
Clinical Study Protocol

Study Intervention	Tezepelumab
Study Code	D5180C00025
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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

Sponsor Name: AstraZeneca

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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: Not Applicable (N/A)

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

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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) 70 mg dose of tezepelumab in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma (Global Initiative for Asthma [GINA] 2019 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 70 mg dose of tezepelumab.

Objectives and Endpoints

Objectives	Outcome Measures
Primary	
<ul style="list-style-type: none"> To describe the PK parameters following a single SC administration of tezepelumab 70 mg in children with mild, moderate, or severe asthma 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> To evaluate the immunogenicity of tezepelumab 	<ul style="list-style-type: none"> Presence of anti-drug antibodies (ADA)
Safety	
<ul style="list-style-type: none"> To evaluate the safety and tolerability following a single SC administration of tezepelumab 70 mg 	<ul style="list-style-type: none"> Adverse events/serious adverse events Vital signs Laboratory parameters Electrocardiogram (ECG)

PK Pharmacokinetic; SC Subcutaneous.

For the exploratory objective (PD) and outcome measures, see Section 2 of the protocol.

Overall Design

This is a multicentre, open-label study designed to evaluate the PK profile of tezepelumab following a single SC 70 mg dose in children ≥ 5 to 11 years of age with mild, moderate, or severe asthma.

The study will be conducted in 3 to 5 sites in the United Kingdom.

Approximately 24 subjects will be enrolled such that at least 12 subjects complete the study. At least 12 paediatric subjects aged ≥ 5 to 11 years (inclusive) will receive a single SC 70 mg dose of tezepelumab. 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 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 70 mg 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 (AUC_{0-inf} , AUC_{0-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.

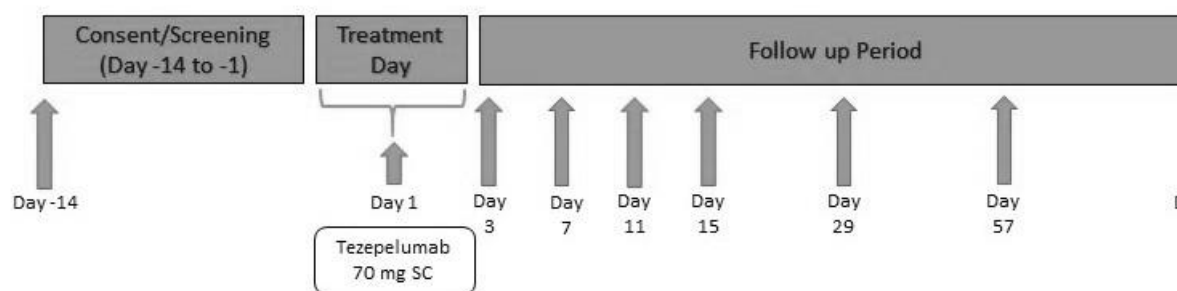
All PK summaries will be based on the PK analysis set. Anti-drug antibodies (ADA) and PD parameter summaries and safety presentations will be based on the safety analysis set.

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 treated with tezepelumab is considered sufficient to provide adequate data to characterise PK of tezepelumab in children ≥ 5 to 11 years of age.

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 3.1, Appendix Error! Reference source not found.
Assignment of SID number	X									Section Error! Reference source not found.
Verify eligibility criteria	X	X								Sections 3.1, 3.2
Demography	X									Section 3.1
Medical history	X									Section 3.1
Physical examination	X ^a	X ^a		X ^b			X ^b	X ^b	X ^a	Section Error! Reference source not found.
Weight	X	X					X		X	Sections 3.1, Error! Reference source not found. , Error! Reference source not found.

Table 1 Schedule of Activities

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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)	
Height	X	X							X	Section Error! Reference source not found.
12-lead ECG	X	X					X		X	Section Error! Reference source not found.
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	Section Error! Reference source not found.
Concomitant medications	X	X	X	X	X	X	X	X	X	Section Error! Reference source not found.
Vital signs	X	X ^c	X	X	X	X	X	X	X	Section Error! Reference source not found.
Serum chemistry and haematology ^d	X	X				X	X		X	Sections Error! Reference source not found., Error! Reference source not found.

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)	
Total IgE		X					X		X	Section Error! Reference source not found.
Urinalysis	X	X				X	X		X	Section Error! Reference source not found.
Pregnancy test (serum β-HCG)	X ^e									Section Error! Reference source not found.
Urine pregnancy test (dipstick)		X ^e							X ^e	Section Error! Reference source not found.
Urine drug screen		X								Section Error! Reference source not found.
Virology: HBsAg, HCAb; HIV-1, HIV-2	X									Section Error! Reference source not found.
Blood sample for PK analysis ^f		X ^g	X	X	X	X	X	X	X	Section Error! Reference source not found.

