Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00011
Version	2.0
Date	03 July 2019

A Multicenter, Randomized, Open-label, Parallel-group, Functionality, and Performance Study of an Accessorized Pre-filled Syringe and Autoinjector with Home-administered Subcutaneous Tezepelumab in Adolescent and Adult Subjects with Severe Asthma (PATH-HOME)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

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VERSION HISTORY

Version 2.0, 03 July 2019

Changes to the protocol are summarized below.

Section 1.1 Schedule of Activities (SoA)

- Added a new footnote at "Review of the APFS/AI IFU and the Administration Questionnaire" to clarify review of the APFS/AI IFU and the administration questionnaire at Visit 1, review of the APFS/AI IFU, and completion of the administration questionnaire at Visits 2-7.
- Updated from "12-lead Electrocardiogram" to "12-lead (or 15-lead) Electrocardiogram" to permit 15-lead ECG.
- Updated footnote c from "The ±3-day window is related to the IP administration at home and not the clinic visit, which should occur no later than 48 hours after IP administration" to "The IP should be administered at home within a ±3-day window. The clinic visit should be done no later than 48 hours after IP administration." for clarity.
- The CSP section for ACQ-6 was corrected from "See Section 8.1.3" to "See Section 8.3.1".
- Footnote h was updated from "Pre- and post-bronchodilator spirometry can be done at Visit 1, optional Visit 1A, OR Visit 2." To "Pre- and post-bronchodilator spirometry can be done at Visit 1. If not met at Visit 1, pre- and/or post-BD spirometry can be done at optional Visit 1A OR Visit 2 to demonstrate reversibility." to specify the requirement.
- Footnote k was corrected from "PK and immunogenicity samples collected on dosing visits (Week 0, Week 4 and Week 20) should be collected prior to dosing." to "PK and immunogenicity samples collected on dosing visits should be collected prior to dosing." to be consistent with the table.

Section 5.1 Inclusion criteria

- Inclusion criterion #5 was updated from " Evidence of asthma as documented by either Airway reversibility after use of an inhaled short-acting beta-agonist (SABA) (FEV1 ≥12% and 200 ml) demonstrated at Visit 1, Visit 1A, or Visit 2 OR documented in the previous 12 months" to " Evidence of asthma as documented by postbronchodilator (albuterol/salbutamol) reversibility of $FEV_1 \geq 12\%$ AND ≥200 mL (15-60 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 12 months prior to V1, or demonstrated at V1, V1A, or at V2." to clarify lung function criteria.

- Inclusion criterion #8 was updated from "One or more exacerbation that required oral or systemic corticosteroids in the previous year, or an exacerbation that resulted in inpatient hospitalization for ≥ 24 hours" to " One or more exacerbations that required oral or systemic corticosteroids within 12 months prior to visit 1, or an exacerbation that resulted in inpatient hospitalization for ≥ 24 hours within 12 months prior to visit 1" to clarify the language.

Section 5.2 Exclusion criteria

- Exclusion criterion #4 was updated from "An acute upper or lower respiratory infection requiring antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the screening/run-in period." to "Either an acute upper or lower respiratory infection requiring antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the screening/run-in period, or an asthma exacerbation which resolved < 2 weeks before Visit 1 or which occurred during the screening/run-in period." in order to keep the screening assessments within 2 weeks of randomization.
- Exclusion criterion #6 was updated from "Current smokers or former smokers with a smoking history of ≥10 pack years. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible." to "Current smokers or former smokers with a smoking history of ≥10 pack years. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Users of electronic cigarettes, e.g. vaping, must have stopped for at least 6 months prior to Visit 1 to be eligible." to clarify that tobacco restrictions also apply to vaping and e-cigarette products.
- Added one additional exclusion criterion "Non-leukocyte depleted whole blood transfusion in 120 days prior to visit 1." to keep consistency with Appendix D Genetics.

Section 5.3.2 Alcohol, tobacco, and other

- Updated from "Current smokers or subjects with smoking history ≥ 10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Smoking is not allowed throughout the course of the study. The use of e-cigarettes is also not allowed during the course of the study." to "Current smokers or subjects with smoking history ≥ 10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Use of electronic cigarettes, e.g. vaping, is not allowed within 6 months of Visit 1. Smoking and vaping are not allowed throughout the course of the study.″ to clarify that tobacco restrictions also apply to vaping and e-cigarette products.

Section 5.4 Screen failures

- Updated from "Subjects who experience an asthma exacerbation during the screening/run-in period may remain in screening and proceed with study visits 14 days after they have completed their course of oral steroids or returned to their maintenance dose of oral steroids." to "Subjects who experience an asthma exacerbation during the screening/run-in period will be screen failed and may be re-screened after 14 days of complete resolution of the asthma exacerbation, and when the subjects return to baseline, at Investigator's discretion." in order to keep the screening assessments within 2 weeks of randomization.

Section 6.2.2 Dose Administration

- Updated from "The same person must administer the IP throughout the study, whether it is the subject or caregiver. For adolescent subjects who will self-administer the IP, the caregiver or an adult must supervise IP administration." to "The same person must administer the IP throughout the study, whether it is the subject or caregiver. The caregiver administering study drug must accompany the subject to all dosing visits after signing consent. Caregiver attendance to the EOT/IPD and Follow up visits is optional. For adolescent subjects who will self-administer the IP, the caregiver or an adult must supervise IP administration." to clarify that the caregiver attendance to the EOT/IPD and Follow up visits is optional.

Section 6.2.3 methods for return of used APFS/AI devices

- Updated from "Instruction for Use (IFU) provided to the subject with each IP kit will include instructions on how to properly package the used APFS/AI device in the Bio-bottle. Subjects will be instructed to bring the used APFS/AI device packaged in the Bio-bottle along with the completed administration questionnaire to the clinic during next center visit." to "Instruction for Use (IFU) is provided to the subject with each IP kit. Subjects will be instructed on how to properly package the used APFS/AI device in the Bio-bottle and return it along with the completed administration questionnaire to the clinic during next center visit."to keep consistent.

Section 6.5 Concomitant therapy

- Updated from "Prior to the date of randomization, a history of continuous treatment with medium or high dose ICS plus a second controller medication for at least 6 months prior to Visit 1 should be documented in source documents and recorded in the eCRF." to "Prior to the date of randomization, a history of continuous treatment with medium or high dose ICS for at least 6 months prior to Visit 1 plus a second controller medication for at least 3 months prior to Visit 1 should be documented in source documents and recorded in the eCRF." to keep consistent with inclusion criterion #6.

Section 7.1 Discontinuation of study treatment

- Removed the bullet point from "Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. The subject is at any time free to discontinue treatment, or to discontinue from the study without prejudice to further treatment".
- Added "Subjects or subjects with caregivers who are unable or unwilling to administer investigational product (IP) at Week 8 (Visit 4)" to clarify that subjects/caregivers unwilling to administer IP is a discontinuation criterion.
- Updated from "Development of any study specific criteria for discontinuation, including any malignancy" to "Development of any study specific criteria for discontinuation, including any malignancy except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided the malignancy is excised and determined to have clean margins" for clarity.

Section 7.1.1 Procedures for discontinuation of study treatment

- Updated from "All subjects who prematurely discontinue IP should return to the study centre and complete the procedures described in the Premature IP Discontinuation (IPD) visit after 4 weeks (± 3 days) and the procedures for the Follow-up visits after 10 weeks (± 3 days) and 16 weeks (± 3 days) of the last IP administration." to "All subjects who prematurely discontinue IP and who do not withdraw their consent from the study, should return to the study centre and complete the procedures described in the Premature IP Discontinuation (IPD) visit after 4 weeks (± 3 days) and the procedures for the Follow-up visits after 10 weeks (± 3 days) and 16 weeks (± 3 days) of the last IP administration." to clarify the language.

Section 8.1.4.1 General requirements

- Updated from "If possible, subjects should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below" to "Subjects should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below" to clarify the language.

Section 8.2.1.1 Pregnancy test

- Updated from "Serum ß-human chorionic gonadotropin (ß-HCG) – the test will be mandatory at enrolment (Visit 1) and at EOT visit, for women of child-bearing potential (WOCBP)." to "Serum ß-human chorionic gonadotropin (ß-HCG) – the test will be mandatory at enrolment (Visit 1) and if any positive urine test result, for women of child-bearing potential (WOCBP)." to keep consistent with Section 1.1 Schedule of Activities (SoA).

Section 8.2.4 Electrocardiograms

- Updated from "A 12-lead ECG will be taken in supine position and after the subject has rested for at least 15 minutes." to "A 12-lead *(or 15-lead)* ECG will be taken with the subject in the supine position and after the subject has rested for at least *5* minutes." to permit 15-lead ECG and clarify 5 minutes rest is sufficient to ensure accurate reading.

Section 8.3.1 Asthma Control Questionnaire (ACQ-6)

- Updated from "Patient reported outcomes using ACQ-6 will be performed at the study site with paper questionnaires. Subjects will be given a paper questionnaire and be asked to complete and return these in accordance to the schedule provided in the Schedule of Activities (SoA). The Investigator/authorized delegate will check the questionnaires for completion to minimize missing data and record responses in the eCRF." to "Patient reported outcomes using ACQ-6 will be performed at the study site with paper questionnaires. Subjects will be given a paper questionnaire and be asked to complete and return these in accordance to the schedule provided in the Schedule of Activities (SoA). ACQ-6 should be completed as a first procedure during the visit. The Investigator/authorized delegate will check the questionnaires for completion to minimize missing data and record responses in the eCRF." to clarify that ACQ-6 should be first performed during the visit.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

- Corrected a typo from "Specific guidance on managing liver abnormalities can be found in Section 6.1 of the Clinical Study Protocol." to "Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.".

Appendix F Maintenance Therapy Equivalence Table

- Removed as part of the table "Inhaled Corticosteroid in ICS/LABA combination" and footnote e as it is not part of GINA 2018.

Appendix I Accessorized Prefilled Syringe Administration Questionnaire for the D5180C00011 Clinical Study; Appendix J Autoinjector Administration Questionnaire for the D5180C00011 Clinical Study

- Removed one box in the kit ID because the kit ID is comprised of 5 digits.
- Added "Date and time Investigational Product (IP) is removed from the refrigerator" to ensure adequate documentation of IP administration.
- Specified "Left and Right locators for injection in the Abdomen (belly)" to keep consistent with Figure 2 Suggested schema of rotation of injection sites.

• Added "Date and time administration questionnaire was completed by person performing the injection" for clarification to ensure adequate documentation of IP administration.
Version 1.0, 19 February 2019
Initial Version, 1.0

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.

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1. PROTOCOL SUMMARY

For a detailed schedule of activities (SoA), please see Section 1.1 below:

1.1 Schedule of Activities (SoA)

Table 1 - Schedule of Assessments

All assessments will be done at clinic visits unless otherwise specified.

