Clinical Study Protocol	
Study Intervention	Tezepelumab
Study Code	D5180C00021
Version	7.0
Date	21Sep2023

A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma (DIRECTION)

Sponsor Name: AstraZeneca AB

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

Regulatory Agency Identifier Number(s):

CFDA CTP No.: 2018L02852

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

Protocol Number: Version 7.0, 21Sep2023

Amendment Number: 6.0

Study Intervention: Tezepelumab
Study Phase: Phase 3

Short Title: Study to Evaluate Tezepelumab in Adults With Severe Uncontrolled Asthma

Study Physician Name and Contact Information will be provided separately

International Co-ordinating Investigator:

PPD

PPD
PPD
151 Yan Jiang Road., Guangzhou 510120, P.R. China

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	21-Sep-2023
Amendment 5	10-Oct-2022
Amendment 4	17-May-2022
Amendment 3	25-Aug-2021
Amendment 2	10-Aug-2020
Amendment 1	18-Feb-2019
Original Protocol	28-Nov-2017

Amendment 6 Date - 21-Sep-2023

Overall Rationale for the Amendment:

This Clinical Study Protocol has been amended to provide clarity around the timing of study database locks (DBLs) and unblinding of the data.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 4.1 Overall Design Section 6.3 Measures to Minimise Bias: Randomization and Blinding Section 9.4 Statistical Analyses	Added the specification of two database locks (DBLs): the primary (after completion of the treatment period) and final (after completion of the follow-up period) DBL. Clarified that only the sponsor staff will know the study treatment allocation for participants after the primary DBL, and investigators/site staff/participants will remain blind until the final DBL.	Provide clarification for the timing of study DBLs and unblinding of the data.	Substantial
Section 4.3 Justification for Dose	Corrected study number 20101183	To keep consistent wording in CSP	Non-Substantial
Section 8.3.10.1 Medication Error,Drug Abuse and Drug Misuse	Added definition of medication error	To align with AstraZeneca CSP template version 9.0	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4 Statistical Analyses	• Added the specification of statistical analyses at the two DBLs. • Clarified the final SAP amendment will complete prior to unblinding at the primary DBL. • Clarified the important protocol deviations will be identified prior to unblinding at the primary DBL. • Clarified the AEs will be coded using the MedDRA version in force at the primary DBL	Provide clarification for the statistical analyses at two DBLs, and the timing of SAP completion, important protocol deviations identification and MedDRA version for AE coding.	Non-Substantial
A 3 Informed Consent Process	Removed the wording related to genetic research	Error correction	Non-Substantial
Appendix B4 Medication Error	Changed IVRS/IWRS into IRT/RTSM	To keep consistent wording in CSP	Non-Substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma (DIRECTION)

Short Title: Study to Evaluate Tezepelumab in Adults With Severe Uncontrolled Asthma
Rationale: The purpose of this regional study is to confirm the efficacy and safety of 210 mg dose of tezepelumab administered subcutaneously (SC) every 4 weeks (Q4W) in adults (18 to 80 years of age inclusive) with a history of asthma exacerbations and severe, uncontrolled asthma receiving medium or high dose inhaled corticosteroid (ICS) plus at least one additional asthma controller medication with or without oral corticosteroids (OCS). The study will evaluate the incidence of asthma exacerbations and other efficacy parameters such as lung function, asthma control and quality of life as well as a safety evaluation to further characterize the benefit-risk profile of the drug.

Objectives and Endpoints

Primary Objective	**Endpoint/variable**
• To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult participants with severe uncontrolled asthma compared with placebo	• **Primary endpoint:** Annualized asthma exacerbation rate (AAER) • **Primary outcome measure:** AAER ratio vs placebo over 52 weeks
Key Secondary Objectives	**Endpoint/variable**
• To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo	• **Secondary endpoint:** change from baseline in pre-dose/pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV1) • **Key outcome measure:** Mean difference vs placebo at Week 52
• To assess the effect of 210 mg of tezepelumab SC Q4W on health status/health related quality of life compared with placebo	• **Secondary endpoint:** Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score • **Key outcome measure:** Mean difference vs placebo at Week 52
• To assess the effect of 210 mg of tezepelumab SC Q4W on asthma control compared with placebo	• **Secondary endpoint:** Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) Score • **Key outcome measure:** Mean difference vs placebo at Week 52

• To assess the effect of 210 mg of tezepelumab SC Q4W on asthma symptoms compared with placebo	• **Secondary endpoint:** Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) score • **Key outcome measure:** Mean difference vs placebo at Week 52
Safety Objective	**Endpoint/variable**
• To evaluate the safety and tolerability of tezepelumab	• Adverse events (including serious adverse events [SAEs]) • Vital signs • 12-lead electrocardiograms • Clinical laboratory tests (haematology, clinical chemistry, urinalysis)

For Tertiary/Exploratory objectives and outcome measures, see Section 3 of the protocol.

