicates that TSLP may also mediate non-allergic (non-Th2) inflammation (Tanaka et al 2009, Ziegler et al 2013).

Tezepelumab is a fully human IgG 2λ mAb directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with the TSLP receptor. Owing to the central role of TSLP as an upstream and pleiotropic cytokine in mediating asthma pathophysiology, anti-TSLP therapy is anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

Results of a completed inhaled allergen challenge study in 31 adult subjects with mild atopic asthma (Study 20101183) demonstrated that tezepelumab attenuated the late allergic response and the early allergic response to allergen challenge, as measured by the AUC for the percentage fall in the forced expiratory volume in one second (FEV_1) and the maximum percentage fall in FEV_1. Tezepelumab also attenuated the increase in CCI [redacted] value on the post-allergen day compared with the pre-allergen day. Multiple doses of tezepelumab 700 mg administered intravenously demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed ADA after receiving tezepelumab (Gauvreau et al 2014). Based upon these data, MedImmune/AstraZeneca performed a randomised, double-blind, placebo-controlled, dose-range finding study in asthmatics who were inadequately controlled with medium or high-dose ICS/LABA with or without other controller medications.

Study CD-RI-MEDI9929-1146 (PATHWAY) was a Phase IIb multicentre, multinational,

dose-ranging, double-blind, randomised, parallel-group, placebo-controlled study to evaluate the effect of 3 dose levels of tezepelumab on the AAER in adult subjects with inadequately-controlled severe asthma. Subjects were randomised in a 1:1:1:1 ratio to one of 3 dose levels of SC tezepelumab (70 mg every 4 weeks [Q4W], 210 mg Q4W, 280 mg every 2 weeks [Q2W]) or placebo (Q2W) for 52 weeks. A total of 584 subjects received at least 1 dose of tezepelumab or placebo. Anomalous data at a single site were identified following completion of the study and due to Good Clinical Practice (GCP) non-compliance, all data related to 34 subjects from this site were excluded and the Clinical Study Report (CSR) revised. Consequently, a total of 550 subjects received at least one dose of tezepelumab or placebo. An AAER reduction of 62%, 71% and 66% for the 70 mg Q4W, 210 mg Q4W and 280 mg Q2W tezepelumab groups, respectively, compared with placebo were observed in the intent-to-treat population ($p<0.001$). After repeated SC administration, mean serum trough concentration increased over time and achieved steady-state by Week 12. Tezepelumab exhibited linear PK across the 3 doses. A total of 6 (4.3%) placebo subjects and 7 (1.7%) tezepelumab subjects who had no detectable ADA at baseline had detectable ADA post-treatment; no subjects developed neutralising ADA in the study. The results of this study did not identify safety concerns associated with tezepelumab for any dosing regimen. The frequencies of treatment-emergent AEs (TEAEs) were similar between the placebo (65.9%) and the total tezepelumab (66.0%) dose groups and a majority of subjects had TEAEs that were mild or moderate in severity and not related to investigational product (IP). Few subjects had TEAEs that resulted in permanent discontinuation of IP. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no identified safety risks were noted (Corren et al 2017).

Study D5180C00002 was a Phase I open label study to evaluate the PK of a single SC 140 mg dose of tezepelumab in adolescents with mild to moderate asthma aged 12 to 17 years (inclusive). Tezepelumab was slowly absorbed with a time to achieve maximum observed serum concentration (t_{max}) ranging from approximately 4 to 6 days postdose and a mean maximum observed serum concentration (C_{max}) of 24.0 ± 6.59 µg/mL. Mean CL/F was 0.159 ± 0.0443 L/day and the $t_{1/2}$ was estimated to be 25.3 ± 4.70 days, similar to that previously observed in the adult population. The younger adolescent subjects (aged 12 to 14 years, inclusive) had higher exposure and lower CL/F compared with the older subjects (aged 15 to 17 years, inclusive), consistent with lower average body weight in the younger subjects and the impact of body weight on the PK of tezepelumab. Overall, the PK was consistent with previous experiences with this molecule and typical of human mAbs directed towards soluble antigens. Tezepelumab treatment was well-tolerated with an acceptable safety profile and supported further clinical development in this subject population. In safety assessments, 4 subjects in each cohort experienced at least one TEAE. There were no treatment-emergent SAEs. All TEAEs were mild or moderate in severity. One subject had ADAs both before treatment and postbaseline. No neutralising ADAs were detected in any subject.

Study D5180C00007 (NAVIGATOR) was a Phase 3, multicenter, global, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 210 mg of 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 subjects 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 subjects were randomized in a 1:1 ratio to tezepelumab or placebo and 1059 subjects received at least one dose of IP. Tezepelumab treatment resulted in a statistically significant and clinically meaningful reduction in AAER by 56% ($p < 0.001$) compared with placebo in the overall population and by 41% compared with placebo in subjects 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 subjects treated with tezepelumab. Neutralizing antibodies to tezepelumab were detected in only one (0.2%) of the subjects treated with tezepelumab. On-treatment AEs were similar between the placebo (80.8%) and the total tezepelumab (77.1%) dose groups and a majority of subjects had on-treatment AEs that were mild or moderate in severity and not related to investigational product (IP). The percentage of subjects 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 IP 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 subjects with severe, uncontrolled asthma. (Menzies-Gow et al 2021).

Eighty-two adolescent subjects aged 12 to 17 years were included in the NAVIGATOR safety set; duration of exposure was similar for the adolescents in the tezepelumab and placebo groups. The overall incidence of AEs in adolescent subjects during the on-treatment period was similar between the tezepelumab (73.2%) and placebo (70.7%) groups. The most common AEs in adolescent subjects (reported in ≥ 5% of subjects) in the tezepelumab group were: nasopharyngitis (19.5% in the tezepelumab group vs 12.2% in the placebo group), upper respiratory tract infection (14.6% and 7.3%), rhinitis (9.8% and 2.4%), pharyngitis (7.3% and 4.9%), and viral upper respiratory tract infection (7.3% and 4.9%). The incidence of SAEs was low and similar between the tezepelumab and placebo groups (one subject [2.4%] in the tezepelumab group and 2 subjects [4.9%] in the placebo group, all of which were PT asthma). There were no AEs leading to discontinuation of IP for adolescents in either treatment group. In conclusion, tezepelumab was well tolerated in adolescent subjects in NAVIGATOR with an AE profile that appears generally similar to that seen in adult subjects with severe uncontrolled asthma.

Additional studies with tezepelumab have been completed. These include a mechanistic study (D5180C00013; CASCADE) conducted in adults with inadequately controlled asthma, study

D5180C00009 (SOURCE) conducted in adults with oral corticosteroid (OCS)-dependent asthma, study D5180C00011 (PATH-HOME), an at-home use study in adults and adolescents with severe asthma, and study D5180C00019 (NOZOMI), a Japanese long-term safety study in subjects with inadequately controlled asthma.

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

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of tezepelumab may be found in the IB.

2.3.1 Risk Assessment

Clinical and nonclinical experience with tezepelumab demonstrates no safety or tolerability concerns to date. Potential risks based on the mechanism of action of tezepelumab include serious infections, helminth infections, and serious hypersensitivity reactions. Risk minimisation strategies associated with tezepelumab have been identified, described in the current IB and are included in this protocol. The risk mitigation strategies include but are not limited to: monitoring the subject for vital signs for a minimum of 2 hours post-IP, following each subject at every visit for AEs, as well as frequent study visits in the days following the administration of IP allowing for more intense monitoring of the subject by eg, physical examinations, ECGs, urinalysis, serum chemistry and haematology. Additional risks associated with the conduct of the study (eg, collection of blood for safety, PK and PD assessments, and spirometry testing) have a minimal impact on subjects in the study.