Schedule of screening, treatment, and follow-up periods														
	Screening/Run-in		**Randomization**	**Treatment**					**EOT**	**IPD**	**FU**	**FU**	**UNS[t]**	**Details in CSP Section or Appendix**
Visit number	**V1**	**V1A[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**		**V9**	**V10**		
Procedure / Study week	**W -2**		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		**W30**	**W36**		
Visit window (days)[b]	**0**	**V1 + max. 3 days**	**±3**	**±3**	**±3**	**±3[c]**	**±3[c]**	**±3**	**±3**		**±3**	**±3**	**NA**	
Routine Clinical Procedures														
Written informed consent	X													See Appendix A 3
Inclusion/exclusion criteria	X	X	X											See Section 5.1 & 5.2
Demography	X													See Section 4
Medical/surgical and asthma history	X													See Section 4
Weight, Height, BMI	X													See Section 8.2.5
Review of the APFS/AI IFU and the Administration Questionnaire[d]	X		X	X	X	X	X	X						See Section 4.1 and 6.2.3

Schedule of screening, treatment, and follow-up periods														
	Screening/Run-in		Randomization	Treatment					EOT	IPD	FU	FU	UNS[t]	Details in CSP Section or Appendix
Visit number	**V1**	**V1A[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**		**V9**	**V10**		
Procedure / Study week	**W -2**		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		**W30**	**W36**		
Visit window (days)[b]	**0**	**V1 + max. 3 days**	**±3**	**±3**	**±3**	**±3[c]**	**±3[c]**	**±3**	**±3**		**±3**	**±3**	**NA**	
Routine Safety Procedures														
Complete physical examination	X								X	X		X		See Section 8.2.2
Brief physical examination			X	X	X	X	X	X			X		X	See Section 8.2.2
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	See Section 8.2.3
12 lead (or 15 lead) Electrocardiogram	X													See Section 8.2.4
Adverse Events (AEs/SAEs)	X		X	X	X	X	X	X	X	X	X	X	X	See Section 8.7
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X	See Section 6.5
Laboratory Assessments														
Serum chemistry	X		X						X	X		X	X	See Section 8.2.1
Hematology	X		X						X	X		X	X	See Section 8.2.1
Serology (Hepatitis B, C, HIV-1, HIV-2)	X													See Section 8.2.1.2
Urinalysis	X		X						X	X		X	X	See Section 8.2.1
Blood concentration (theophylline)[e]	X													See Section 6.5

Schedule of screening, treatment, and follow-up periods														
	Screening/Run-in		Randomization	Treatment					EOT	IPD	FU	FU	UNS[t]	Details in CSP Section or Appendix
Visit number	**V1**	**V1A[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**		**V9**	**V10**		
Procedure / Study week	**W -2**		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		**W30**	**W36**		
Visit window (days)[b]	**0**	**V1 + max. 3 days**	**±3**	**±3**	**±3**	**±3[c]**	**±3[c]**	**±3**	**±3**		**±3**	**±3**	**NA**	
Pregnancy test (serum βHCG)	X													See Section 8.2.1.1
FSH[f]	X													See Section 8.2.1.1
Urine pregnancy test (dipstick)[g]			X	X	X	X	X	X	X	X	X	X		See Section 8.2.1.1
At home urine pregnancy test before IP administration[g]						X	X							See Section 8.2.1.1
Lung Function Assessments														
Pre- and post-bronchodilator spirometry[h]	X	X	X[i]											See Section 8.1.4
Patient Reported Outcomes Assessments														
ACQ-6	X		X	X	X	X	X	X	X	X				See Section 8.3.1
Pharmacokinetic Assessments														
Serum for PK			X[k]	X[k]				X[k]	X	X		X		See Section 8.4
Serum for Immunogenicity[j]			X[k]	X[k]					X	X		X		See Section 8.4.2
Pharmacogenetic Sampling														
Blood for DNA (Optional)[l]			X											See Section 8.6
Study Treatment Administration														

Schedule of screening, treatment, and follow-up periods														
	Screening/Run-in		Randomization	Treatment					EOT	IPD	FU	FU	UNS[t]	Details in CSP Section or Appendix
Visit number	**V1**	**V1A[a]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**		**V9**	**V10**		
Procedure / Study week	**W -2**		**W0**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**		**W30**	**W36**		
Visit window (days)[b]	**0**	**V1 + max. 3 days**	**±3**	**±3**	**±3**	**±3[c]**	**±3[c]**	**±3**	**±3**		**±3**	**±3**	**NA**	
Randomization			X											See Section 6.3
IP Administration at site			X[m]	X[n]	X[o]			X[o]						See Section 6.2.1
At home IP administration						X[o]	X[o]							See Section 6.2.1
Completion of Administration Questionnaire at site			X[p]	X[q]	X[r]			X[r]						See Section 4.1
At home completion of Administration Questionnaire						X[r]	X[r]							See Section 4.1 & 6.2.3
Visit reminder call[s]						X	X							See Section 6.2.1
Return of APFS/AI and the Administration Questionnaire						X	X							See Section 6.2.3

[a] Visit 1A is optional for spirometry measurement only if criteria not met at Visit 1.
[b] All visits are to be scheduled from the date of Visit 2 but not from the date of previous visit except in the case of early discontinuation from IP.
[c] The IP should be administered at home within a ±3-day window. The clinic visit should be done no later than 48 hours after IP administration.
[d] Review of the APFS/AI IFU and the Administration Questionnaire at visit 1. Review of the APFS/AI IFU and complete the Administration Questionnaire at visit 2-7.
[e] If not documented prior to Visit 1, to be obtained at Visit 1 for subjects who are on theophylline.
[f] FSH test done only for female subjects to confirm postmenopausal status in women <50 years who have been amenorrhoeic for >12 months.
[g] For WOCBP only, a urine HCG test must be done prior to IP administration at Visits 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), and Visit 7 (Week 20) at the study center. At-home urine pregnancy tests are to be done by WOCBP prior to IP administration at Visit 5 (Week 12) and Visit 6 (Week 16) and repeated by the site staff at Visits 5 and 6. In the case of a positive urine pregnancy test at home, the subject is NOT to administer IP and is to call the study

center. Urine pregnancy tests will also be done at the study center at the EOT Visit 8 (Week 24), Follow-up Visits 9 (Week 30) and 10 (Week 36), and IPD visit (if applicable).

[h] Pre- and post-bronchodilator spirometry can be done at Visit 1. If not met at Visit 1, pre- and/or post-BD spirometry can be done at optional Visit 1A, OR Visit 2 to demonstrate reversibility.

[i] Visit 2 spirometry only to be performed if criteria not met at Visit 1 or Visit 1A and if no documented historical reversibility.

[j] In the event of suspected immunologically related adverse event, an unscheduled ADA sample will be collected.

[k] PK and immunogenicity samples collected on dosing visits should be collected prior to dosing.

[l] If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit (see Appendix D)

[m] Study drug to be administered on site by HCP in the upper arm, thigh, or abdomen.

[n] At Visit 3, the subject/caregiver has the option to administer the study drug on site under HCP supervision.

[o] At Visits 4 and 7, the subject/caregiver must administer the study drug on site under HCP supervision. At Visits 5 and 6 the subject/caregiver must administer the study drug at home. If self-administered by the subject, the study drug can be given in the thigh or abdomen. If administered by the caregiver, the sites of injection are in the arm, thigh, or abdomen.

[p] Administration questionnaire to be completed by HCP immediately after administration of IP.

[q] Administration questionnaire to be completed by HCP, subject, or caregiver (whomever administered the injection) immediately after administration of IP.

[r] Administration questionnaire to be completed by subject or caregiver (whomever administered the injection) immediately after administration of IP.

[s] Study center to perform visit reminder call to the subject within 48 hours prior to scheduled home administration date for Visit 5 (Week 12) and Visit 6 (Week 16).

[t] At unscheduled visits, the assessment/activity listed above is only the minimum needed to be performed. Unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

ACQ-6 Asthma Control Questionnaire; APFS Accessorized prefilled syringe; β-HCG Beta human chorionic gonadotropin; BMI Body-mass index; EOT End of Treatment, FSH Follicle-stimulating hormone; FU Follow Up; HCP Health care professional; HIV Human immunodeficiency virus; IFU Instructions for use; IP Investigational product; IPD Investigational Product Discontinuation; AI Autoinjector; NA Not applicable; V Visit; WOCBP Women of childbearing potential.

1.2 Synopsis

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Protocol Title: A Multicenter, Randomized, Open-label, Parallel-group, Functionality, and Performance Study of an Accessorized Pre-filled Syringe and Autoinjector with Home-administered Subcutaneous Tezepelumab in Adolescent and Adult Subjects with Severe Asthma (PATH-HOME)

Short Title: Tezepelumab Home Use Study

Rationale:

The purpose of this study is to assess the functionality and performance of the accessorized pre-filled syringe (APFS) and autoinjector (AI) used to administer a fixed 210 mg dose of tezepelumab subcutaneously (SC) in the clinic and in an at-home setting.

Objectives and Endpoints	
Primary objective:	**Endpoint/variable:**
To assess the successful administration of tezepelumab 210 mg SC by injection with an APFS or AI device in clinic and at home	• Proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an APFS • Proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an AI
Secondary objectives:	**Endpoint/variable:**
To assess the functionality of the APFS or AI devices utilized to administer tezepelumab in clinic and at home	• Proportion of used/returned APFS devices that passed functional tests and visual inspection and showed no evidence of malfunction • Proportion of used/returned AI devices that passed functional tests and visual inspection and showed no evidence of malfunction

Objectives and Endpoints	
To assess the performance of APFS or AI devices used to administer tezepelumab in clinic and at home	• Proportion of APFS devices that have been reported as malfunctioning (Product Complaints) • Proportion of AI devices that have been reported as malfunctioning (Product Complaints)
To monitor the metrics of asthma control	• Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) score
To assess the pharmacokinetics and immunogenicity of tezepelumab administered via APFS or AI in clinic and at home	• Serum trough concentrations • Anti-drug antibodies (ADA)
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of tezepelumab	• Adverse events/serious adverse events • Laboratory parameters

Overall design:

This is a Phase 3, multicenter, randomized, open-label, parallel-group study designed to assess HCPs and subjects/caregivers reported functionality and performance of a single-use APFS and AI with a fixed 210 mg dose of tezepelumab administered SC in the clinic and an at-home setting.

The study will consist of a screening/run-in period up to 2 weeks, a treatment period of 24 weeks and post-treatment follow-up period of 12 weeks. During the treatment period, one dose level of tezepelumab 210 mg will be administered via a single-use APFS or AI subcutaneously (SC) every 4 weeks (Q4W) starting at Week 0 until Week 20. IP will not be administered at Week 24.

Study Period:

Estimated date of first subject enrolled Q2 2019.

Estimated date of last subject completed Q3 2020.

Number of Subjects:

No hypotheses will be tested statistically. Approximately 210 subjects with severe asthma will enter the treatment period to receive 6 SC doses (Week 0, Week 4, Week 8, Week 12, Week 16, and Week 20) of tezepelumab. The first 3 doses of tezepelumab will be administered in the clinic, the next 2 doses will be administered at home, and the last dose will be administered at the clinic. Approximately 20 adolescents aged ≥12 to <18 years will be included.