Overall Design:

This is a regional, multicentre, randomized, double-blind, placebo controlled, parallel group, phase 3 study designed to evaluate the efficacy and safety of 210 mg Q4W (SC) of tezepelumab in adults with severe, uncontrolled asthma on medium to high-dose ICS and at least one additional asthma controller medication with or without OCS.

Study Period:

First participant enrollment Jun 2019

Estimated date of last participant completed Q3 2024

Disclosure Statement:

This is a regional, multicentre, randomized, double-blind, placebo controlled, parallel group, phase 3 study

Number of Participants:

A total of 396 participants will be randomized in the study in a 1:1 ratio to either tezepelumab or placebo (198 per group), with at least 70% of the participants from China. The rest of the participants will come from other countries. The participants will be stratified by region (China/non-China).

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

Intervention Groups and Duration:

The study will consist of a screening/run in period between 5-6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. Participants will be randomized in a 1:1 ratio to either 210 mg of tezepelumab or matching placebo both administered Q4W SC. During the treatment period, IP will be administered from Day 0 until week 48. No IP will be administered at week 52. Participants will complete a 12 week off-treatment follow-up period for assessments including safety and anti-drug antibodies. Participants who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52 weeks period (see section 7.1.1).

Please note: If participants are unable to come to the site during the COVID-19 pandemic, please refer to Appendix H for further guidance.

Data Monitoring Committee: No

Independent Adjudication Committee:

An independent adjudication committee is constituted to provide an external independent assessment of blinded data during the Phase 3 trials to confirm the diagnosis and causality of MACE events (defined in the IAC charter), serious cardiac events, deaths, as well as the diagnosis of malignancies that occur from randomization until the end of the follow up period.

The IAC also assess whether cases of ER or urgent care visits and hospitalizations, that occur from randomisation until the end of the follow-up period, are due to a worsening of asthma. Details on the adjudication process, including scope of adjudication and the committee membership, is included in the Adjudication Committee Charter/Manual of Operations.

Statistical Methods:

Approximately 396 participants (198 per treatment group) are needed for this study to achieve approximately 90% power based on the primary objective (primary endpoint AAER is defined in section 3). The study is powered based on the primary endpoint (AAER) only and not for the subsequent multiple testing procedures of the key secondary endpoints (pre-BD FEV_1, AQLQ(S)+12, ACQ-6 score and ASD score).

Participants who meet the eligibility criteria will be randomized (1:1) to receive either tezepelumab 210 mg Q4W SC or placebo. Efficacy analyses will be performed using the full analysis set (FAS), which consists of all participants randomized and receiving any IP. All participants in the FAS will be included in the main efficacy analyses, including participants who discontinue IP prior to Week 52 (for which every attempt will be made to collect data after discontinuation of IP up until Week 52).

A hierarchical testing strategy will be implemented to test for superiority of tezepelumab over placebo in each of the primary and key secondary endpoints, whilst controlling the overall Type 1 error rate at 0.05 (2-sided), as follows:

- Level 1: AAER over 52 weeks (primary endpoint)
- Level 2: Change in pre-BD FEV_1 from baseline at Week 52 (key secondary endpoint)
- Level 3: Change in AQLQ(S)+12 total score from baseline at Week 52 and change in ACQ-6 score from baseline at Week 52 (simultaneous testing of these 2 key secondary endpoints)
- Level 4: Change in weekly mean daily ASD score at Week 52 from baseline (key secondary endpoint)

The primary analysis of the primary endpoint will compare AAER over 52 weeks between treatment groups using a negative binomial model. The response variable will be the number of asthma exacerbations experienced by the participant over the study period. Treatment, region (China or non-China) and history of exacerbations (≤2 or >2 in previous 12 months) will be included as factors in the model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable.