2.3.1.1 Study Conduct During COVID-19 Pandemic

Coronavirus disease 2019 (COVID-19) has emerged as a worldwide pandemic disease with significant implications for public health. AstraZeneca will monitor the participating countries and sites, and the study will not begin until local and national guidelines and clinical sites have indicated that it is acceptable to conduct clinical studies and the safety of site staff and subjects can be ensured.

2.3.1.2 Requirements During the COVID-19 Pandemic

Please Note: Changes below should only be implemented if study site is closed or travel restrictions are in place due to the COVID-19 pandemic.

During the COVID-19 pandemic, changes are being implemented in order to ensure the safety of study subjects, to minimise the risk to subjects of COVID-19 exposure, to maintain compliance with GCP, and to minimize risks to data integrity.

Visit 1 and Visit 2 must be performed on-site.

If an on-site visit for Visits 3 through 9 cannot occur due to pandemic related study site closure or travel restrictions, alternative visits should be performed, where allowable by local health authorities, ethics committees and healthcare provider guidelines (e.g. hospital policies), at the site's discretion in agreement with the Sponsor. The options are specified below:

1. Visit(s) to be performed at an alternate site (where applicable): Study visits including study assessments and bloodwork according to the SoA can take place at an alternative location away from infection risk zones, or closer to the subject's home, provided this is acceptable within local regulation/guidance.

2. Visit(s) to be performed at home by study site staff. Study visits including study assessments and bloodwork according to the SoA can take place at home, provided this is acceptable within local regulation/guidance.

3. Visit(s) to be performed at home by qualified third-party vendor. Study visits including study assessments and bloodwork according to the SoA can take place at home, provided this is acceptable within local regulation/guidance.

For further details, please refer to Appendix I.

2.3.1.3 COVID-19 Risk Mitigations

Severe asthma may be a risk-factor for severe COVID-19 illness. Subjects with suspicion of current or recent (within 8 weeks of Visit 1) COVID-19 infection or positive local COVID-19 viral rapid test during screening will not be included in the study (Section 5.2, Exclusions #22 and #23).

Paediatric cases of COVID-19 have been reported. However, there have historically been relatively fewer cases of COVID-19 among children compared with cases among adult patients.

Among cases in children reported from China, most had exposure to household members with confirmed COVID-19 (CDC 2020a).

Data on the incubation period for COVID-19 in the paediatric population is limited, it is thought to be similar to adult patients with COVID-19. In studies from China, the reported incubation period among paediatric patients ranged from 2 to 10 days.

Paediatric patients with COVID-19 may experience the following signs or symptoms over the course of the disease:

- Fever
- Cough
- Nasal congestion or rhinorrhoea
- Sore throat
- Shortness of breath
- Diarrhoea
- Nausea or vomiting
- Fatigue
- Headache
- Myalgia
- Poor feeding or poor appetite

The predominant signs and symptoms of COVID-19 reported to date among all patients are similar to other viral respiratory infections, including fever, cough, and shortness of breath. Although these signs and symptoms may occur at any time during the overall disease course, children with COVID-19 may not initially present with fever and cough as often as adult patients. In a report of 9 hospitalised infants in China with confirmed COVID-19, only half presented with fever. Gastrointestinal symptoms, including abdominal pain, diarrhoea, nausea, and vomiting, were reported in a minority of adult patients. In 1 paediatric case of COVID-19, diarrhoea was the only symptom reported.

There have been multiple reports to date of children with asymptomatic COVID-19 infection. The prevalence of asymptomatic COVID-19 infection and duration of pre-symptomatic infection in children are not well understood, as asymptomatic individuals are not routinely tested.

One of the complications of COVID-19 infection in children is multisystem inflammatory syndrome (MIS-C) (CDC 2020b). Patients with MIS-C can present with a persistent fever, fatigue, and a variety of signs and symptoms including multiorgan (eg, cardiac, gastrointestinal, renal, hematologic, dermatologic, neurologic) involvement, and elevated inflammatory markers. Not all children will have the same signs and symptoms, and some children may have other symptoms. MIS-C symptoms typically appear two to six weeks (although occasionally longer) after a child has been infected with SARS-CoV-2 (Son and Friedman 2021).

Sites will be required to provide documentation of a COVID-19 screening and mitigation plan that describes how and where subjects would be tested if they are suspected of being infected with COVID-19. The plans should also describe mitigation activities designed to protect site staff and others at the site, including other subjects and patients.

To ensure the safety of the subject, caregiver, and site staff, every visit will follow these guidelines:

All subjects will have a COVID-19 screening assessment performed by telephone within 24 hours prior to every study visit, whether visit is on-site or remote. Questions should include, but not be limited to, signs and symptoms of active COVID-19 infection, in addition to travel, known contacts, and testing. The questionnaire will include questions about exposures and household health. The site will determine the appropriate course of action based on the responses to the questions.

Screening V1:

- If there is no suspicion of COVID-19 infection based on questionnaire responses, the subject can proceed with the scheduled site visit, have temperature and vital signs recorded, and, if afebrile, proceed with Visit 1 and COVID-19 testing.
    - Any suspicion of COVID-19 infection based on questionnaire responses should be managed according to local and national guidelines and subject should be screen failed. These subjects can be rescreened within 2 to 4 weeks, as long as they are COVID-19 negative and rescreen is approved by the Contract Research Organisation (CRO) Medical Monitor and AZ study physician.
- If local COVID-19 viral rapid test is positive at V1, the subject should be screen failed.

Treatment Day V2:

- If there is no suspicion of COVID-19 infection based on questionnaire responses, the subject can proceed with the scheduled site visit, have temperature and vital signs recorded, and, if afebrile, proceed with Visit 2 and COVID-19 testing.
    - Any suspicion of COVID-19 infection based on questionnaire responses should be managed according to local and national guidelines and subject should be screen failed. These subjects can be rescreened within 2 to 4 weeks, as long as they are COVID-19 negative and approval by the CRO Medical Monitor and AZ study physician.
- Local COVID-19 viral rapid test should be performed with negative results prior to spirometry, CCI , and study IP administration.
    - If local COVID-19 viral rapid test is positive at V2, the subject should be screen failed.

All other study visits:

- If there is no suspicion of COVID-19 infection based on questionnaire responses, the subject can proceed with the scheduled site visit, have temperature and vital signs recorded, and, if afebrile, proceed with the scheduled study visit.

    - Any suspicion of COVID-19 infection based on questionnaire responses should be managed according to local and national guidelines.
- Study sites may perform a local COVID-19 viral rapid test or central viral test after Visit 2 and throughout the study if it is considered clinically appropriate by the Investigator. If test results are positive, the subject may or may not be withdrawn from the study, depending on extent of illness and Investigator judgement, and the CRO Medical Monitor and AZ study physician must be notified.

It is recognised that depending on the location and facilities of a clinical site, study visit attendance may place subjects at risk of exposure to COVID-19. Furthermore, it is recognised that more general population-level measures to reduce infection rates (eg, travel restrictions) may inhibit the ability of subjects to attend study visits. Necessary healthcare responses at sites to the pandemic (eg, additional infection control measures) may also inhibit the ability of a clinical site to effectively and properly conduct the study. Study visit attendance for dosing and for clinical assessments are critical for the scientific value of the study.