Subjects will be randomized globally in a 1:1 ratio to the following groups.

- Tezepelumab 210 mg to be administered SC via APFS

- Tezepelumab 210 mg to be administered SC via AI

It is anticipated that approximately 5% of subjects will drop out and thus it is estimated that approximately 100 subjects will complete the study for each device.

Treatments and treatment duration:

After initial enrolment and confirmation of entry criteria (Visit 1), subjects will proceed to a run-in period of 2 weeks. Subjects who meet the eligibility criteria during screening and randomization criteria at Day 0 will be randomized to a 24-week treatment period. Follow-up visits will be conducted at Week 30 and Week 36. The total planned study duration is a maximum of 38 weeks.

Statistical methods

The primary endpoint assessing successful administrations and the secondary endpoints assessing the functionality and performance of the device, will be presented by visit using proportions and 95% confidence intervals for the proportions for each of the AI and APFS. The secondary endpoint, change from baseline in ACQ-6 score, will be summarized descriptively by device.

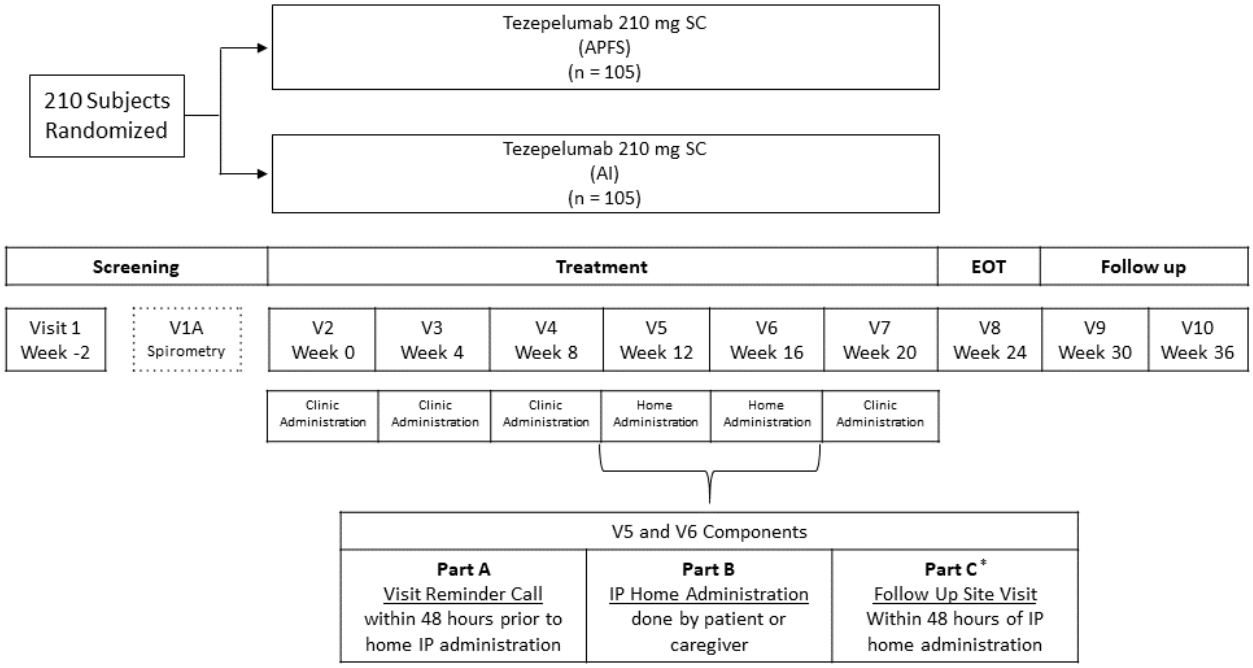
Safety endpoints will be analysed using the safety analysis set, with subjects assigned to the device they used to administer study medication. Descriptive statistics will be used to summarize the safety outcomes by treatment group. Laboratory data will be summarized by presenting shift tables and summary statistics.

Tezepelumab serum trough concentrations will be summarized using descriptive statistics at each visit for each device separately. The prevalence and incidence of anti-drug antibodies (ADA) will be reported for each device. ADA data will be summarized using descriptive statistics at each visit by device.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



Sponsor recommends home IP administration to be performed during study center working hours in case of any questions/issues

* Patient is to return used APFS or AI with completed administration questionnaire to the Study Site.

APFS - Accessorized prefilled syringe; IP - Investigational product; AI - autoinjector; SC - Subcutaneous; V - Visit

2. INTRODUCTION

2.1 Study rationale

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP and is currently being evaluated for severe asthma.

In the current global Phase 3 asthma clinical program, 210 mg of tezepelumab (or placebo) is administered as a single 1.91 mL subcutaneous (SC) injection (110 mg/mL) via vial (with disposable syringe) Q4W at the clinic. An accessorized pre-filled syringe (APFS) and auto-injector (AI) have been developed to enable safe, effective and convenient tezepelumab administration by caregivers and patients in a home use environment in addition to administration by health care professionals (HCPs) in the clinic. The purpose of this study is to assess the functionality and performance of the APFS and AI used to administer a fixed 210 mg dose of tezepelumab SC in the clinic and an at-home setting.

2.2 Background

Biologic therapies have been shown to reduce the annualised asthma exacerbation rate (AAER) in severe asthma patients who are uncontrolled with medium to high dose ICS and additional asthma controller medications. Omalizumab provided benefit for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with an inhaled corticosteroid (ICS) plus a long-acting beta-agonist (LABA) (Xolair US PI 2018). Four additional biologics, mepolizumab, reslizumab, benralizumab and dupilumab, have recently been approved for severe asthma with an eosinophilic phenotype (Nucala US PI 2017;Cinqair US PI 2019; Fasenra US PI 2017; Dupixent US PI 2018). Biologics targeting IL-5 and IgE are now included in international treatment guidelines (GINA 2018) as an add-on treatment to patients uncontrolled with ICS/LABA treatment. However, even when using currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2016; Fasenra US PI 2017; Froidure et al. 2016; Swedin et al. 2017). Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among patients with severe asthma, independently of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in responses to proinflammatory stimuli (e.g., infectious, allergic and environmental stimuli) and trauma. TSLP 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 T2 driven asthma (Kaur and Brightling 2012). Asthma is recognized as a heterogeneous disease, though, and there are subsets of patients that do not exhibit T2-associated disease (Wenzel 2012). Emerging data indicates that TSLP may also mediate non-allergic (non-T2) inflammation (Tanaka et al. 2009, Ziegler et al. 2013).

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with the TSLP receptor (TSLPR). Owing to the central role of TSLP as an upstream and pleiotropic cytokine in mediating asthma pathophysiology, anti-TSLP therapy is anticipated to have a 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 area-under-the-curve (AUC) for the percent fall in the forced expiratory volume in one second (FEV_1) and the maximum percent fall in FEV_1. Tezepelumab also attenuated the increase in fractional expired nitric oxide value on the post-allergen day compared with the pre-allergen day. Multiple doses of 700 mg IV tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed anti-drug antibodies (ADA) after receiving tezepelumab (Gauvreau et al. 2014). Based upon these data, the MedImmune/AstraZeneca conducted a randomized, 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 was a Phase 2b multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, 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 randomized in a 1:1:1:1 ratio to 1 of 3 dose levels of subcutaneous (SC) tezepelumab (70 mg every 4 weeks [Q4W], 210 mg Q4W, 280 mg every two weeks [Q2W]) or placebo (Q2W) for 52 weeks. Anomalous data at a single site was identified following completion of this study and due to GCP non-compliance, all data relating to 34 subjects from this site were excluded and the CSR revised. Consequently, a total of 550 subjects received at least 1 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 pharmacokinetics (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 neutralizing 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 adverse events (TEAEs) were similar between the placebo (65.9%) and the total tezepelumab (66.0%) dose groups. 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, and at similar incidence between the tezepelumab (5 subjects [1.2%] overall) and placebo (1 subject [0.7%]) groups. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no identified safety risks were noted (Corren et al, 2017).

A detailed description of the chemistry, pharmacology, efficacy, and safety of tezepelumab is provided in the Investigator's Brochure.

2.3 Benefit/risk assessment

In order to evaluate the clinical benefit-risk balance for tezepelumab, preclinical and clinical data have been taken into consideration, as well as a review of the available information for monoclonal antibodies that are approved for or are in development for the treatment of severe asthma. Benefits for tezepelumab over placebo include a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics.

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

The benefit/risk assessment for tezepelumab in severe asthma based on the development through Phase 2 is favorable. The future benefit / risk assessment will largely be defined by results from the Phase 3 program.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tezepelumab may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 2 - Study objectives

Objectives and Endpoints	
Primary objective:	**Endpoint/variable:**
To assess the successful administration of tezepelumab 210 mg SC by injection with an APFS or AI device in clinic and at home	• Proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an APFS • Proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an AI
Secondary objectives:	**Endpoint/variable:**

Objectives and Endpoints	
To assess the functionality of the APFS or AI devices utilized to administer tezepelumab in clinic and at home	• Proportion of used/returned APFS devices that passed functional tests and visual inspection and showed no evidence of malfunction • Proportion of used/returned AI devices that passed functional tests and visual inspection and showed no evidence of malfunction
To assess the performance of APFS or AI devices used to administer tezepelumab in clinic and at home	• Proportion of APFS devices that have been reported as malfunctioning (Product Complaints) • Proportion of AI devices that have been reported as malfunctioning (Product Complaints)
To monitor the metrics of asthma control	• Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) score
To assess the pharmacokinetics and immunogenicity of tezepelumab administered via APFS or AI in clinic and at home	• Serum trough concentrations • Anti-drug antibodies (ADA)
Safety objective:	**Endpoint/variable:**
To assess the safety and tolerability of tezepelumab	• Adverse events/serious adverse events • Laboratory parameters

4. STUDY DESIGN

4.1 Overall design

For an overview of the study design see Section 1.3, Figure 1. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

This is a Phase 3, multicenter, randomized, open-label, parallel-group study designed to assess the performance of a single-use APFS and AI with a fixed 210 mg dose of tezepelumab administered SC in the clinic and an at-home setting.

Approximately 210 subjects with severe asthma will enter the treatment period to receive 6 SC doses (Week 0, Week 4, Week 8, Week 12, Week 16, and Week 20) of tezepelumab. The first 3 doses of tezepelumab will be administered in the clinic, the next 2 doses will be administered at home, and the last dose at the clinic. Approximately 20 adolescents aged ≥12 to <18 years will be included as subjects.