The main analysis of the key secondary endpoints will compare mean changes at Week 52 between treatment groups using a linear model for repeated measures. The response variable will be the change from baseline at each scheduled post-randomization visit up to and including Week 52. Treatment, visit, region (China or non-China) and treatment by visit interaction will be included as factors in the model. The baseline of the corresponding endpoint will also be included in the model as a continuous linear covariate. Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant.

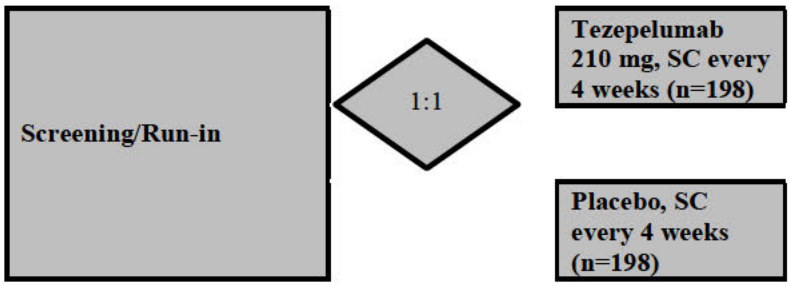
Relevant sensitivity and subgroup analyses will be performed. Details will be provided in a separate statistical analysis plan. All safety variables will be summarized descriptively. The safety analysis will be performed using the safety analysis set.

1.2 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design

V1	V2-V2a	V3	V4-V16	V17	V18, V19
Day -42 to -35	Day -28 to -25	Week 0	Week 2 to 48	Week 52	Week 58, 64
Screening	**Run-in**	**Randomization**	**Treatment Phase**	**End of Treatment**	**Follow-up**


Screening/Run-in
1:1
Tezepelumab 210 mg, SC every 4 weeks (n=198)
Placebo, SC every 4 weeks (n=198)

V: Visits

1.3 Schedule of Activities

Table 1 Schedule of Assessments - Screening

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window (day)	**0**	**±4[p]**	**±4[p]**	
Procedures				
Informed consent	X			Section 5.1
Inclusion /exclusion criteria	X	X	X	Section 5.1 and Section 5.2
Demography	X			Section 5.1
FENO[m]		X	X	Section 8.1.4
Clinical Lung Function Assessments				
Spirometry (pre-BD FEV_1, FVC and FEV_1/FVC)[c]		X[b]	X	Section 8.1.2
Reversibility (post-BD FEV_1, FVC and FEV_1/FVC)[d]		X[b]	X	Section 8.1.2.2
Home peak flow monitor training and distribution		X[e]	X[e]	Section 8.1.3
Check Home peak flow compliance and technique		Compliance check throughout screening period		Section 8.1.3
Home assessment every morning and evening PEF		Measurements every morning and evening		Section 8.1.3
Patient Reported Outcome assessments at Visit				
SNOT-22		X[i]	X[i]	Section 8.1.6.6
Distribute ePRO device		X[f]	X[f]	Section 8.1.6

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window (day)	**0**	**±4[p]**	**±4[p]**	
eDiary device training		X	X	Section 8.1.6
ACQ-6[g]	X			Section 8.1.6.2
Check compliance with PRO assessments and follow-up as needed to maintain compliance (every 7 days)		Compliance check throughout screening period		Section 8.1.3
Patient Reported Outcome assessments at home				
Daily Diary[h]		Completed twice daily at home on eDiary		Section 8.1.6.1
Routine safety measurements				
Complete Physical examination	X			Section 8.2.1
Vital signs	X			Section 8.2.3
Weight, Height	X			Section 8.2.2
12-lead ECG[n]	X			Section 8.2.4
Adverse events (AEs/SAEs)	X	X	X	Section 8.3
Medical and asthma history	X			Section 5.1
Assessment of historical asthma exacerbations in the past 12 months	X			Section 8.1.1
Concomitant medication[j]	X	X	X	Section 6.5
Laboratory Assessments				
Serum Chemistry	X			Section 8.2.4

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window (day)	**0**	**±4[p]**	**±4[p]**	
Haematology (full)[o]	X			Section 8.2.4
CCI [redacted]	X			Section 8.6.2
Pregnancy or FSH test[l]	X			Section 8.2.5.1
Serology (Hepatitis B, C; HIV-1; HIV-2)	X			Section 8.2.5.1
Urinalysis	X			Section 8.2.4

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

[b] Visit 2a is an optional visit. It can be performed if Pre-BD FEV_1 (inclusion criteria 7) and/or reversibility (inclusion criteria 8) is not met at Visit 2. If any one of these inclusion criteria is met at Visit 2, there is no need to repeat the assessment that was met at Visit 2a.