Therefore, investigators should not enrol subjects unless they have reasonable confidence that throughout the duration of the study:

- Subjects and caregivers will be able to attend study visits, whilst avoiding contact with concentrations of COVID-19 patients (eg, hospital entrances used by such patients); and
- The site will be able to conduct the study effectively and safely, considering relevant national and local factors; and
- Subjects and caregivers agree to alternate site visits or home visits as an alternative to on-site visits if pandemic restrictions are in place

If, for reasons related to the COVID-19 pandemic, a subject/caregiver is not able to attend their scheduled study visit at the site, refer to CSP Section 1.2 and Appendix I for alternative study visit options.

The Sponsor will monitor the number of discontinuations, withdrawals, missed visits and other missing data and collect such information in the eCRF.

Subjects may be tested for COVID-19 infection by local viral rapid test at any time during study conduct if it is considered clinically appropriate by the investigator (Table 1).

Subjects with a suspicion of COVID-19 infection or active COVID-19 infection detected during study conduct may be withdrawn from the study based on severity of illness and Investigator discretion. An AE should be recorded in the eCRF to capture the event. Such subjects may be replaced at the Sponsor's discretion. Each situation is likely to be unique, therefore the CRO Medical Monitor and AZ study physician must be notified.

All site staff should wear personal protective equipment in accordance with local or national guidelines.

2.3.2 Benefit Assessment

In the Phase 3 and 2b studies, clinical benefits and improvements on biomarkers were already observed at the first assessment 2 weeks and 4 weeks after the first dose, respectively. However, in the context of this study, the probability of therapeutic benefit following a single SC dose of tezepelumab CCI cannot be predicted. Nevertheless, it may be anticipated that subjects will derive benefit from the regular review by healthcare professionals during the study.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to subjects in this study, the current benefit: risk profile appears favourable and justifies the administration of tezepelumab in this study.

3 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are shown in Table 2.

Table 2 Objectives and Endpoints

Objectives	Outcome Measures
Primary	
• To describe the PK parameters following a single SC administration of tezepelumab CCI in children with mild, moderate, or severe asthma	• Maximum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) • Terminal phase elimination half-life ($t_{1/2}$) • Apparent clearance (CL/F) • Apparent steady-state volume of distribution (V_{ss}/F)
Secondary	
• To evaluate the immunogenicity of tezepelumab	• Presence of anti-drug antibodies (ADA)
Safety	
• To evaluate the safety and tolerability following a single SC administration of tezepelumab CCI	• Adverse events/serious adverse events • Vital signs • Laboratory parameters • Electrocardiogram (ECG)
Exploratory	
• CCI [redacted]	[redacted]

CCI [redacted]

PK Pharmacokinetic; CCI [redacted] SC Subcutaneous.

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, open label study designed to evaluate the PK profile of tezepelumab following a single SC CCI dose in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma.

The study will be conducted globally with approximately 10 study sites.

Approximately 24 subjects will be enrolled and approximately 14 paediatric subjects aged ≥ 5 to 11 years (inclusive) will receive a single SC CCI dose of tezepelumab in an attempt to have at least 12 paediatric subjects complete the study. At least 4 subjects will have body weight < 25 kg and a minimum of 3 subjects will have body weight ≥ 25 kg to < 40 kg.

Subjects who are eligible to participate but do not go on to receive tezepelumab, or subjects who do not complete the required evaluations through to Day 85 may be replaced to maintain the stipulated number of evaluable subjects, at the discretion of the Sponsor.

The 99-day study consists of:

- A consent/screening period of up to 14 days
- Treatment and follow-up period of 85 days.

The study design is summarised in Figure 1.

Subjects will attend the study site and informed consent will be obtained from the legal representative and informed assent will be obtained from the subject. Screening assessments should be completed within 14 days (Day --14 to Day --1). Subjects who meet eligibility criteria will receive a single SC CCI dose of tezepelumab, administered in the anterior thigh by a healthcare professional on Day 1 and remain at the study centre for 2 hours after dosing. The subjects will then return to the centre for outpatient Follow-up visits on Days 3, 7, 11, 15, 29, 57 and 85 (EOS). The study will be completed after the EOS visit on Day 85.

4.2 Scientific Rationale for Study Design

This study design has been reviewed and approved by the Paediatric Committee of the European Medicines Agency as part of the tezepelumab Paediatric Investigation Plan.

This is an open label study. A placebo group is not considered required for this study since the primary objective is to determine the PK of a single SC CCI dose of tezepelumab in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma and no formal assessment of efficacy will be made. The assessment of the safety and tolerability of tezepelumab can be made without a placebo group.

The primary, secondary and CCI were chosen to evaluate whether PK, immunogenicity, safety and CCI of tezepelumab in children are similar to the adult and adolescent populations. All PK time points in this study are based on the PK information obtained in previous adult and adolescent studies.

4.3 Justification for Dose

A single SC CCI dose has been selected for this study to evaluate the PK/PD of tezepelumab in children aged ≥ 5 to 11 years. This was established from exposure comparability between the proposed effective dose and safe exposure in the adult population based on Phase IIb data. Population PK modelling based on Phase I and Phase II data suggested body weight was a significant covariate for the PK of tezepelumab. Using the population PK model, simulations were conducted to predict the tezepelumab exposure in children aged ≥ 5 to 11 years, taking into account the difference in body weight distribution between the adult and paediatric populations. Based on the simulation, the predicted exposure following CCI SC Q4W dose in children aged ≥ 5 to 11 years is comparable to that in adults at 210 mg SC Q4W, which was selected as the optimal dose in adult patients with severe asthma based on the Phase IIb data and used in the ongoing 52-week Phase III study in adults and adolescents. The Phase IIb data showed the dose of 210 mg SC Q4W for 52 weeks was well tolerated and led to near maximum CCI improvement, as well as reduction in CCI and CCI, 4 weeks after the first dose. Hence, given the linear PK of tezepelumab and similar exposure to 210 mg single SC dose in adults, a single SC CCI dose is predicted to be safe and achieve near maximum PD effects while being sufficient to characterise PK in children aged ≥ 5 to 11 years.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed his/her last scheduled contact.

The end of study is defined as the date of the last visit of the last subject in the study.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Informed Consent

1 Written informed consent and written informed assent and any locally required authorisation obtained from the subject and legal representative prior to any study-related procedure taking place.

The informed consent form (ICF) process is described in Appendix A 3.

Age

2 Age 5 to 11 years (inclusive) at Visit 1 and Visit 2 (Day 1).

Type of Subject and Disease Characteristics

3 Documented physician diagnosed asthma, defined by the regional guidelines (ie, National Institutes of Health [NIH], GINA, American Thoracic Society [ATS], European Respiratory Society [ERS], etc), for at least 6 months prior to Visit 1. If the subject is naïve to the study site, the participant/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the participant/guardian.

4 Documented treatment with total daily dose of either low, medium, or -high-dose ICS (≥ 100 µg fluticasone propionate dry powder inhaler [DPI] or equivalent; see Appendix H) for at least 6 months, as described in Step 2 to Step 4 of GINA guidelines (GINA 2020) with stable dose for at least 3 months prior to Visit 1.

5 Additional controller medication according to standard practice of care is permitted (LABA, leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA] only) and must be documented and stable for at least 3 months prior to Visit 1.

6 Inclusion criterion 6 (historical or current airway reversibility) removed with version 3.0 of Clinical Study Protocol.