As part of the informed consenting process, the APFS and AI Instructions For Use (IFU) and administration questionnaire (see Appendix I and Appendix J) will be reviewed. Following a 2-week screening period, eligible subjects will receive 4 SC doses of tezepelumab 210 mg at the clinic (Week 0, Week 4, Week 8 and Week 20) and 2 SC doses of tezepelumab 210 mg at home (Week 12 and Week 16). At Week 0, the HCP will administer the study drug. At Week 4, the subject or caregiver will have the option of administering the study drug under HCP supervision to ensure they understand the procedure and are capable of doing so. At Week 8, the subject or caregiver will have to perform the injection, again under HCP supervision. Subjects or subjects with caregivers who are unable or unwilling to administer investigational product (IP) at Week 8 (Visit 4) will be discontinued from the study.

At Week 12 and Week 16, tezepelumab will be self-administered by the subject or administered by the caregiver at home on weekdays when the physician office or clinic is open. The subject or caregiver will be given the IFU to refer for home administrations. After each of these administrations, the subject will return for a scheduled on-site visit within 48 hours. For adolescent subjects who will self-administer the IP, the caregiver or an adult must supervise IP administration. For adult subjects who will self-administer the IP, an adult must be present for IP administration.

The final dose of tezepelumab (Week 20) will be self-administered by the subject or administered by the caregiver at the clinic under HCP supervision in order to evaluate administration technique.

When IP is administered in the clinic at Week 0, Week 4, Week 8, and Week 20, the person administering the dose will fill out an administration questionnaire designed to indicate if the dose was successfully administered. The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

When IP is administered at home (Week 12 and Week 16), whether the subject is self-administering, or the caregiver is administering to the subject, the person administering the dose will fill out an administration questionnaire designed to indicate whether the dose was successfully administered. Both the completed questionnaire and the used device are to be returned to the site during each of the on-site visits scheduled within 48 hours of the home administration of IP (Week 12 and Week 16). The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

The same person must administer the IP at Weeks 4 (if administered by subject/caregiver), 8, 12, 16, and 20, whether it is the subject or caregiver. The caregiver must accompany the subject to all dosing visits after signing consent. Caregiver attendance to the EOT/IPD and Follow up visits is optional.

Section 6.5 (Table 4 and Table 5) provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial. In cases of asthma worsening/exacerbation (see Section 6.5), subjects should be evaluated at the study center when feasible.

4.2 Scientific rationale for study design

This is a multicenter, open-label trial designed to confirm the successful use and gain relevant information on the HCPs and subjects/caregivers use of the AI and APFS devices with tezepelumab both in the clinic and an at-home setting. The study design provides for HCP administration at Week 0, followed by HCP or optional subject/caregiver administration at Week 4. Subject/caregiver administration will take place at Week 8 and Week 20 in the clinic and at Week 12 and Week 16 at home. The design and duration of the study is intended to allow adequate time for HCP and subject/caregiver familiarity with the devices, provide oversight by site staff while in the clinic, and establish suitability of subject/caregiver use at home.

4.3 Justification for dose

A 210 mg Q4W dosing regimen was selected for the Phase 3 studies based on efficacy data and an exposure-response analysis from the Phase 2b Study CD-RI-MEDI9929-1146 using population PK/PD methodology. The population PK model of tezepelumab was developed based on all available data from 5 Phase 1 studies (Study 20070620, Study 20080390, Study 2010118, Study D5180C00003, Study D5180C00002), and 2 Phase 2 studies (Study D5240C00001 and Study CD-RI-MEDI9929-1146). The exposure-response analysis was based on the Phase 2b Study CD-RI-MEDI9929-1146.

Analysis of data from the Phase 2b study identified a statistically significant exposure-response against the primary efficacy endpoint of AAER and the pharmacodynamic (PD) endpoint of FeNO. These relationships indicate that the dose of 70 mg Q4W is a sub-optimally effective dose and the dose of 210 mg Q4W is optimally effective. In summary, characterization of AAER data from Study CD-RI-MEDI9929-1146 indicate the 210 mg Q4W dose provides improved efficacy over the 70 mg Q4W dose, whereas the 280 mg Q2W dose did not further reduce AAER. Tezepelumab was well-tolerated at all doses and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship to TEAEs in the adult population.

This study will use the same dose as the Phase 3 studies.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

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

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

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

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" subjects are defined as those who sign informed consent. "Randomized" subjects are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Provision of signed and dated written informed consent form prior to any mandatory study specific procedures, sampling, and analyses for subjects who are at, or over the age of majority (as per local law). For subjects, less than the age of majority, in addition to the subject providing informed assent, the subject's legal guardian must also provide their informed consent.

2. Provision of signed and dated written genetic informed consent prior to collection of optional sample for genetic analysis. Applicable to adult subjects only. (if applicable, refer to Appendix D for specific requirements for genetic sampling)

Age

3. Male and female subjects aged 12 to 80 years of age at the time of Visit 1.

Type of subject and disease characteristics

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

5. Evidence of asthma as documented by postbronchodilator (albuterol/salbutamol) reversibility of $FEV_1 \geq 12\%$ AND ≥ 200 mL (15-60 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 12 months prior to V1, or demonstrated at V1, V1A, or at V2.

6. Documented history of current treatment with medium- or high-dose ICS for at least 6 months prior to Visit 1 as per GINA guideline (GINA 2018) and at least one additional

asthma controller medication according to standard practice of care (e.g., LABA, LTRA, theophylline, LAMA, cromones, etc). Use of additional asthma controller medications must be documented for at least 3 months prior to Visit 1.

The ICS dose must be greater than or equal to 500 µg/day fluticasone propionate dry powder formulation or equivalent daily.

7. Morning pre-bronchodilator (pre-BD) FEV_1 of >50% predicted normal at Visit 1, Visit 1A, or Visit 2.

8. Not well controlled asthma as documented by either:

   – An ACQ-6 ≥1.5 at Visit 1 or Visit 2 OR
   – One or more exacerbations that required oral or systemic corticosteroids within 12 months prior to visit 1, or an exacerbation that resulted in inpatient hospitalization for ≥ 24 hours within 12 months prior to visit 1

9. Subject or caregiver must be willing and able to administer the IP. Caregiver must be 21 years of age or older at the time of Visit 1, if applicable.

Weight

10. Weight of ≥40 kg at Visit 1.

Reproduction

11. Negative serum pregnancy test for female subjects of childbearing potential at Visit 1.

12. Females of childbearing potential who are sexually active 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. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

    - A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Highly effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner, Etonogestrel (e.g. Implanon™), female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Medroxyprogesterone (e.g. Depo-Provera™) injections, oral contraceptive, Norelgestromin/ Ethinyl Estradiol patch (e.g. Evra Patch ™) or etonogestrel/ethinyl estradiol vaginal ring (e.g. Nuvaring™).

    - Adolescent specific recommendations: If subject is female and has reached menarche or has reached Tanner stage 3 breast development (even if not

having reached menarche), the subject will be considered a female of child bearing potential.

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age specific requirements apply:
    - Women < 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.
    - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

Inclusion criteria at randomization

13. For females of childbearing potential only: Have a negative urine pregnancy test prior to administration of the IP at day of Visit 2 (Week 0).

5.2 Exclusion criteria

Medical conditions

1. Any clinically important pulmonary disease other than asthma (e.g. active lung infection, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g. allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome).

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

3. History of cancer:

   - Subjects who have had basal cell carcinoma or localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible to participate in the study provided that curative therapy was completed at least 12 months prior to Visit 1.

   - Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to Visit 1.

4. Either an acute upper or lower respiratory infection requiring antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the screening/run-in period, or an asthma exacerbation which resolved < 2 weeks before Visit 1 or which occurred during the screening/run-in period.

5. 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.

6. Current smokers or former smokers with a smoking history of ≥10 pack years. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Users of electronic cigarettes, e.g. vaping, must have stopped for at least 6 months prior to Visit 1 to be eligible.

7. History of chronic alcohol or drug abuse within 12 months prior to Visit 1.

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

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

10. Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures requiring general anesthesia or in-patient status for >1 day during the conduct of the study.

Prior/concomitant medication therapy

11. Receipt of any marketed (e.g., omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 or receipt of any investigational non-biologic agent within 30 days or 5 half-lives (whichever is longer) prior to Visit 1.

12. Treatment with the following medications within the last 12 weeks prior to randomization: Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, etc.) except for OCS used in the treatment of asthma/asthma exacerbations.

13. Receipt of long acting beta-agonists as a reliever (e.g., Symbicort Maintenance and Reliever Treatment) within 15 days prior to Visit 1.

14. Receipt of the T2 cytokine inhibitor suplatast tosilate within 15 days prior to Visit 1.

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

16. Receipt of live attenuated vaccines 30 days prior to the date of Visit 2 (Week 0) and during the study, including the follow-up period.

    - Receipt of inactive/killed vaccinations (e.g., inactive influenza) is allowed provided they are not administered within 5 days before/after any tezepelumab administration.

17. Subjects who have been treated with bronchial thermoplasty in the 24 months prior to Visit 1.

18. Initiation of new allergen immunotherapy is not allowed within 2 months prior to Visit 1. Immunotherapy initiated prior to this period or as a routine part of the subject's seasonal treatment is allowed.

Genetic Research exclusion criteria

19. Previous allogeneic bone marrow transplant

20. Non-leukocyte depleted whole blood transfusion in 120 days prior to visit 1.

Prior/concurrent clinical study experience

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

22. History of anaphylaxis or documented immune complex disease (Type III hypersensitivity reactions) to any biologic therapy.

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

24. Subject randomization in the current study or previous tezepelumab studies.

Diagnostic assessments

25. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening period, 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 subjects' ability to complete entire duration of the study.

26. Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion of the Investigator may put the subject at risk or interfere with study assessments.

27. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase >2 times the upper limit of normal at Visit 1. Subjects with on-going liver disease or inexplicably elevated liver chemistry values should be excluded from the study.

28. 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 enroll.

Other exclusions

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

30. Judgment 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.

31. Pregnant, breast-feeding, or lactating women.

32. A serum β-HCG pregnancy test must be collected for women of childbearing potential at Visit 1. If test result is positive, the subject should be excluded.

5.3 Lifestyle restrictions

Subjects must abstain from donating blood and plasma from the time of informed consent and for 16 weeks (5 half-lives) after last dose of tezepelumab.

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 center.

5.3.2 Alcohol, tobacco, and other

Chronic alcohol, or drug abuse within 12 months is restricted prior to Visit 1 and throughout the conduct of the study.

Current smokers or subjects with smoking history ≥ 10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible. Use of electronic cigarettes, e.g. vaping, is not allowed within 6 months of Visit 1. Smoking and vaping are not allowed throughout the course of the study.

5.3.3 Activity

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

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomized. 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 serious adverse event (SAE).

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

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

Subjects with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the screening/run-in period may be re-screened (exclusion criterion 4) 14 days after recovery, (i.e., completion of the therapy).

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF).

Subjects who experience an asthma exacerbation during the screening/run-in period will be screen failed and may be re-screened after 14 days of complete resolution of the asthma exacerbation, and when the subjects return to baseline, at Investigator's discretion.