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

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

[e] Home peak flow monitor training and distribution should take place only if the participant has met inclusion criteria 7 and 8. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

[f] The ePRO home device training and distribution should take place only after the inclusion criteria 7 and 8 are both met. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

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

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

[i] Visit 2 on the handheld device should only be confirmed once both inclusion criteria 7 and inclusion criteria 8 have been met at either Visit 2 or at Visit 2a as per CSP. ePRO assessments (SNOT-22 and practice diary) need only to be collected once, either at Visit 2 or at Visit 2a if applicable. SNOT-22 questionnaire will only be triggered for participants that have a medical history of current/ongoing nasal polyposis at Visit 2 or Visit 2a as applicable.

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

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

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

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

[n] ECG to be completed prior to any blood draws.

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

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

Table 2 Schedule of Assessments-Randomization, treatment period (Week 0 - Week 52), follow-up (Week 58 - Week 64)

	Randomization	Treatment													EOT Period	IPD[m]	FU	FU	UNS[q]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Procedures																				
Inclusion /exclusion criteria	X																			Section 5.1 and 5.2
Weight								X							X	X				Section 8.2.2
Health care resource Utilization[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.8
CCI at clinic[j]	X	X	X	X	X	X		X			X				X	X		X	X	Section 8.1.4
Patient Reported Outcome Assessments at Visit[n]																				
Check compliance with PRO assessments and follow-up with participant as needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 8.1.6
ACQ-6[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.6.2

	Randomization	Treatment													EOT Period	IPD[m]	FU	FU	UNS[q]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
AQLQ(s) +12	X		X		X			X			X				X	X				Section 8.1.6.3
SGRQ[o]	X							X							X	X				Section 8.1.6.4
SNOT-22[c]									X						X	X				Section 8.1.6.6
Patient Reported Outcome Assessments at Home																				
Daily Diary[d]	Completed twice daily at home on the eDiary																			Section 8.1.6.1
EQ-5D-5L	X	Completed every 2 weeks at home on the eDiary														X				Section 8.1.6.5
Routine safety measurements																				
Complete Physical examination	X														X	X			X	Section 8.2.1
Brief physical examination			X	X	X	X	X	X	X	X	X	X	X	X			X	X		Section 8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1

	Randomization	Treatment													EOT Period	IPD[m]	FU	FU	UNS[q]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
12-lead ECG[e]	X							X							X	X		X		Section 8.2.4
Laboratory Assessments[f]																				
Serum Chemistry	X				X			X			X				X	X		X	X	Section 8.2.4
Haematology (full)[g]	X	X	X		X			X			X				X	X		X	X	Section 8.2.4
Urinalysis	X				X			X			X				X	X		X		Section 8.2.4
Pregnancy test[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Section 8.2.5.1
Serum for Immunogenicity[p]	X							X							X	X		X		Section 8.5
Serum for PK[p]	X							X							X	X		X		Section 8.5
CCI [redacted]	X	X	X		X			X			X				X	X		X	X	Section 8.6.2
Lung Function Assessments																				
Spirometry (pre-BD FEV_1, FVC and FEV_1/FVC)[k]	X	X	X	X	X	X		X			X				X	X	X	X	X	Section 8.1.2
Reversibility (post-BD FEV_1, FVC and FEV_1/FVC)	X							X							X	X			X	Section 8.1.2.2

	Randomization	Treatment													EOT Period	IPD[m]	FU	FU	UNS[q]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Home peak flow compliance and technique check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 8.1.3
Home assessment of PEF	Measurements every morning and evening throughout treatment period																			Section 8.1.3
Study treatment administration																				
Randomization	X																			Section 6.1
Administration of IP[l]	X		X	X	X	X	X	X	X	X	X	X	X	X						Section 6.2

[a] Asthma specific resource utilization (eg unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).

[b] ACQ-6 to be completed before AQLQ(s)+12 and SGRQ.