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)	
Serum for immunogenicity analysis ^{h,i}		X ^j					X		X	Section Error! Reference source not found.
Pre-BD Spirometry	X	X					X		X	Section Error! Reference source not found.
Post-BD Spirometry	X ^k	X ^l								Section Error! Reference source not found.
FENO		X				X	X		X	Section Error! Reference source not found.
PQoL (PAQLQ)		X				X	X		X	Section Error! Reference source not found.
IP Administration		X								Section Error! Reference source not found.

^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 Blood eosinophil levels (a PD endpoint) will be assessed from serum haematology (Section Error! Reference source not found.).

^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 **Error! Reference source not found.**). 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 Post-BD spirometry at V1 should only be done if historical reversibility is not available.
- ^l Post-BD spirometry at V2 is only required if historical reversibility is not available AND airway reversibility was not achieved at V1.

ADA Anti-drug antibodies; AE Adverse event; BD Bronchodilator; β -HCG Beta-human chorionic gonadotrophin; CSP Clinical Study Protocol; ECG Electrocardiogram; EOS End of Study; FENO Fractional exhaled nitric oxide; HBsAg Hepatitis B surface antigen; HCAb Hepatitis C antibody; HIV-1/-2 Human immunodeficiency virus; IgE Immunoglobulin E; IP Investigational product; nAb Neutralising antibodies; PAQLQ Paediatric Asthma Quality of Life Questionnaire; PD Pharmacodynamic; PK Pharmacokinetic; PQoL Paediatric Quality of Life; SAE Serious adverse event; SID Subject identification; V Visit.

2 OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are shown in Table 2.

Table 2 Objectives and Endpoints

Objectives	Outcome Measures
Primary	
<ul style="list-style-type: none"> To describe the PK parameters following a single SC administration of tezepelumab 70 mg in children with mild, moderate, or severe asthma 	<ul style="list-style-type: none"> 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	
<ul style="list-style-type: none"> To evaluate the immunogenicity of tezepelumab 	<ul style="list-style-type: none"> Presence of anti-drug antibodies (ADA)
Safety	
<ul style="list-style-type: none"> To evaluate the safety and tolerability following a single SC administration of tezepelumab 70 mg 	<ul style="list-style-type: none"> Adverse events/serious adverse events Vital signs Laboratory parameters Electrocardiogram (ECG)
Exploratory	
<ul style="list-style-type: none"> To evaluate the PD following a single SC administration of tezepelumab 70 mg 	<ul style="list-style-type: none"> Pulmonary function (FEV_1, FVC) Blood eosinophil levels FENO PQoL

FENO Fractional exhaled nitric oxide; FEV_1 Forced expiratory volume in one second; FVC Forced vital capacity; PD Pharmacodynamic; PK Pharmacokinetic; PQoL Paediatric Quality of Life; SC Subcutaneous.

3 STUDY POPULATION

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

3.1 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 **Error! Reference source not found..**

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 for at least 6 months prior to Visit 1.
- 4 Documented treatment with total daily dose of either low, medium, or high-dose ICS ($\geq 100 \mu\text{g}$ fluticasone propionate dry powder inhaler [DPI] or equivalent; see **Error! Reference source not found.**) for at least 6 months, as described in Step 2 to Step 4 of GINA guidelines (**Error! Reference source not found.**) 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 Evidence of asthma as documented by either:
 - (a) Historical airway reversibility, or
 - (b) Airway reversibility after use of an inhaled short-acting β_2 -agonist (SABA) ($\text{FEV}_1 \geq 12\%$) demonstrated at Visit 1, or at Visit 2 if not achieved at Visit 1 and historical airway reversibility is not available.
- 7 Pre-bronchodilator (BD) FEV_1 of $\geq 70\%$ 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 Body mass index for age at both screening and Day 1 that is between 5th and 95th percentile (Centers for Disease Control Growth Charts; see **Error! Reference source not found.**).

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.

3.2 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 3 months of Visit 1, up to and including Visit 2 (Day 1).
- 3 Use of systemic or intra-articular glucocorticosteroids for conditions other than asthma is not allowed within 3 months prior to Visit 2 and is discouraged until EOS.
- 4 History of hospitalisation (overnight admission) for asthma within 6 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 3 months 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 non-biologic 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 immunoglobulin 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) $> 2 \times$ 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 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

- 23 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.
- 24 Children who are wards of the state or government.
- 25 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).
- 26 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.
- 27 Previous enrolment in the present study.

3.3 Lifestyle Considerations

3.3.1 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 FENO test.

3.3.2 Activity

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

3.4 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. Only one rescreen attempt is allowed in the study and only if the reason for screen failure was transient (including but not limited to equipment failure, exclusion criterion #8 [Section 3.2], or other transient conditions). 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.