7 Pre-bronchodilator (BD) FEV_1 of ≥ 50% of predicted normal value at Visit 1.

8 If on allergen immunotherapy, subjects must be on stable maintenance dose and schedule ≥ 1 month prior to Visit 1.

9 Able and willing to comply with the requirements of the protocol.

10 Acceptable inhaler and spirometry techniques during screening/run-in period as assessed by the Investigator.

Weight

11 Body weight ≥ 16 kg at Visit 1 and Visit 2 (Day 1).

12 Inclusion criterion 12 (Body mass index for age and percentiles) removed with version 4.0 of Clinical Study Protocol.

Sex

13 Male or female.

Reproduction

14 Females of childbearing potential who are sexually active, as judged by the Investigator, 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 IP.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of any clinically significant disease or disorder other than asthma which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

2 History of a deterioration in asthma or asthma exacerbation that required a burst of systemic corticosteroids within 6 weeks of Visit 1, up to and including Visit 2 (Day 1).

3 Exclusion criterion 3 (previous exclusion for intra-articular glucocorticosteroids for conditions other than asthma) removed with version 3.0 of Clinical Study Protocol.

4 History of hospitalisation (overnight admission) for asthma within 3 months of Visit 1, up to and including Visit 2 (Day 1).

5 History of a life threatening asthma exacerbation requiring intubation or mechanical ventilation.

6 History of systemic corticosteroid use for the maintenance treatment of asthma within 6 weeks of Visit 1, up to and including Visit 2 (Day 1) and discouraged until EOS.

7 A helminth parasitic infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

8 History of a clinically significant infection, including upper or lower respiratory tract infection (with or without treatment of antibiotics or systemic antivirals) within 2 weeks of Visit 1 or during screening.

9 Tuberculosis requiring treatment within 12 months prior to Visit 1.

10 Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of Visit 2 (Day 1).

11 History of cancer.

Prior/Concomitant Therapy

12 Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to Visit 1, up to and including Visit 2 (Day 1).

13 Receipt of any investigational nonbiologic agent within 30 days or 5 half-lives (whichever is longer) prior to Visit 1, up to and including Visit 2 (Day 1).

14 Receipt of immunoglobin or blood products within 30 days prior to Visit 1, up to and including Visit 2 (Day 1).

15 Receipt of live attenuated vaccines 30 days prior to Visit 1, up to and including Visit 2 (Day 1).

Prior/Concurrent Clinical Study Experience

16 Subjects with known hypersensitivity to tezepelumab or any excipients of the product.

17 History of hypersensitivity or anaphylactic reaction to any biologic therapy.

18 Concurrent enrolment in another drug-related interventional clinical trial.

Diagnostic assessments

19 Any clinically relevant abnormal findings in physical examination, ECG, vital signs, haematology, clinical chemistry, or urinalysis during screening, which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study, or may influence the results of the study, or the subject's ability to complete entire duration of the study.

20 Evidence of active liver disease, including jaundice or aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2 × the upper limit of normal (ULN) at Visit 1. Subjects with ongoing liver disease or inexplicably elevated liver chemistry values should be excluded from the study.

21 Positive hepatitis B surface antigen or hepatitis C virus antibody serology at Visit 1, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to enrol.

22 Any clinical signs, symptoms, or abnormal findings during screening that may be indicative of past or present MIS-C.

23 Positive local COVID-19 viral rapid test at Visit 1.

24 Positive local COVID-19 viral rapid test results at Visit 2.

25 A history of known immunodeficiency disorder, including a positive human immunodeficiency virus (HIV) test at Visit 1, or the subject is taking antiretroviral medications as determined by medical history and/or subject's verbal report.

Other Exclusions

26 Parent/guardian/subject has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (eg, inability to read, comprehend, or write) which will limit the validity of consent to participate in this study.

27 Children who are wards of the state or government.

28 Parent/guardian involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, Contract Research Organisation [CRO] staff and/or staff at the study site).

29 Judgement by the Investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

30 Previous enrolment in the present study.

31 Participants who have had a confirmed COVID-19 infection and have not fully recovered (based on Investigator judgement) for at least 8 weeks prior to Visit 1.

32 Participants with a history of severe COVID-19 infection requiring hospitalisation.

33 Receipt of any COVID-19 vaccine 28 days prior to Visit 2 (Day 1).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the centre.

Subjects should not eat or drink one hour prior to having the CCI test.

5.3.2 Activity

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the centre.

5.4 Screen Failures

Screen failures are defined as subjects who signed the ICF to participate in the clinical study but are not subsequently assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects 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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreen attempts are allowed in the study only if only if the reason for screen failure was transient (including but not limited to equipment failure, exclusion criterion #8 [Section 5.2], or other transient conditions) and the Study Physician has deemed that the reason for the rescreen is valid and has approved the rescreen.

Rescreened subjects should be assigned the same subject number as for the initial screening and be re-consented.

Rescreening should be discussed with the CRO Medical Monitor. If rescreening is performed within 30 days of initial screening, assessments from initial screening may be used, however clinically significant findings must be reassessed, and the subject must meet all entry criteria noted in the protocol. Subjects rescreened more than 30 days after initial screening must repeat all assessments and meet all entry criteria noted in the protocol.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the Clinical Study Protocol (CSP). Study intervention in this study refers to tezepelumab.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Product

Investigational product details are provided in Table 3.

Table 3 Investigational Product

Arm Name	Treatment 1
Intervention Name	Tezepelumab
Type	Drug
Dose Formulation	CCI [redacted]
Dosage Level	CCI [redacted]
Route of Administration	SC injection
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labelling	Study intervention will be provided in single use 5 mL vials. Each vial will be labelled in accordance

Table 3 Investigational Product

	with GMP Annex 13 per country regulatory requirement.
Former Names	MEDI9929 and AMG 157

GMP Good Manufacturing Practice; IMP Investigational medical product; NIMP Non-investigational medical product; SC Subcutaneous.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 The Investigator or designee must confirm appropriate temperature conditions of 2°C to 8°C 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 subjects enrolled in the study may receive study intervention and only authorised site staff may administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

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).

The IP will be supplied to the site in cartons with one vial of tezepelumab in each carton. Each vial as well as each carton will be labelled.

The IP kit will be allocated to the subject on a random basis by the site based on the available unused kits in the pharmacy.

The Investigator(s) will:

1 Obtain signed assent from the potential subject and consent from their guardian/legal representative, before any study specific procedures are performed.

2 Determine subject eligibility.

3 Assign the potential subject a unique enrolment number, ie, ‘subject identification (SID) number’.

All unused supplies of IP will be destroyed by the site in accordance with their local Standard Operating Procedure (SOP). Investigational product destruction is not to be performed until approval has been granted by the sponsor.

Upon request by the site or following database lock (DBL), IQVIA will ask the sponsor for approval for the sites to destroy their IP. Approval from the sponsor will be forwarded to the

sites by the IQVIA site monitor.

6.2.1 Dose Preparation

Each vial should be visually inspected prior to dose preparation. The IP will be provided to the study sites as a colourless to slightly yellow clear solution contained in a 5 mL single use glass vial to be stored at 2°C to 8°C until used. If defects are noted with the IP, the Investigator and site monitor should be notified immediately. Preparation of IP must be performed by a qualified person (eg, pharmacist, Investigator or qualified designee) at the site.

Preparation of the IP is to be performed aseptically. Total in-use storage time from needle puncture of the IP vial to start of administration should not exceed 4 hours at room temperature. If storage time exceeds this limit, a new dose must be prepared from a new vial.