Any re-screened subject will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF), or assent form, and after all Visit 1 assessments have been performed as listed in Table 1 (with the exception of testing for HIV1 and HIV2, hepatitis B and C, and FSH).

Re-screened subjects should be assigned the same subject number as for the initial screening. However, re-screening should be documented so that its effect on study results, if any, can be assessed.

Re-screening of a subject will be allowed only upon approval of the AstraZeneca Study Physician.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to tezepelumab.

6.1 Treatments administered

6.1.1 Investigational products

All investigational products will be manufactured in accordance with Good Manufacturing Practice (GMP).

Table 3 - Study Treatment

	Treatment 1	Treatment 2
Study treatment name	Tezepelumab	Tezepelumab
Dosage formulation	CI	CI
Route of administration	Subcutaneous	Subcutaneous
Packaging and labelling	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each APFS will be labelled in accordance with GMP Annex 13 per country regulatory requirement. The labels will be translated into the local language where applicable.	Study treatment will be provided in an AI with 1.91 mL fill volume. Each AI will be labelled in accordance with GMP Annex 13 per country regulatory requirement. The labels will be translated into the local language where applicable.

APFS - Accessorized prefilled syringe; AI - Autoinjector; SC - Subcutaneously.

The APFS combination product is a single use, disposable device that is designed to enable manual, SC administration of tezepelumab from the prefilled syringe and automatically provide a safety mechanism to reduce the occurrence of accidental needlestick after injection.

The AI combination product is a single use, spring-based, disposable device that provides a means to automatically inject tezepelumab from a pre-filled syringe SC and provide needle safety to reduce the likelihood of an accidental needlestick after injection.

6.2 Preparation/handling/storage/accountability

Investigational Product will be supplied to the site in a kit with one device (either APFS or AI) of tezepelumab. Each kit has a unique number that is printed on all labels within the kit (i.e. the outer carton label and the label of each device within the carton).

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and

resolved before use of the IP. Tezepelumab 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 authorized site staff.

The IP must be kept in the original outer packaging and under conditions specified on the label (between 2°C to 8°C [36°F to 46°F], protected from light).

Only subjects enrolled in the study may receive and self-administer study treatment. Only authorized site staff may supply or administer study treatment. Only authorized caregivers may administer study treatment to the specific subject they have consented to provide administration of IP. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For at home administration, the subject will be responsible for refrigerating the product at home. Subjects can transport the IP in uncontrolled temperature conditions but should return it to a refrigerator as soon as possible. The temperature is not monitored during storage by the subject; standard refrigeration is sufficient to maintain appropriate temperatures while the IP is in the subject's possession. The subject will be responsible for returning used APFS/AI devices and completed administration questionnaires to the study center.

In the following cases neither the center staff nor the subject or caregiver should use the affected IP and should immediately contact an AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study center
- Damaged kit upon receipt
- Damaged APFS/AI device

Damaged IP should be documented via IWRS (please refer to IWRS manual for further details).

6.2.1 Dose Preparation

Prior to each IP administration at clinic site:

- Investigator/authorized delegate will assess injection site as per standards of medical care
- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 8.2.1.1)

Prior to each IP administration in at-home setting:

- Investigator/authorized delegate will perform visit reminder call within 48 hours prior scheduled IP administration. The conversation should include only basic information and serve as a reminder to the subject about the next scheduled visit to occur within 48 hours after home administration.
- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 8.2.1.1)

6.2.2 Dose Administration

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the Case Report Form (CRF). The IP will be administered at the study center for the first 3 doses, at home for the following 2 doses, and at the study center for the last dose.

The IP will be administered by the Investigator/authorized delegate/subject/caregiver as specified in Table 1. If subject is not willing or not able to self-administer (or caregiver is not willing/able to administer) at Visit 4, subject will be discontinued from the IP.

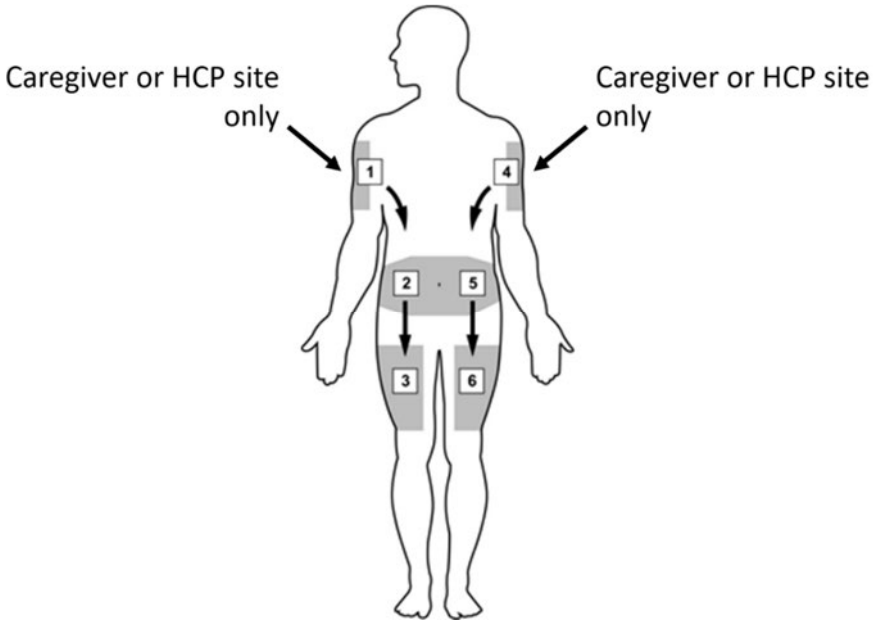
Each subject will receive tezepelumab 210 mg (one 1.91 mL injection) administered SC Q4W for 6 doses in the abdomen, thigh, or upper arm by APFS or AI.

It is suggested that the site of injection of the IP be rotated such that the subject receives IP at a different anatomical site each time. Suggested injection site rotation sequence is presented below (see Figure 2). In the case when rotation of the injection site is not favourable for the subject and/or Investigator, the reason should be recorded in the source documents. The injection site must be recorded in the source documents and the eCRF at each treatment visit.

If IP is self-administered by the subject, the injection should be done in the abdomen or thigh; when the injection is performed by the health care professional (HCP) or caregiver the injection can be made in the abdomen, thigh or upper arm (upper arm reserved only for injections performed by HCP or caregiver). The same person must administer the IP throughout the study, whether it is the subject or caregiver. The caregiver administering study drug must accompany the subject to all dosing visits after signing consent. Caregiver attendance to the EOT/IPD and Follow up visits is optional. For adolescent subjects who will self-administer the IP, the caregiver or an adult must supervise IP administration. For adult subjects who will self-administer the IP, an adult must be present for IP administration.

Further details on IP administration are provided in the Instruction for Use (IFU). Investigational product administration must be carried out in line with the instructions provided.

Figure 2 Suggested schema of Rotation of Injection Sites



At Visits 2 and 3 (Weeks 0 and 4), subjects should be observed by the HCP for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed by the HCP (or adult if injection was done at home) for a minimum of 1 hour after IP administration for the appearance of any such reaction. If IP administration was performed at home, the subject should visit the study center for the previously scheduled center visit within 48 hours after IP administration.

If any of the following occur, the Investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The subject received allergen immunotherapy injection on the same day as 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 (e.g., viral illnesses)
- The subject is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.

The subject and caregiver, if applicable, should be informed about these conditions and reminded prior to at-home administration. In case of any doubts before at-home administration, subject should contact study center.

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

6.2.3 Methods for return of used APFS/AI devices

Study sites will be shipped an appropriate number of Bio-bottles (hard plastic, wide-mouth bottles approved for containing and shipping biohazardous and/or sharps materials). Subjects who are given IP to administer at home will also be given one Bio-bottle for each of the two doses to be administered at home. The Bio-bottle will be given at the time the IP is provided to the subject.

Instruction for Use (IFU) is provided with each IP kit. Subjects will be instructed on how to properly package the used APFS/AI device in the Bio-bottle and return it along with the completed administration questionnaire to the clinic during next center visit.

The completed administration questionnaire and the Bio-bottle containing the used APFS/AI will be returned to the Sponsor by the clinical site following the APFS/AI Return Working Instruction document provided to the study sites. Authorized site staff participating in the study will receive training prior to study start.

6.2.4 Reporting product complaints

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

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

6.2.5 Reporting defects

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

- **Component Issue:** Defect in container or dosing mechanism of the IP. The component defect may be damaged, missing, or broken. Component examples for the AI include the Autoinjector and the prefilled syringe housed within the autoinjector. For the APFS, component examples include syringes and the accessory housing the syringe.

- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description in the IFU.

- **Packaging/Labelling Issue:** Defect in the packaging or labelling of the product. The packaging (e.g. carton, thermo-fitted tray, or tamper-evident seal) or labelling defects may be damaged or unreadable, or the label may be missing.

6.2.6 Single Use APFS/AI device malfunction

An AI malfunction is when the AI device appears normal during verification of shipment and then does not work during administration, e.g., the autoinjector activated prematurely, the autoinjector stalled or did not expel the full volume, needle guard safety feature did not deploy or remain locked, glass syringe breakage, needle bent or broke upon use.

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

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

If a device malfunction is identified at the study center:

- Before IP administration has started, another IP kit (replacement) should be dispensed to perform IP administration;
- After IP administration has started and subject has been administered unknown dose of IP, another IP kit must not be dispensed, and subject must not be administered with another IP kit. The AstraZeneca study physician and study monitor should be notified.

If a device malfunction occurs during home administration at Week 12 or Week 16, the subject or caregiver should contact the study site immediately. If it is determined that a replacement should be issued based on the same guidance for device malfunction at study center described above, the subject will return to the study site to obtain the replacement device.

Site staff will be asked to send all devices back to the depot or local sponsor company according to local procedures. Address and attention for malfunctioning device is available in the Device Malfunction Return Instruction.

6.3 Measures to minimize randomization bias

The Investigator(s) will:

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

2. Assign the potential subject a unique enrolment number (which begins with an ‘E’) via the Interactive Web Response System/Interactive Voice Response System (IWRS).

3. Determine subject eligibility.

4. Assign the eligible subject unique randomization code via the Interactive Web Response System (IWRS).

5. Subjects will be allocated to receive tezepelumab 210 mg via a single-use APFS or AI subcutaneously (SC) in a 1:1 ratio and stratified. by age (adults/adolescents) and country. Randomization numbers will be grouped in blocks. If a subject withdraws from the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

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

Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the subject from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the subject. In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about IP, all randomized subjects should remain in the study and the subjects should continue to be followed up in accordance with defined study procedures.

Methods for assigning treatment groups

Randomization codes will be assigned strictly sequentially within each stratum as subjects become eligible for randomization.

The randomization code will be assigned from a randomization list prepared by a computerized system provided by PAREXEL Informatics on behalf of AZ (AZRand). All subjects will be stratified at randomization by age (adults/adolescents) and country.