[c] SNOT-22 questionnaire will only be completed during the treatment period for those participants who have completed SNOT-22 at Visit 2.

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

[e] ECG must be collected prior to any blood draws, spirometry, BD administration and IP administration

[f] All blood sampling should be done prior to IP administration.

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

[h] For WOCBP, urine or serum pregnancy test (HCG) will only be performed at treatment visits, prior to IP administration.

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

[j] At clinic CCI must be performed prior to spirometry assessments. All CCI measurements will be blinded for sites and participants throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the CCI values post randomization.

[k] Visit 3 spirometry must be performed on the day of randomization prior to IP administration after appropriate restriction are met as per section 8.1.2.1. For every other visit, pre-BD spirometry assessments must be performed only after appropriate restrictions are met as per section 8.1.2.1, if not this should be rescheduled to the earliest opportunity within the allowed visit window.

[l] IP should be administered after all other assessments have been completed to a scheduled visit.
[m] Refer to section 7.1.
[n] The ePRO questionnaires should be completed prior to FENO and spirometry assessments at clinic.
[o] SGRQ to be completed after AQLQ(s)+12
[p] Serum for PK and immunogenicity must be collected prior to IP administration. In case of re-screening, these assessments will not need to be repeated if already completed at the original Visit 3.
[q] At unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed above is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

EOT End-of-Treatment; FU Follow-up; IPD Investigational Product Discontinuation; UNS Unscheduled; W Week.

CHANGES REQUIRED DURING THE COVID-19 PANDEMIC

Please Note: Changes below should only be implemented during the COVID-19 pandemic.

During the COVID-19 pandemic, changes are being implemented in order to ensure the safety of study participants, to maintain compliance with good clinical practices, and to minimize risks to data integrity. Where allowable by local health authorities, ethics committees and healthcare provider guidelines (e.g. hospital policies), these changes include:

- Re-consent will be obtained remotely and/or verbally if allowed by local and regional guidelines. The rationale for this change is to ensure that the participant agrees to the changes implemented during the COVID-19 pandemic while minimizing the risk to participants of COVID-19 exposure.

- The option of home visits including home administration of study intervention performed by a qualified Health Care Professional (HCP). Additional information related to the visit can be obtained remotely by phone call and/or video conference. The rationale for this change is to minimize the risk of participants missing scheduled IP administration and visit assessments due to inability/unwillingness to visit the site during the COVID-19 pandemic. Home IP administration will apply to participants that have completed at least two IP administrations on-site.

- Remote visits (phone call and/or video conference) to replace on-site visits, if participants cannot attend the visits at the study site, at an alternate site or have home visits. The rationale for this change is to ensure that assessments and collection

of information continue for visits that cannot be done at the site, at an alternate site or at the participant's home. This will reduce the risk of participant exposure to COVID-19

- Screening visit and all run-in visits must be conducted on-site to complete the required assessments according SoA in order to confirm eligibility criteria.

For further details, please refer to Appendix H.

2 INTRODUCTION

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

Progressive pathologic airway remodeling and scarring may occur in persistent asthma resulting in only partially reversible or irreversible airway obstruction (Pascual and Peters 2005).

The etiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise when a person becomes hypersensitive to allergens. Despite the availability of multiple therapeutic options, asthma continues to be a major health problem. Worldwide, asthma currently affects approximately 300 million people; by 2020, asthma is expected to affect 400 million people (Partridge 2007). Each year in the US, asthma accounts for an estimated 8.9 million outpatient visits, 1.9 million emergency room visits, 479,000 hospitalizations (DeFrances et al 2008), and 3400 deaths (Centers for Disease Control and Prevention 2017). In China the prevalence of asthma was reported to be 1%-5%, approximately 30 million patients. Its prevalence is in an increasing trend in China. A national survey conducted in 2010-2011 reported that it increased by up to 147.9% and 190.2% in Beijing and Shanghai, respectively, as compared to that in 2002-2004 (China Asthma Guideline 2016). In China, a recent national survey reported that in asthma patients receiving current therapies 40.5% reached asthma control, but the hospitalization rate in the past year was 22.6% (0.45/patient.year) and the ER visit rate in the past year 27.0% (0.67/patient.year) (Su et al 2014).