Dose preparation steps:

1. Allow the vial to equilibrate at room temperature (about 30 minutes to one hour). Ensure that the vial is adequately protected from light during the warming process. Gently swirl the vial to ensure the contents are mixed to a clear, homogeneous solution. Do not shake.
2. To prepare IP for administration remove the tab portion of the vial cap and clean the stopper with 70% ethyl alcohol or equivalent.
3. Attach a 21G 1½-inch sterile disposable needle to a 1 mL sterile syringe.
4. CCI
5. Remove and discard the 21G 1½-inch sterile disposable needle from the syringe.
6. Attach a new 27G ½-inch sterile disposable needle to the same syringe in step 5.
7. Apply the appropriate label to the syringe according to local standard practice.

The assigned vial should be used only once to prepare a single dose required at the dosing visit. The IP does not contain preservatives and any unused product in opened and dispensed vials should not be used for subsequent dosing and should be stored until IP accountability has been completed as per the site's SOP. If the opened and dispensed vials must be discarded immediately after dose preparation as per the site's SOP, the vial labels along with the cartons must be retained for IP accountability.

The IP will be administered by one SC injection (see Table 4) according to standard practice. Standard numbing medications/devices and/or distraction techniques may be used with administration of IP.

Table 4 Investigational Product Dose Preparation

Dose	Number of vial(s) required	Syringe size required	Total volume administered
CCI	1	1 mL	CCI

The volume of IP drawn up and injected as well as any dosing issues encountered will be recorded in the electronic case report form (eCRF).

6.2.2 Dose Administration

If any of the following has occurred, the IP should not be administered:

- The subject received allergen immunotherapy injection within 7 days of scheduled IP administration.
- The subject has an intercurrent illness that in the opinion of the Investigator may compromise the safety of the subject in the study (eg, viral illnesses).
- The subject is febrile ($\geq$ 38°C; $\geq$ 100.4°F) within 72 hours prior to IP administration.

The visit should be rescheduled to another date and IP should be administered at that visit. Delay of the dosing visit can be extended for an additional 14 days.

The IP will be administered in the anterior thigh by a qualified healthcare professional (eg, Investigator or qualified designee) at the site. The injection site must be recorded in the source documents and in the eCRF. The person administering the dose will wipe the skin surface of the anterior thigh with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The IP will be slowly injected (no longer than 5 seconds duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection.

Note: Time of dispensing of IP, time IP taken out of the fridge and time of IP administration should be recorded in a specific log. This log must be a part of the subject's source documents.

Subjects should be observed for a minimum of 2 hours after administration of the IP for the appearance of any acute drug reactions (see Appendix G).

If the subject/parent/legal representative reports an injection site reaction, the Investigator or qualified designee will complete the AE eCRF page.

6.2.3 Procedures for Handling Incorrectly Enrolled Subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive study IP. There can be no exceptions to this rule.

If a subject does not meet all the eligibility criteria but is enrolled in error, or incorrectly receives IP, the Investigator should inform the AstraZeneca Study Physician immediately. All subjects who receive study IP should remain in the study and the subjects should continue to be followed up in accordance with defined study procedures.

6.3 Measures to Minimise Bias: Randomisation and Blinding (Not applicable)

Blinding is not applicable as this is an open label, non-randomised study.

6.4 Study Intervention Compliance

When subjects 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 subject 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.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction of all unused IP. The date and time of all IP administrations should be recorded in the appropriate section of the eCRF.

6.5 Concomitant Therapy

Throughout the study, Investigators may prescribe concomitant medications or treatments (including rescue medication as required) deemed necessary to provide adequate supportive care. All use of concomitant medications and supplements (nutritional and prophylactic) will be recorded on the concomitant medication eCRF.

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

Refer to Section 8.1.1.1 for details of maintenance therapy restrictions on the days when lung

function testing is performed and to Section 8.1.2 for restrictions prior to the CCI test.

Asthma worsenings/exacerbations should be treated with oral, inhaled, or other medications (including corticosteroids and rescue medication) according to standard practice. The decision and the administration may be at the discretion of the Investigator and/or parent/legal guardian/subject upon temporary worsening of asthma signs and symptoms. In cases of asthma worsening/exacerbation, subjects should be evaluated at the study centre when feasible.

All medications taken for asthma or other conditions in the 6 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment by the Investigator/authorised delegate at each visit.

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

6.5.1 Restricted Medications

Restricted medications are shown in Table 5.

Table 5 Restricted Medications

Restricted medication/class of drug	Usage
Asthma maintenance treatments	Changes in either dose or regimen are discouraged from Visit 1 and throughout the study, unless there is an absolute medical need as judged by the Investigator. Once daily LABA and LAMA should be withheld for at least 24 hours prior scheduled spirometry and CCI at site visits apart from any unscheduled visits due to asthma worsening. Twice daily LABA- and LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry and CCI at site. LTRA should be restricted for at least 24 hours prior to scheduled spirometry and CCI at site.
Short-acting β2-agonists (SABA)	Regular scheduled use is not allowed from Visit 1 and preferably throughout the study, unless there is an absolute medical need as judged by the Investigator. As required (PRN) use is allowed; however, attention should be paid to the following restriction: • If possible, SABA should be withheld at least 6 hours prior to scheduled spirometry, CCI and ECG. May be used for managing an asthma exacerbation event.
Short-acting antimuscarinics (SAMA; ipratropium)	If possible, SAMA should be withheld at least 6 hours prior to scheduled spirometry, CCI and ECG.
Inactive/killed vaccinations (eg, inactive influenza)	Allowed, provided they are not administered within 7 days before or after IP administration/Visit 2.

Table 5 Restricted Medications

Restricted medication/class of drug	Usage
COVID-19 vaccination	Allowed, provided that vaccination is not administered within 28 days before and 14 days after IP administration/Visit 2
Allergen immunotherapy	Allowed, if on stable therapy for at least 1 month prior to Visit 1 with no anticipated change during the study. This should not be administered within 7 days before or after IP administration/Visit 2.

ECG Electrocardiogram; CCI ; IP Investigational product; LABA Long-acting β2-agonist; LAMA Long-acting muscarinic antagonist; LTRA Leukotriene receptor antagonist.

6.5.2 Prohibited Medications

Therapies excluded at screening and throughout the study (Section 5.2) are prohibited and may only be administered if necessary, to provide adequate supportive care (Table 6).

Table 6 Prohibited Medications

Prohibited medication/class of drug	Usage
Live Attenuated Vaccines	Not allowed 30 days prior to Visit 1 and preferably throughout the study. If there is an absolute medical need as judged by the Investigator, do not administer prior to 4 weeks after dose of IP.
Any systemic immunomodulators or immunosuppressives	Not allowed throughout the study, unless there is an absolute medical need as judged by the Investigator. Systemic corticosteroids may be used for managing an asthma worsening/exacerbation event.
Immunoglobulin or blood products	Not allowed 30 days prior to Visit 1 and throughout the study, unless there is an absolute medical need as judged by the Investigator.
Any marketed (eg, omalizumab, mepolizumab, reslizumab) or to be marketed, or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1 and throughout the study.
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 and throughout the study, unless there is an absolute medical need as judged by the Investigator.
Medications not currently licensed for use in the treatment of asthma in children, (eg, theophylline), and not part of current standard of care	Not allowed from Visit 1 and throughout the study, unless there is an absolute medical need as judged by the Investigator.

IP Investigational product.

6.6 Dose Modification (Not applicable)

6.7 Intervention after the End of the Study

Subjects who complete Day 85/EOS should be given standard of care therapy at the discretion of the Investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

This is a single-dose study, therefore discontinuation from IP treatment is not applicable.