6.4 Treatment compliance

Any change from the dosing schedule or dose discontinuations should be recorded in the eCRF.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The date and time of all IP administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant therapy

All prior biologics taken for asthma must be recorded in the eCRF. To satisfy inclusion criterion 6, all ICS asthma medications taken in the 6 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment. Prior to the date of randomization, a history of continuous treatment with medium or high dose ICS for at least 6 months prior to Visit 1 plus a second controller medication for at least 3 months prior to Visit 1 should be documented in source documents and recorded in the eCRF.

A history of all asthma controller medications for the 6 months prior to Visit 1 until the end of the study should be documented in source documents and recorded in the eCRF.

Changes to background asthma medications are discouraged throughout the duration of the study. Any and all changes to the subject's background medication must be recorded in the eCRF and documented in source documents along with rationale for change.

Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

All other medications taken for conditions other than asthma in the 6 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment by the Investigator/authorized delegate at each visit (as shown in Table 1).

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

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the 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

Table 4 - Restricted medications

Short-acting beta-agonists	Regularly scheduled or prophylactic SABA use is discouraged from enrollment and throughout the study duration. PRN use is allowed if needed.

Table 4 - Restricted medications

Short-acting anticholinergics (e.g. ipratropium)	Not allowed as a rescue treatment for worsening asthma symptoms from Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP. They may be used to manage an asthma exacerbation.
Additional maintenance controllers	Subjects on theophylline should have blood concentration levels that do not exceed the upper limit of therapeutic range documented prior to treatment with IP and documented in source documents.
Inactivated/killed vaccines	Not allowed within 5 days before/after any IP administration.
Allergy immunotherapy	Not allowed if newly initiated within 2 months prior to Visit 1 or on the same day as IP administration.

Table 5 - Prohibited medications

Prohibited medication/class of drug:	**Usage**
Long-acting beta-agonists as a reliever (e.g., Symbicort Maintenance and Reliever Treatment)	Not allowed 15 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed within 15 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Live attenuated vaccines	Not allowed 30 days prior to the date of randomization, and during the study including the follow-up period.
Any immunomodulators or immunosuppressives (except for OCS used in the treatment of asthma/asthma exacerbations)	Not allowed 12 weeks prior to randomization, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Immunoglobulin or blood products	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.

Table 5 - Prohibited medications

Prohibited medication/class of drug:	Usage
Any marketed (e.g., omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to Visit 1, during screening/run-in and throughout the IP treatment (even if the subject has discontinued IP) and until the follow up visit week 36.
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, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP and for the duration of the study.

6.5.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.5.2 Rescue medication

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

6.5.3 Bronchial Thermoplasty

Subjects should not be treated with bronchial thermoplasty during the study.

6.6 Dose modification

N/A

6.7 Treatment after the end of the study

Subjects who complete Week 36 should be given treatment as per standard of care at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product (IP) in the following situations.

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. The subject is at any time free to discontinue treatment, or to discontinue from the study without prejudice to further treatment.

- An Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Subjects or subjects with caregivers who are unable or unwilling to administer investigational product (IP) at Week 8 (Visit 4)
- Pregnancy
- Development of any study specific criteria for discontinuation, including:
    - An anaphylactic reaction to the IP requiring administration of epinephrine
    - A helminth parasitic infestation requiring hospitalization
    - An asthma-related event requiring intubation
    - Any malignancy except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided the malignancy is excised and determined to have clean margins
- Development of one or more of the following:
    - Confirmed ALT or AST increase of ≥8 x ULN
    - Confirmed ALT or AST increase of ≥5 x ULN for more than 2 weeks
    - Confirmed ALT or AST increase of ≥3 x ULN and total bilirubin of ≥2 x ULN
    - ALT or AST of ≥3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥5%)

See the SoA for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

Subjects are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Discontinuing study treatment is not the same as study withdrawal. Procedures to follow for study withdrawal are detailed below. If the subject decides to withdraw consent, then the reason for this must be recorded separately in the eCRF.

A subject that decides to discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Subjects permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until week 36 even if the subject has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. For additional information regarding pharmacokinetic and pharmacodynamic effects of tezepelumab reference should be made to the Investigator brochure.

All subjects who prematurely discontinue IP and who do not withdraw their consent from the study, should return to the study centre and complete the procedures described in the Premature IP Discontinuation (IPD) visit after 4 weeks (± 3 days) and the procedures for the Follow-up visits after 10 weeks (± 3 days) and 16 weeks (± 3 days) of the last IP administration. The reason for premature discontinuation of IP should be recorded in the eCRF.

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as ‘Development of study specific discontinuation criteria’ on the Disposition (DS) form in the eCRF.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she 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 on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject or next of kin by either repeated telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject’s medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study, the subject should be considered to be lost to

follow-up with unknown vital status at end of study and censored at latest follow-up contact.

A subject is considered lost to follow-up when any of the following attempts of contact are failed: 3 attempts of either phone calls, faxes or emails; having sent 1 registered letter/certified mail; or one unsuccessful effort to check the status of the subject using publicly available sources, if allowed by local regulations.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g. withdraw consent), at any time (IP and assessments) at his/her own request, without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow-up subjects as medically indicated. A withdrawal visit is essential to collect as much data as possible for the subject as per EOT visit described in the SoA, Section 1.1.

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, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

If the subject only withdraws consent for the retention of blood samples for future exploratory use (e.g. DNA, study of markers of asthma, identifying potential new drug targets for asthma, or for assay development purposes), the subject will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF as well as in the Informed Consent Form (ICF) or assent form.

7.3.1 Withdrawal due to recruitment completion

When the required number of subjects are randomized in the study, ongoing subjects in run-in will not be randomized and will be withdrawn from the study. The reason of the withdrawal should be documented in the source notes and eCRF. As with screen failures, no further study related follow-up of these subjects is required.

7.3.2 Discontinuation or suspension of the whole study program

If AstraZeneca decides to prematurely terminate or suspend the study, the PI, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The PI will immediately notify the decision to the subjects and if relevant give appropriate medical treatment; take necessary measures and document these in the source notes.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA).

The Investigator will ensure that data are recorded on the electronic Case Report Forms (eCRFs). The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (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.

The amount of blood collected from each subject over the duration of the study (excluding optional blood samples and any extra assessments that may be required) will be approximately 84 mL and will not exceed 180 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

The primary endpoint of interest is the proportion of HCPs and subjects/caregivers who successfully administered tezepelumab with an APFS/AI at the clinic and at home. A successful administration is defined as an injection completed based on a user-recorded answer of "Yes" to all 5 questions in the APFS/AI Questionnaire (please see Appendix I and Appendix J) and satisfactory in vitro evaluation (visual test + functional evaluation) of the returned devices.

8.1.1 Assessment of returned APFS/AI device through in vitro evaluation

In addition to the Questionnaire filled out and returned to the Sponsor with each administered dose, the used APFS/AI will be returned to the Sponsor for in vitro evaluation. The data collected in the vitro evaluation of the APFS/AI devices falls into 2 categories: 1) Visual inspection, and 2) Functional evaluation.

The visual inspection will assess the returned devices for any visible damage or disassembly, full plunger travel indicating a complete dose was expelled, and needle guard deployment. The functional evaluation will challenge the needle safety guard to assess whether it deployed correctly and continued to provide protection against accidental needle stick injuries. As

mentioned in Section 8.1.1, a satisfactory in vitro evaluation of the returned devices and a completed questionnaire with an answer of "Yes" to all 5 questions in the questionnaire will constitute a successful administration. Any device defects reported during the in vitro evaluation will result in a full product complaint investigation.

In the event that the answers to one or more of the questions on the questionnaire indicate that the user was unable to complete a successful administration, an evaluation will be performed on the returned device. The evaluation will take into account information provided on the administration questionnaire. If the in vitro evaluation of the device shows no observable device defect, then the unsuccessful administration may be classified as a use error and not a device malfunction (e.g. user removes AI or APFS from the injection site before the injection is complete).

8.1.2 Assessment of Product Complaints

Please refer to Sections 6.2.4 through to 6.2.6.

8.1.3 Assessment of historical asthma exacerbations

The list below defines what is acceptable documentation for historical exacerbations:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized/treated with systemic steroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- Evidence of prescriptions for systemic steroids used during an exacerbation.
- A documented conversation that is recorded in a timely manner between the Investigator/nurse or nurse practitioner and a subject who is already on an OCS action plan, detailing the diagnosis and treatment of an asthma exacerbation.
- A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a subject was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure subject records have been unsuccessful.

During the study, asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice.

8.1.4 Spirometry

8.1.4.1 General requirements

Lung function (Reversibility, FEV_1 and FVC) will be performed by the Investigator or authorized delegate on site-supplied equipment according to American Thoracic

Society/European Respiratory Society (ATS/ERS) guidelines or local guidelines (Miller et al. 2005).

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

Important!

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

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

Note: If any of the above restrictions are not met, the spirometry assessment should be rescheduled within the allowed visit window.

8.1.4.2 Time of day for scheduled centre visit spirometry

Spirometry testing should be done according to the Schedule of Activities (SoA). For adult subjects, spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the screening or re-screening period and at randomization visits (Visit 2). Spirometry testing can be initiated during the whole day for adolescent subjects.

8.1.4.3 Spirometry technique

- Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the centre.
- Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the centre.

Forced expiratory maneuvers 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 patient for each forced expiry maneuver. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the maneuver.

The forced expiratory maneuvers (FEV_1 and FVC) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the subject to continue the expiration to be fast and forceful throughout the maneuver. Ensure that none of the following has occurred: coughing during the first second, glottis closure, or leak or obstruction of the mouthpiece (by the tongue).

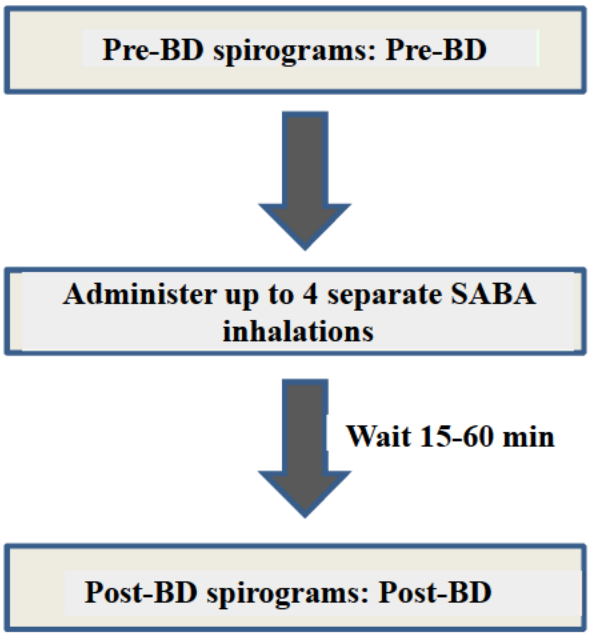
Multiple forced expiratory efforts (at least 3, but no more than 8) will be performed for each centre spirometry session and the 1 best effort (highest FEV_1) that meet the ATS/ERS (or local guidelines) acceptability and reproducibility criteria will be recorded in the eCRF. The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value will be recorded. The best effort values will be based on the one with highest FEV_1.