Approximately 5% to 10% of asthma patients have severe asthma, which may be inadequately controlled by ICS and LABA combinations together with additional controller therapies (Brightling et al 2008). In China a national survey reported that 6.0% of asthma cases were severe (Su N et al 2016). These patients are at risk of asthma exacerbations (Tough et al 1998, Turner et al 1998) and have the greatest medical need among the asthmatic population today. Patients with severe asthma represent the greatest economic cost (>50% of total asthma-related health care costs) (Antonicelli et al 2004, Serra Batlles et al 1998, Barnes and Kuitert 1996).

2.1 Study Rationale

Tezepelumab is in development for the treatment of severe asthma. A proof-of-concept study (Gauvreau et al 2014) showed that tezepelumab attenuated the late allergic response (LAR), the early allergic response (EAR) and the increase in FENO levels after an allergen challenge. A Phase 2b study (CD-RI-MEDI9929-1146) showed that doses of 70 mg and 210 mg administered Q4W and 280 mg of tezepelumab administered Q2W SC resulted in a reduction of the AAER by 61%, 71% and 66% respectively.

This phase 3 study is designed to evaluate the effect of tezepelumab on the AAER, lung function, asthma control, and safety in adult participants with uncontrolled severe asthma receiving medium or high-dose ICS plus at least one additional asthma controller medication with or without OCS. This will allow the benefit-risk profile of tezepelumab in the treatment of severe asthma to be further characterized and to enable a better understanding of how best to position tezepelumab in the severe asthma treatment pathway.

2.2 Background

Biologic therapies have been shown to reduce 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 ICS plus LABA (XOLAIR US PI 2019, XOLAIR SmPC 2019). Four additional biologics, mepolizumab, reslizumab, benralizumab, and dupilumab, have been approved for severe asthma with an eosinophilic phenotype and/or those requiring oral corticosteroid (OCS) therapy (NUCALA SmPC 2019, NUCALA US PI 2019, CINQAERO SmPC 2021, CINQAIR US PI 2020, FASENRA SmPC 2019, FASENRA US PI 2019, DUPIXENT SmPC 2020, DUPIXENT US PI 2019).

Biologics targeting IL-5 and IgE are now included in international treatment guidelines (GINA 2017) 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, 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 Th2 driven asthma (Kaur and Brightling, 2012). Asthma is recognized as a heterogeneous disease. There are subsets of patients that do not exhibit Th2-associated disease (Wenzel et al, 2012), and there are emerging data that TSLP may also mediate non-allergic (non-T helper cell 2) inflammation (Tanaka et al 2009, Ziegler et al 2013).

Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is therefore anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

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 TSLP receptor (TSLPR). Owing to the central role of TSLP in initiating and maintaining a Th2 response, anti-TSLP therapy may provide an opportunity to treat the upstream underlying mechanisms of asthma by reversing the established inflammatory responses to asthma triggers.

Results of a completed inhaled allergen challenge study in 31 adult participants with mild atopic asthma (Study 20101183) demonstrated that tezepelumab attenuated the LAR and EAR to allergen challenge, as measured by the AUC (Area Under the Curve) for the percent fall in FEV_1 and the maximum percent fall in FEV_1. Tezepelumab also attenuated the increase in FENO 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 participants with mild atopic asthma. No participants developed anti-drug antibodies (ADA) after receiving tezepelumab. Based upon these data, MedImmune/AZ have conducted a randomized, double-blind, placebo-controlled, dose range finding study in asthmatics who were inadequately controlled with medium or high dose ICS/long-acting β2 agonist (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 participants with inadequately controlled, severe asthma. Participants were randomized in a 1:1:1:1 ratio to 1 of 3 dose levels of SC tezepelumab (280 mg Q2W, 210 mg Q4W, 70 mg Q4W) or placebo (Q2W) for 52 weeks. A total of 584 participants received at least 1 dose of tezepelumab or placebo. An AAER reduction of 61%, 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 (ITT) 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 3 doses. A total of 5 (4.1%) placebo participants and 8 (1.8%) tezepelumab participants who had no detectable ADA at baseline

had detectable ADA post-treatment; no participants developed neutralizing ADA in the study. The results of this study did not identify safety signals associated with tezepelumab for any dosing regimen. The frequencies of treatment emergent adverse events (TEAEs) were similar between the placebo (62.2%) and the total tezepelumab (64.2%) dose groups and a majority of participants had TEAEs that were mild or moderate in severity and not related to study intervention. Few participants had TEAEs that resulted in permanent discontinuation of IP. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no safety signals were identified.