7.2 Participant Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her or parent/legal representative's request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A subject who considers withdrawing from the study should be encouraged to remain in the study and attend all study visits to have a minimum of AEs, SAEs and concomitant medication information collected. If the subject or parent/guardian does not agree to continue in-person study visits, modified follow-up options (eg, telephone contact with the subject or parent/guardian) should be arranged to ensure the collection of safety information through the Day 85 time point.
- At the time of withdrawal from the study, if possible, an EOS visit should be conducted, as shown in the SoA (Table 1). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, it should be confirmed if he/she or their parent/legal representative still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent 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.

7.2.1 Replacement of Subjects

Subjects who are eligible to participate but do not go on to receive tezepelumab, or subjects who do not complete the required evaluations through to Day 85 may be replaced to maintain the stipulated number of evaluable subjects, at the discretion of the Sponsor.

7.3 Lost to Follow-up

A subject 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 subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject/parent/legal representative on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject/parent/legal representative (where possible, 3 telephone calls and, if necessary, a certified letter to the subject/parent/legal representative's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

Discontinuation of specific sites or of the study are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the IQVIA Global Therapeutic Medical Adviser immediately upon occurrence or awareness to determine if the subject should continue or discontinue in the study.
- 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 subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Planned sampled blood volume will be compliant with recommendations relating to GCP in the conduct of clinical trials (European Commission 2008, Howie 2011); the maximum amount of blood collected, including any losses in the manoeuvre, from each subject should not exceed 3% of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time during the study (Table 7). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 7 Maximum Volume of Blood to be Drawn from a Subject

Subject weight (kg)	Total blood volume (mL) [a]	Maximum blood volume (mL) to be drawn at any visit	Maximum blood volume (mL) to be drawn within a 4-week period
15-20	1200-1600	12.0-16.0	36.0-48.0
21-25	1680-2000	16.8-20.0	50.4-60.0
26-30	2080-2400	20.8-24.0	62.4-72.0
31-35	2480-2800	24.8-28.0	74.4-84.0
36-40	2880-3200	28.8-32.0	86.4-96.0
41-45	3280-3600	32.8-36.0	98.4-108.0
46-50	3680-4000	36.8-40.0	110.8-120.0
51-55	4080-4400	40.8-44.0	122.4-132.0
56-60	4480-4800	44.8-48.0	134.4-144.0
61-65	4880-5200	48.8-52.0	146.4-156.0
66-70	5280-5600	52.8-56.0	158.4-168.0
71-75	5680-6000	56.8-60.0	170.4-180.0
76-80	6080-6400	60.8-64.0	182.4-192.0
81-85	6480-6800	64.8-68.0	194.4-204.0
86-90	6880-7200	68.8-72.0	206.4-216.0
91-95	7280-7600	72.8-76.0	218.4-228.0
96-100	7680-8000	76.8-80.0	230.4-240.0

[a] The total blood volume is estimated at 80 mL/kg body weight.

The total volume of blood to be drawn from each subject at each study visit is shown in Table 8.

Table 8 Volume of Blood to be Drawn from Each Subject

Visit (Study day)	Sample	Sample blood volume (mL)	Visit total blood volume (mL)
Screening	Chemistry (including β-HCG if required)	3.5	10.5
	Haematology	2.0	
	Serology (HIV)	2.5	
	Hepatitis B/Hepatitis C	2.5	
V2 (Day 1)	Chemistry	3.5	15.5
	Haematology	2.0	
	PK	2.5	
	ADA	5.0	
	IgE	2.5	
V3 (Day 3)	PK	2.5	2.5
V4 (Day 7)	PK	2.5	2.5
V5 (Day 11)	PK	2.5	2.5
V6 (Day 15)	Chemistry	3.5	8.0
	Haematology	2.0	
	PK	2.5	
V7 (Day 29)	Chemistry	3.5	15.5
	Haematology	2.0	
	PK	2.5	
	ADA	5.0	
	IgE	2.5	
V8 (Day 57)	PK	2.5	2.5
V9 (Day 85/EOS)	Chemistry	3.5	15.5
	Haematology	2.0	
	PK	2.5	
	ADA	5.0	
	IgE	2.5	
Total blood volume (mL)			**75.0**

Volumes exclude serum pregnancy testing (with the exception of Visit 1) and exclude any re-testing requirements. If serum pregnancy testing is needed at any other visits, then an additional 2.5 mL blood collection will be required.
ADA Anti-drug antibodies; β-HCG Beta-human chorionic gonadotrophin; EOS End of Study; HIV Human immunodeficiency virus; IgE Immunoglobulin E; PK Pharmacokinetic; V Visit.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 1).

8.1.1 Spirometry

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[redacted]

8.1.1.2 Spirometry Testing

Spirometry testing can be completed at any time during the day and within ± 1.5 hours of the time the screening spirometry was completed. For example, if the screening spirometry is at 0800, then all spirometry testing at subsequent visits need to be completed between 0630 and 0930. On Day 1, spirometry testing will be performed before administration of IP.

The subject should wear comfortable clothing which does not restrict the chest or abdomen. The subject should rest for at least 15 minutes prior to the test and should be sitting during spirometry testing. Forced expiratory manoeuvres should be performed with the subject seated in an upright position. If this is not comfortable for the subject, standing is permitted. The same position should be used by the subject for each forced expiratory manoeuvre throughout the study. A nose-clip should be used for the manoeuvre and the head must not be tilted during manoeuvres. Mouthpieces of the same dimension and shape should be used by the subject throughout the study.

The forced expiratory manoeuvre (FEV_1) should start with a maximal inspiration and then be followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the subject to continue the expiration to be fast and forceful throughout the manoeuvre. 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 spirometry session and the 2 best efforts that meet ATS/ERS acceptability and reproducibility criteria will be recorded in the eCRF. The best efforts will be based on the highest FEV_1. The maximum FEV_1 of the 2 best efforts will be used for the analysis. The percentage of predicted normal value for FEV_1 will be recorded using the local spirometer at the site with predicted values derived from the appropriate reference value of choice, eg, NHANES III 2010, Quanjer et al 2012, etc.

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8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

Physical examinations will be performed at timelines as specified in the SoA (Table 1).

- 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, musculoskeletal (including spine and extremities) and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the following: general appearance, respiratory, cardiovascular and abdominal systems.

See Section 8.3.5 for reporting AEs based on physical examinations.

8.2.1.1 Weight and Height

Weight and height will be measured in accordance with the SoA (Table 1).

The subject's weight will be recorded in kilograms, and height will be recorded in centimeters. Weight and height measurements will be performed in light clothing and with shoes off.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Table 1). If required, this may be done by a study nurse at the subject's home on the Day 11 visit, if previously approved and agreed with AstraZeneca.

Vital signs (blood pressure [BP], heart rate, respiratory rate and body temperature) will be obtained in accordance with SoA.

On Day 1, vital signs will be assessed within 1 hour prior to and at 1 hour and 2 hours post-IP administration.

Vital signs will be taken prior to blood drawing, and, if possible, usual asthma controller medication.

Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Pulse rate will be obtained before BP, if the manual measurement technique is used.

Respiration rate will be obtained after the subject has been resting for at least 5 minutes, by counting number of breaths (ie, how many times the chest rises) for one minute.

Body temperature will be measured prior to IP administration, in accordance with local standards.

See Section 8.3.5 for reporting AEs based on vital signs.

8.2.3 Electrocardiograms

A 12-lead ECG will be performed at timelines as specified in the SoA (Table 1), using local site equipment.

Electrocardiograms will be taken in supine position, prior to blood draw and spirometry.