8.1.4.4 Post-BD spirometry and FEV_1 reversibility assessment

All subjects must meet inclusion criteria 5 either by having documented historical reversibility or by demonstrating reversibility either at Visit 1, optional Visit 1A, or Visit 2. Even if documented historical reversibility is available, the post-BD spirometry procedures must be performed at Visit 1 to categorize subjects (establish baseline characteristic) prior to randomization. The documented historical reversibility must be recorded in the eCRF/spirometer prior to randomization.

Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 4 inhalations. It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 3.

Figure 3 Reversibility Algorithm



After a gentle and complete exhalation, up to a maximum of 4 inhalations of salbutamol (100 µg metered dose) or albuterol (90 µg metered dose) should be administered using a spacer device. In rare cases where a subject has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45 µg metered dose, up to a maximum of 4 inhalations) can be used. (Sorkness et al. 2008). A nebulizer should not be used. A lower total dose (e.g. 2 inhalations instead of 4 and if required up to a maximum of 4 puffs) can be used if there is a concern about any effect on the subject's heart rate, tremor or safety; the reason should be noted in the subject's medical record. It is acceptable to stop the reversibility assessment procedure if technically acceptable spirometry is achieved and the criteria for reversibility are met.

If the subject does not meet reversibility criteria at Visit 1, further attempts to demonstrate reversibility criteria are allowed at optional Visit 1A or Visit 2.

Reversibility is calculated as follows:

% Reversibility = (post-BD FEV_1- pre-BD FEV_1) × 100/pre-BD FEV_1

8.1.4.5 Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at study centre for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number. If a printout cannot be printed, the mean value of the measurements will be recorded in the subject's charts.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA).

8.2.1 Clinical safety laboratory assessments

See Table 6 for the list of clinical safety laboratory tests to be performed, and the Schedule of Activities (SoA)for the timing and frequency. All protocol-required laboratory assessments, as defined in Table 6, must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA).

The Investigator should assess the available results with regards to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.7.7.

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

Table 6 - Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb)	S-Alkaline phosphatase (ALP)
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-Blood urea nitrogen (BUN)
B-Mean Corpuscular Volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Chloride
	S-Creatinine
Urinalysis (dipstick)*	S-Creatinine kinase (CK)
U- Blood	S-C Reactive Protein (CRP)
U-Protein	S-Gamma-glutamyl transpeptidase (GGT)
U-Glucose	S-Glucose
	S-Phosphorus
U-Microscopy and culture as required**	S-Potassium
	S-Sodium
	S-Total cholesterol
	S-Uric acid

*The urine dipstick test is not only limited to Blood, Protein and Glucose, but also additional test analytes as defined by central lab.

**Urine samples will be analyzed locally with the urine dipstick test and sent to the central laboratory only for further microscopy and culture analysis only when a positive dipstick result for any parameter is observed.

NB. In case a subject shows an AST **or** ALT ≥ 3xULN together with total bilirubin ≥ 2xULN please refer to Appendix E for further instructions.

8.2.1.1 Pregnancy Test

The following tests are applicable to female subjects only and will be conducted in accordance with the schedule provided in Section 1.1.

- Serum ß-human chorionic gonadotropin (ß-HCG) – the test will be mandatory at enrolment (Visit 1) and if any positive urine test result, for women of child-bearing potential (WOCBP).
- FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months.
- Urine HCG – the test will be performed for WOCBP at each treatment visit before IP administration using a dipstick. Positive urine test result must be confirmed with serum β-HCG.

8.2.1.2 Serology

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

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

8.2.2 Physical examinations

A complete physical examination will be performed and include an assessment 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. Brief physical examination will also be performed and include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination, only, information on whether the assessment was performed or not will be recorded.

Physical examination (complete and brief) will be performed at timelines as specified in the Schedule of Activities (SoA). Investigators should pay special attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as adverse events, see Section 8.7.6 for details.

8.2.3 Vital signs

Vital signs (e.g. pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with the Schedule of Activities (SoA).

Vital signs will be taken prior to blood drawing, IP administration, 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 (e.g. television, cell phones).

Pulse rate will be obtained before blood pressure if the manual measuring technique is used.

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

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

8.2.4 Electrocardiograms

A 12-lead (or 15-lead) ECG will be taken with the subject in the supine position and after the subject has rested for at least 5 minutes. The assessment should be performed prior to blood draw and spirometry. Measurements will be performed on site-supplied equipment.

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of the clinical significance of any potential ECG findings. In case of any 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, quality checked and kept in case of further need for re-evaluation. The results of the ECG evaluation will be recorded in the eCRF.

8.2.5 Weight, Height and BMI

Weight and height will be measured in accordance with the SoA. The subject’s weight will be recorded in kilograms, and height will be recorded in centimetres. Weight and height measurements will be performed in light clothing and with shoes off. BMI will be automatically calculated in the eCRF.

8.3 Patient Reported Outcomes

8.3.1 Asthma Control Questionnaire (ACQ-6)

Patient reported outcomes using ACQ-6 will be performed at the study site with paper questionnaires. Subjects will be given a paper questionnaire and be asked to complete and return these in accordance to the schedule provided in the Schedule of Activities (SoA). ACQ-6 should be completed as a first procedure during the visit. The Investigator/authorized delegate will check the questionnaires for completion to minimize missing data and record responses in the eCRF.

The ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and short-acting β2-agonist use. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma, and a score >1.5 indicates uncontrolled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful, and a decrease of at least 0.5 is the responder definition for ACQ-6.

8.4 Pharmacokinetics and Immunogenicity

8.4.1 Collection of samples and drug concentration

Serum determination of tezepelumab will be collected pre-dose according to the SoA (Section 1.1).

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

Samples for determination of tezepelumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report.

Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.4.2 Collection of samples to measure the presence of ADAs

The presence of ADA will be assessed in serum samples according to the SoA (Section 1.1).

Samples will be measured for the presence of ADAs for tezepelumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points statistically determined from drug-naïve samples will be employed. Samples confirmed positive for ADA will be archived for possible testing for neutralizing antibodies (nAb).

8.4.3 Storage and destruction of pharmacokinetic/ADA samples

Any residual back-up PK and ADA samples may be used for future exploratory biomarker research and retained for future use at AstraZeneca or designee for a maximum of 15 years following Last Subject's Last Visit.

Pharmacokinetic and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics

8.6.1 Optional exploratory genetic sample

The blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the separate Laboratory Manual provided to the sites.

The results of the analyses will be reported separately from the CSR in a scientific report or publication.

8.6.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.7 Collection of 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.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.7.3.

8.7.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.7.2 Time period and frequency for collecting AE and SAE information

Adverse Events, including SAEs will be collected from time of signature of informed consent form throughout the treatment period and the follow-up periods.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the Investigator must notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs/non-serious AEs/AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up

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 CRF. 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.

8.7.4 Adverse event data collection

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- Select the appropriate as required: 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
- Reason of AE is being serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

8.7.5 Causality collection

The Investigator will assess causal relationship between IP and each Adverse Event, 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 IP?'

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.7.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff**: Have you had any health problems since the previous visit/you were last asked?** or revealed by observation will be collected and recorded in the CRF. 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

8.7.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values/vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign/ECG 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 (e.g. anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

8.7.8 Disease progression

Asthma signs or symptoms such as wheeze, cough, chest tightness, breathlessness, etc. will be recorded as AEs only when:

- The sign or symptom is serious according to definition, see Appendix B
- The patient discontinues the study due to the sign or symptom.
- The sign or symptom is new to the patient or is not consistent with the patient's pre-existing asthma history as judged by the Investigator.

Asthma exacerbations should be recorded as an AE or SAE in the eCRF only if it fulfils any of the above criteria.

8.7.9 Adverse Events of Special Interest

An adverse event 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 antiviral medications, intravenous antibiotics or medications for helminth parasitic infection or
  - Requiring a permanent discontinuation of study drug
- Injection site reactions
- Opportunistic infections
- Guillain Barre Syndrome

8.7.10 Hy's law

Cases where a subject shows elevation in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.8 Safety reporting and medical management

8.8.1 Reporting of serious adverse events

All SAEs must 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 during the study, then Investigators or other site personnel must inform the appropriate AstraZeneca representatives within one day e.g., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within 1 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 adverse events where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative(s).

If the WBDC system is not available, then the Investigator or other study site staff must report a SAE to the appropriate AstraZeneca representative(s) by telephone.

The AstraZeneca representative(s) will advise the Investigator/study site staff how to proceed.

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

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

8.8.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study subject has received any study drug. If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.8.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event 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 must inform the appropriate AstraZeneca representatives within 1 day i.e., 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 1 or 5 calendar days for SAEs (see Section 8.8.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.8.2.2 Paternal exposure

Pregnancy of the subject's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

8.8.3 Overdose

A dose in excess of 280 mg administered within a 2-week period is considered an overdose.

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

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.8.3. For other overdoses, reporting must occur within 30 days.

8.8.4 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 1 day i.e., 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 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.8.4) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B 8.

8.8.5 Management of IP-related reactions

Prior to the first 2 administrations, which will be performed at the study center, subjects will have had a pre-assessment (i.e., vital signs) prior to IP administration, and will be observed after IP administration for a minimum of 2 hours for the appearance of any acute drug reactions. Study site personnel should inform subjects that, for subsequent administrations, they should be observed for at least 1 hour after IP administration for the appearance of any such reactions. As with any medication, in case of anaphylactic reaction at home, the subject or caregiver should immediately contact an emergency care unit or emergency transportation as per standard medical practice, and contact study site personnel.

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions, must be immediately available when IP is being administered at the study site. Study site personnel must be trained to recognize 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 and may cause death (Sampson et al. 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction.

2. Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms.

3. Reduced blood pressure after exposure.

If an anaphylactic reaction occurs, a blood sample will be drawn from the subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase. The sample will be tested at the local lab or central lab where applicable. In addition, in order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn during the event for ADA testing (if not already scheduled for this visit).

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No statistical hypotheses will be tested in this study.

9.2 Sample size determination

A total of 210 subjects will be randomized, out of which 105 will receive a dose of tezepelumab 210 mg via APFS injection and 105 will receive the same dose administered via AI. Approximately 20 adolescents aged ≥12 to <18 years will be included. It is anticipated that approximately 5% of subjects will drop out and thus it is estimated that approximately 100 subjects will complete the study for each device.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Full Analysis Set	All subjects randomized to study treatment who received or attempted to receive at least one dose of IP, irrespective of their protocol adherence and continued participation in the study
Pharmacokinetics Analysis Set	All subjects in the full analysis set who received tezepelumab and from whom PK blood samples are assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received).
Safety Analysis Set	All subjects who received tezepelumab

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed prior to first patient enter treatment period, and any subsequent amendments will be documented, with final amendments (if any) finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

All analyses will be descriptive only and no formal statistical testing will be performed.