Electrocardiograms should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

The Investigator or authorised 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 will take precedence and should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced, and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine is used for assessment of the subject throughout the study.

The ECG data and evaluation will be recorded in the eCRF.

See Section 8.3.5 for reporting AEs based on vital signs.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the visits indicated in the SoA (Table 1).

Local clinical routine procedures to reduce pain and discomfort from blood sampling in children will be followed, eg, offering topical anaesthesia, coordinated sampling to avoid repeated punctures as appropriate in accordance with ethical and instruction guidelines for paediatric blood sampling.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date of collection will be recorded on the appropriate eCRF.

Instructions for sample collection, processing, storage and shipment will be provided in a separate Laboratory Manual provided to the sites.

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory.

Table 9 shows the laboratory variables to be measured.

Table 9 Laboratory Safety Variables

Haematology (CBC with differential)	Clinical chemistry (serum or plasma)
B-Haemoglobin (Hb)	S-Alkaline phosphatase (ALP)
B-Basophil differential count (absolute count)	S-Alanine aminotransferase (ALT)
B-Lymphocyte differential count (absolute count)	S-Aspartate aminotransferase (AST)
B-Platelet count	S-Bilirubin, total
B-Eosinophil differential count (absolute count)	S-Blood urea nitrogen
B-Monocyte differential count (absolute count)	S-Calcium, total
B-Neutrophil differential count (absolute count)	S-Chloride
White blood cell (WBC) count	S-Creatinine
	S-Creatinine kinase (CK)
Urinalysis (dipstick) [a]	S-C-reactive protein (CRP)
U-Hb/Erythrocytes/Blood	S-Glucose
U-Protein/Albumin	S-beta-Human chorionic gonadotrophin (β-HCG)
U-Glucose	S-Potassium
U-Microscopy and culture as required[b]	S-Sodium
Virology screen	**COVID-19 testing**
Hepatitis B surface antigen (HBsAg)	Local viral rapid test
Hepatitis C virus (HCV)	
Human immunodeficiency virus (HIV)	

B Blood; CBC Complete blood count; COVID-19 Coronavirus disease 2019; S Serum; U Urine.
[a] The urine dipstick test is not only limited to blood, protein, and glucose, but also additional test analytes as defined by central laboratory.
[b] Urine samples will be analysed locally with the urine dipstick test and sent to the central laboratory only for further microscopy and culture analysis when an abnormal dipstick result for any parameter is observed.

NB. In case a subject shows an AST or ALT ≥ 3 × ULN together with total bilirubin (TBL) ≥ 2 × ULN, please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' (HL), for further instructions. See Section 8.3.5 for reporting AEs based on laboratory values.

8.2.4.1 Pregnancy Test

The following tests will be performed for female subjects of childbearing potential (determined at the discretion of the Investigator), as specified in the SoA (Table 1).

- Serum beta-human chorionic gonadotrophin (β-HCG) at Visit 1.
- Urine pregnancy test (dipstick) at Visit 2 (treatment day) and EOS visit. A positive urine test result must be confirmed with a serum pregnancy test.

8.2.5 Other Safety Assessments

8.2.5.1 Virology

Hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCAb), HIV-1 and HIV-2 antibodies will be assessed at Visit 1 only. All testing for these will be performed at a central laboratory.

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

Instructions for sample collection, processing, storage and shipment will be provided in a separate Laboratory Manual provided to the sites.

8.2.5.2 COVID-19 Testing

Due to the changing landscape surrounding COVID-19 testing, a local COVID-19 rapid test has become available during study conduct and is permitted for site use per the SoA (Table 1) provided:

- Test turnaround time is less than 60 minutes in order to minimise subject/caregiver time spent at site visits
- Sensitivity and specificity are at least 95%
- Test is approved by the Sponsor

After local COVID-19 viral rapid testing at V1 and V2, repeat testing may be performed at any time for a subject suspected of having COVID-19 using either viral rapid testing or testing via the central laboratory.

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

Instructions for sample collection, processing, storage and shipment will be provided in a separate Laboratory Manual provided to the sites.

8.3 Adverse Events and Serious Adverse Events

The Investigator 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 B.

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

The Investigator and any designees are responsible for detecting, documenting and recording events that meet the definition of an AE. For information on how to follow-up AEs, see Section 8.3.2.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from time of signature of ICF throughout the treatment day and the follow-up period.

Serious AEs will be recorded from the time of signing of the ICF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a subject 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 subject'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 subject 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)
- Severity
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation

- 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 IP 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 investigational product?'

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 provided in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject 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 summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP, 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 an unscheduled (non-protocol mandated) 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, anaemia versus low haemoglobin 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 Hy's Law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 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 HL.

8.3.7 Adverse Events of Special Interest

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

- Anaphylactic reactions
- Immune complex disease (Type III 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.
- Injection site reactions
- Opportunistic infections
- Guillain Barre Syndrome.

8.3.8 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform

the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works 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 is undertaken immediately. Investigators or other site personnel inform AstraZeneca 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 web-based data capture (WBDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study-site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study-site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for tezepelumab.

8.3.9 Pregnancy

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

- If the pregnancy is discovered before the study subject has received any IP.

8.3.9.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, she should be discontinued from the study immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the subject

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 AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 SAEs (see Section 8.3.8) 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 PREGOUT is used to report the outcome of the pregnancy.

8.3.10 Medication Error

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within one (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 8.3.8) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.3.11 Management of Anaphylaxis

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available at the clinical research site where IP is administered. Study personnel must be trained to recognise and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix G.

Anaphylaxis will be defined as a serious reaction that is rapid in onset (minutes to hours) and that may result in death (Sampson et al 2006). Anaphylaxis to an IP that the subject has not been previously exposed to (such as tezepelumab) is deemed highly likely when Sampson criterion 1 is fulfilled. Sampson criteria 2 and 3 are also listed for completeness:

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 BP or symptoms of end-organ dysfunction.

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient including: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms and/or persistent gastrointestinal symptoms.

3 Reduced BP after exposure.

Patients will have had a pre-assessment (ie, vital signs) prior to IP administration and the sponsor recommends that patients should be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local laboratory at the discretion of the Investigator.

8.4 Overdose

For this study, any dose of tezepelumab greater than 140 mg will be considered an overdose.

- 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 drug occurs at Visit 2, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 8.3.8) 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 C.

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 (PK) samples will be disposed of after the Bioanalytical Report finalisation or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 characterisation 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.

Standard numbing medications/devices and/or distraction techniques may be used with blood draws.

8.5.1 Pharmacokinetics

Blood samples for the determination of serum concentrations of tezepelumab will be collected as specified in the SoA (Table 1). A serum sample for PK analysis will be collected within ± 1 hour of the time the baseline Day 1 sample was collected, across the different study days. On Day 1, the serum sample for PK analysis will be taken 1 hour prior to IP administration.

If required, blood samples for PK analysis may be taken by a study nurse at the subject's home on the Day 11 visit, if previously approved and agreed with AstraZeneca.

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

8.5.1.1 Pharmacokinetic Drug Assays

Blood samples for determination of tezepelumab concentrations in serum will be analysed by a designated third party on behalf of AstraZeneca, using a validated assay.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

8.5.2.1 Immunogenicity Testing

Blood samples for determination of anti-tezepelumab antibodies in serum will be analysed by a designated third party on behalf of AstraZeneca, using a validated assay.

Blood samples for determination of anti-tezepelumab antibodies in serum will be collected as specified in the SoA (Table 1). A serum sample for immunogenicity analysis will be collected within ± 1 hour of the time the baseline Day 1 sample was collected, on Day 29 and Day 85/EOS. On Day 1, the serum sample for immunogenicity analysis will be taken within 1 hour prior to IP administration.