9.4.1 Efficacy analyses

The efficacy endpoints will be summarized using the Full Analysis Set. To assess successful administration, functionality, and performance of the tezepelumab 210 mg injection via APFS and AI both in clinic and at home, 3 outcomes will be measured for APFS and AI devices separately:

- Primary endpoint: Proportion of HCPs and subjects/caregivers who successfully administer tezepelumab in clinic or at home. Successful administration is defined in Section 8.1. The denominator will be the number of subjects who received or attempted to receive an administration at each visit.
- Secondary endpoint: Proportion of used/returned devices that pass functional tests and visual inspection and show no evidence of malfunction. The denominator will be the number of used and returned devices at each visit.
- Secondary endpoint: Proportion of devices that have been reported as malfunctioning (Product Complaints). The denominator will be the number of used and returned devices at each visit.

For each of these endpoints, proportions and 95% confidence intervals (CIs) will be presented by visit for AI and APFS separately. For the primary endpoint specifically, the HCP and the subject/caregivers will be assessed separately, which is achieved through the by-visit presentations described above.

In addition, summaries combining visits may also be presented to assess at home use separately from clinic use as well as HCP use separately from subject/caregiver use. The details will be presented in the SAP.

For the additional secondary endpoint change from baseline in mean ACQ-6 score, the data will be summarized descriptively. Based on ACQ-6, subjects will also be categorized according to their asthma control and responder status. Number and percentage of subjects in these categories will be presented.

9.4.2 Safety analyses

Safety variables will be summarized using Safety Analysis Set. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in force at database lock. The definition of on-treatment and post-treatment for adverse event analyses will be given in the SAP.

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

AEs of Special Interest (AESIs) will also be summarized descriptively by treatment group.

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

9.4.3 Other analyses

PK variables will be summarized using Pharmacokinetics Analysis Set. Tezepelumab serum concentrations will be summarized using descriptive statistics at each visit for each device separately. No formal PK data analysis is planned due to sparse sampling and variations of sampling time following tezepelumab self-administrations. Observed serum concentrations of tezepelumab for each individual will be listed by visit to confirm tezepelumab administration.

The prevalence and incidence of anti-drug antibodies (ADA) will be reported for each device using the Safety Analysis Set. ADA data will be summarized using descriptive statistics at each visit by device. Samples confirmed positive for ADA will be archived for possible testing for neutralizing antibodies (nAb). The potential effects of ADA status and ADA titer on pharmacokinetics of tezepelumab will be evaluated. The potential association of immunogenicity with efficacy and safety may be evaluated.

9.5 Interim analyses

No interim analyses are planned in this trial.

9.5.1 Data safety monitoring board (DSMB)

A data safety monitoring board will not be utilized for this study.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and Sub-Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

If subject declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the subject and he/she will not be excluded from other aspects of the study.

If a subject's partner becomes pregnant from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP, the partner is asked to sign the Adult Study Informed Consent Form for Pregnant Partners of Study Subjects and provide information about the pregnancy accordingly.

Subjects who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The subject will give a separate agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will indicate this in the ICF. If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the monitoring plan.

A 9 Study and Site Closure

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

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

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

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

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement. Authorship will be

determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect?
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

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

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of such events are:

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

B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B.

B 7 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

B 8 Medication Error

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

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

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

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

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

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

- Errors related to or resulting from IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product
- Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

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

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

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

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

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are (e.g. Ebola, Lassa fever virus):

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are (e.g. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2). They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they be packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting subjects.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject´s DNA, i.e. the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on tezepelumab continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and:** Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.3 of the main Clinical Study Protocol.

Collection of samples for genetic research

Blood samples for genetic research will be obtained from subjects at randomisation visit and only after the consent is signed. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Randomisation Visit, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

The link between the subject enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or

designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in this appendix.

Informed consent

The genetic component of this study is optional, and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study as applicable. Copies of the signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdraw from the genetic aspect of the study at any time.

Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.

AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

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

Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.

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

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

E 3 Identification of potential Hy's Law cases

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

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Central laboratories being used:

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

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

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

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition.

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.

  Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available.

E 5 Review and assessment of potential Hy's Law cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety

Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

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

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

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

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

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory.

If required, additional assistance on which tests could be used to evaluate other potential causes of liver dysfunction consult with the Hepatic Safety Knowledge Group. Any test results need to be recorded.

Hy's Law lab kit for central laboratories

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

*HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

References

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

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’

Appendix F Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids[a]

Asthma Therapy	Total Daily Dose (µg/day)	
Inhaled Corticosteroid[b]	**Medium**	**High**
Beclomethasone dipropionate (CFC)[c]	>500–1000	>1000
Beclomethasone dipropionate (HFA)[d]	>200–400	>400
Budesonide	>400–800	>800
Ciclesonide	>160–320	>320
Fluticasone furoate (eg. Arnuity®)	n.a.	200
Fluticasone propionate	>250–500	>500
Fluticasone propionate HFA	>250–500	>500
Mometasone furoate	>220–440	>440
Triamcinolone acetonide	>1000–2000	>2000

[a] The Japanese asthma pediatric guidelines will be followed for the Japanese adolescent subject (the medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥ 200 µg/day of FP or other ICSs of equivalent dose).
[b] The ICS doses were derived from GINA 2018.
[c] CFC: Chlorofluorocarbon propellant
[d] HFA: hydrofluoroalkane propellant

Appendix G Anaphylaxis: signs and symptoms, management

G 1 Introduction

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

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

G 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

   (a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, hypoxemia).

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

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

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

   b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, hypoxemia).

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

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

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

Immune Complex Disease

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

G 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating

- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

G 4 Management of Acute Anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (e.g. dopamine).

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

(g) Consider atropine for symptomatic bradycardia.

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

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

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

Appendix H Abbreviations

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AAER	Annualized Asthma Exacerbation Rate
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AI	Autoinjector
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized Pre-filled Syringe
ATS	American Thoracic Society
AST	Aspartate Aminotransferase
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRP	C Reactive Protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ER	Emergency Room
EOT	End of Treatment
FAS	Full Analysis Set

Abbreviation or special term	Explanation
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FU	Follow-Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonization
ICI	International Co-ordinating Investigator (If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally).
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LRTI	Low Respiratory Tract Infection

Abbreviation or special term	Explanation
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit
MAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAB	Neutralizing Antibodies
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PT	Preferred Term
Q4W	Every 4 Weeks
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SoA	Schedule of Activities/Assessments
SOC	System Organ Class
SDV	Source Data Verification
TSLP	Thymic Stromal Lymphopoietin
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

Appendix I Accessorized Prefilled Syringe Administration Questionnaire for the D5180C00011 Clinical Study

1. TO BE FILLED OUT BY CLINICAL STUDY STAFF WHEN SUPPLYING IP TO SUBJECT OR CAREGIVER

Center Number:

E-Code:

E							

Kit ID (found on carton label, digits only):

2. TO BE FILLED OUT BY SUBJECT OR CAREGIVER (OR HEALTH CARE PROFESSIONAL AT WEEK 0 AND WEEK 4 IF ADMINISTERED BY HCP) AT TIME OF INJECTION

Date and time Investigational Product (IP) is removed from the refrigerator:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:			

Date and time of injection:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:		

Kit ID (found on carton label, digits only):

At which location was the injection administered (Mark one)

☐ **Study site/Clinic** ☐ **Home**

Person giving the injection (Mark one):

☐ **Health Care Professional/Designee**

☐ **Subject (self-injection)** ☐ **Caregiver**

Where on the body the subject was injected (Mark one):

☐ **Left Abdomen (belly)** ☐ **Right Abdomen (belly)**

☐ **Left Thigh** ☐ **Right Thigh**

☐ **Left Upper Arm** ☐ **Right Upper Arm**

☐ **Other (please specify):**_____

Was the device stored in the refrigerator? (Mark one):

☐ **Yes** ☐ **No**

If No, please specify:_____

The following questions should be answered *immediately after* the injection by the person who gave the injection to the subject. For example, if the subject gave himself or herself the injection, the subject would answer the following questions. Adult caregivers should review all responses for accuracy if an adolescent subject self-administers the injection. If the injection was given to the subject by a caregiver, the caregiver would answer the following questions. For week 0 (and potentially week 4), the HCP who gave the injection will complete the questionnaire.

Questions	**Yes**	**No**	**If answer was no, please explain**
Were you able to inspect the syringe contents?	☐	☐	
Were you able to perform the injection?	☐	☐	
Were you able to fully depress the plunger during injection?	☐	☐	
Were you able to administer the full dose?	☐	☐	
Were you able to activate the needle safety guard?	☐	☐	

Date and time the questionnaire is completed by the person giving the injection:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:		

Appendix J Autoinjector Administration Questionnaire for the D5180C00011 Clinical Study

1. TO BE FILLED OUT BY CLINICAL STUDY STAFF WHEN SUPPLYING IP TO SUBJECT OR CAREGIVER

Center Number:

E-Code:

E							

Kit ID (found on carton label, digits only):

2. TO BE FILLED OUT BY SUBJECT OR CAREGIVER (OR HEALTH CARE PROFESSIONAL AT WEEK 0 AND WEEK 4 IF ADMINISTERED BY HCP) AT TIME OF INJECTION

Date and time Investigational Product (IP) is removed from the refrigerator:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:		

Date and time of injection:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:		

Kit ID (found on carton label, digits only):

At which location was the injection administered (Mark one)

☐ **Study site/Clinic** ☐ **Home**

Person giving the injection (Mark one):

☐ **Health Care Professional/Designee**

☐ **Subject (self-injection)** ☐ **Caregiver**

Where on the body the subject was injected (mark one)

☐ **Left Abdomen (belly)** ☐ **Right Abdomen (belly)**

☐ **Left Thigh** ☐ **Right Thigh**

☐ **Left Upper Arm** ☐ **Right Upper Arm**

☐ **Other (please specify):**_____

Was the device stored in the refrigerator? (Mark one):

☐ **Yes** ☐ **No**

If No, please specify:_____

The following questions should be answered *immediately after* the injection by the person who gave the injection to the subject. For example, if the subject gave himself or herself the injection, the subject would answer the following questions. Adult caregivers should review all responses for accuracy if an adolescent subject self-administers the injection. If the injection was given to the subject by a caregiver, the caregiver would answer the following questions. For week 0 (and potentially week 4), the HCP who gave the injection will complete the questionnaire.

Questions	**Yes**	**No**	**If answer was no, please explain**
Were you able to inspect the liquid through the Autoinjector viewing window?	☐	☐	
Were you able to perform the injection?	☐	☐	
Were you able to hold the Autoinjector in place until the injection was completed?	☐	☐	
Did the yellow needle guard slide down to cover the needle after removal from skin?	☐	☐	
Were you able to see the yellow plunger in the viewing window after injection?	☐	☐	

Date and time the questionnaire is completed by the person giving the injection:

(YYYY/MM/DD)

				/			/		

(HH:MM) (24-hour clock)

		:		

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