In the event of a suspected immunologically-related AE, an unscheduled ADA sample will be collected.

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

The presence or absence of ADAs will be determined in the serum samples. A tiered testing scheme will be employed, with the first step being screening. Samples found putative positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo titre determination. Samples confirmed positive for ADA will be archived for possible testing for neutralising antibodies (nAb).

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

8.5.3 Pharmacodynamics

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8.6 Human Biological Sample Biomarkers (Not applicable)

Serum samples will be collected to be analysed for total immunoglobulin E (IgE). The analysis will be performed at the central laboratory.

8.7 Optional Genomics Initiative Sample (Not applicable)

Optional Genomics Initiative research is not applicable in this study.

8.8 Health Economics (Not applicable)

8.9 Pandemic Impact Assessment

To assess the impact of the COVID-19 pandemic on the study, sites will be asked to complete the pandemic related information in the eCRF at each study visit.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypothesis tests will be made. Data will be summarised descriptively.

9.2 Sample Size Determination

No formal sample size calculation was conducted for this study. The number of subjects was based on the desire to obtain adequate PK and safety data while exposing as few paediatric subjects as possible to tezepelumab and study procedures. A total of 12 subjects is considered sufficient to provide adequate data to characterise PK of tezepelumab in children aged ≥ 5 to 11 years. At least 4 subjects will have body weight < 25 kg and a minimum of 3 subjects will have body weight ≥ 25 kg and < 40 kg. Approximately 14 subjects will receive tezepelumab in an attempt to have at least 12 subjects complete the study.

9.3 Populations for Analyses

The following populations are defined (Table 10):

Table 10 Populations for Analysis

Population/analysis set	Description
Enrolled	All subjects who sign the ICF.
Safety	All subjects who receive at least one dose of tezepelumab.
PK	Subjects in the Safety Analysis set that have at least one detectable tezepelumab serum concentration from a sample collected post-dose that is assumed not to be affected by factors such as important protocol deviations (eg, incorrect dose of study IP received).

ICF Informed consent form; PK Pharmacokinetic.

All PK summaries will be based on the PK analysis set. Anti-drug antibodies and CCI [redacted] summaries and safety presentations will be based on the safety analysis set.

9.4 Statistical Analyses

A comprehensive statistical analysis plan will be developed and finalised prior to DBL and 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 key secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

No formal statistical hypothesis tests will be made. Data will be provided in data listings

sorted by subject number. Tabular summaries will be presented. Categorical data will be summarised by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics, including number of subjects, mean, standard deviation, median, minimum and maximum for non-PK data. Median will be presented together with first and third quartile if appropriate. For the summary of PK concentration levels, in addition, geometric mean and coefficient of variation (CV%) based on log-transformed data will be presented. Unless otherwise stated, all summary tables will present descriptive statistics and/or frequency by visit.

Frequency and percentages of subject disposition and reasons for withdrawal from the study will be presented. Subjects who withdraw from the study will be listed along with the reason for discontinuation.

Frequency and percentages of subjects in each analysis population will be provided.

Demographics and subject characteristics will be summarised using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) using both the PK and safety analysis set.

Relevant medical history/current medical conditions will be coded using the version in force at DBL of the Medical Dictionary for Regulatory Activities (MedDRA) and summarised by system organ class (SOC) and preferred term (PT) using frequency and percentage of subjects. Virology results obtained at screening will be summarised using frequency and percentage of subjects presenting HBsAg, HCAb, HIV-1 and HIV-2.

Prior and concomitant medications, categorised according to the World Health Organization (WHO) Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarised as frequency and percentage of subjects reporting usage. Prior medications are defined as those which stopped before IP. Concomitant medications are defined as those which either started or continued after IP.

Important protocol deviations will be defined at subject level prior to DBL and will be summarised and listed. The definitions of each category of important protocol deviation will be fully specified in the study Non-Compliance Handling Plan and will include (but may not be limited to): subjects who received IP without fulfilling key entry criteria; subjects who received prohibited or restricted concomitant medications during the study; subjects who received the incorrect IP dose.

In general, the last valid non-missing measurement taken on or prior to the date of treatment will serve as the baseline measurement. If there is no value on or prior to the date of treatment, then the baseline value will not be imputed and will be set to missing.

Absolute change from baseline is defined as the difference between the relevant post-baseline value and the baseline value. Unless specified otherwise, "change from baseline" is assumed to be absolute change from baseline.

Further details regarding baseline and/or change from baseline definitions will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

All PK analyses will be based on the PK analysis set. Tezepelumab serum concentration data will be listed by individual and summarised by nominal time using descriptive statistics, including N, geometric mean, geometric CV%, arithmetic mean, arithmetic SD, median, minimum and maximum. The mean and individual serum tezepelumab concentrations will be plotted over time. Based on the serum concentration-time data of tezepelumab, the following PK parameters will be estimated using noncompartmental analysis method as appropriate: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, C_{max}, t_{max}, terminal $t_{1/2}$, CL/F and V_{ss}/F. Additional PK parameters may be reported if appropriate. PK parameters will be listed by individual and summarised using descriptive statistics. The PK analysis will be performed using WinNonlin® version 5.1 or higher.

The PK data obtained in this study may be included in a population PK analysis, as appropriate, to assess any PK differences between children aged ≥ 5 to 11 years and adults/adolescents, and guide dosing for future studies of tezepelumab in paediatric subjects. If conducted, this analysis will be reported separately from the CSR.

9.4.2.2 Secondary Endpoints

The prevalence and incidence of ADA to tezepelumab will be reported using the safety analysis set. Anti-drug antibodies data will be summarised using descriptive statistics by visit. Samples confirmed positive for ADA will be archived for possible testing for nAb. The potential effects of ADA on PK and safety will be evaluated, if appropriate.

9.4.2.3 Exploratory Endpoints

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9.4.3 Safety

Safety analyses will be performed using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

Verbatim terms of AEs will be coded to a standardised PT using the MedDRA version in force at DBL.

The overall number and percentage of subjects with AEs and SAEs will be presented. The occurrence of AEs and SAEs will be described also by SOC, PT and separately by severity and by relationship to the IP (as determined by the Investigator). Should a subject report the same PT/SOC within multiple severity or relationship categories, the subject's worst occurrence (most severe/most related) will be tabulated.

Serious AEs, AEs leading to death, AEs leading to withdrawal from study, commonly occurring AEs and AESIs will be summarised by SOC and PT.

Laboratory data, including serum chemistry, haematology and urinalysis will be summarised by presenting summary statistics of observed and change from baseline values at each scheduled assessment visit. Shift tables using normal ranges (baseline to most extreme postbaseline value) will also be presented. The incidence of clinically notable laboratory abnormalities will be summarised. Shift tables will also be provided.

Number of subjects with elevated liver function tests that meet the HL definition will be summarised and evaluated.

Vital signs data will be summarised by presenting summary statistics of observed and change from baseline values at each scheduled assessment visit. The incidence of clinically notable vital signs abnormalities will be summarised.

Abnormal ECGs as per Investigator's overall interpretation will be summarised using frequency and percentage of subjects.

Additional analyses assessing the impact of COVID-19 may be included in the SAP.

9.4.4 Other Analyses

There are no other analyses planned for this study.

9.5 Interim Analyses

There are no interim analyses planned for this study.

9.6 Data Monitoring Committee

The use of an Independent Data Monitoring Committee is not foreseen for this study.

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