Study D5180C00007 (NAVIGATOR) was a Phase 3, multicenter, global, randomized, double blind, placebo-controlled study to assess the efficacy and safety of 210 mg tezepelumab administered SC Q4W for 52 weeks. The population of interest was adults and adolescents with severe, uncontrolled asthma between the ages of 12 and 80 years and both overall and across a broad spectrum of asthma phenotypes as determined by participants with blood eosinophils above and below 300 cells/μL, FeNO above and below 25 ppb, as well as allergic and non-allergic status. A total of 1061 participants were randomized in a 1:1 ratio to tezepelumab or placebo and 1059 participants (including 82 adolescents) received at least one dose of study intervention. Tezepelumab treatment resulted in a statistically significant and clinically meaningful reduction in annualised asthma exacerbation rate (AAER) by 56% ($p < 0.001$) compared with placebo in the overall population and by 41% compared with placebo in participants with baseline blood eosinophils <300 cells/μL ($p < 0.001$). The mean serum trough concentration of tezepelumab increased over time and approached steady state by 12 weeks. Treatment-emergent ADAs were detected at any time during the study in 4.9% (26) of participants treated with tezepelumab. Neutralizing antibodies to tezepelumab were detected in only one (0.2%) of the participants treated with tezepelumab. On-treatment AEs were similar between the placebo (80.8%) and the total tezepelumab (77.1%) dose groups and the majority of participants had on-treatment AEs that were mild or moderate in severity and not related to the study intervention. The percentage of participants who discontinued the trial regimen was 6.8% in the tezepelumab group and 10.7% in the placebo group. On-treatment AEs that resulted in permanent discontinuation of study intervention was 2.1% in the tezepelumab group and 3.6% in the placebo group. Overall, tezepelumab was well tolerated with an acceptable safety profile and no safety signals in both adult and adolescent participants with severe, uncontrolled asthma (Menzies-Gow et al 2021, TEZSPIRE FDA Prescribing Information 2021).

Additional studies with tezepelumab have been completed. These include a mechanistic study (D5180C00013; CASCADE) conducted in adults with inadequately controlled asthma, an OCS sparing study (D5180C00009; SOURCE) conducted in adults with OCS-dependent asthma, an at-home use study in adults and adolescents with severe asthma (D5180C00011; PATH-HOME), and a Japanese long-term safety study in participants with inadequately controlled asthma (D5180C00019; NOZOMI).

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

2.3 Benefit/Risk Assessment

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

2.3.1 Risk Assessment

Use of tezepelumab has been demonstrated to show an important benefit in asthma in a phase 2b and phase 3 studies. Tezepelumab has been well tolerated with an acceptable safety profile and no safety signals in participants with severe, uncontrolled asthma identified in the completed studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 3 program. To date there has been a low incidence of ADA and neutralising antibodies (nAb) reported with tezepelumab treatment in the Phase 2 or Phase 3 studies. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host defense against certain infections, there is no clear preclinical or clinical evidence supporting such a role, and no safety concerns related to serious infections, severe infections or helminth infections have been detected in the completed studies to date.

Risk mitigation measures for important potential risks will be in place during the conduct of this study (refer to Table 3), in conjunction with the performance of the AstraZeneca's routine pharmacovigilance activities.

Table 3 Risk Assessment

Important Potential Risk	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Serious infections are defined as infections fulfilling criteria for regulatory reporting	The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to infection. Although there is a theoretical risk of serious infections with tezepelumab treatment, there is no data to support this potential risk. There is also no evidence for causal relationship with tezepelumab.	Vulnerable participants will be excluded based on eligibility criteria, and randomised participants will be monitored for infection with complete blood counts, including differential white cell count throughout the study; and through standard AE/SAE reporting. Participants will be excluded if they received systemic immunosuppressive or immunomodulating drugs within 12 weeks prior to randomization; or if they have a history of a known immunodeficiency disorder; or have a history of clinically significant infection requiring treatment with systemic antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the run-in period or at randomisation; or who have evidence of active coronavirus disease 2019 (COVID-19) infection during the run-in period; or have had tuberculosis requiring treatment within the 12 months prior to Visit 1. Serious infections are an AESI and participants who develop serious infection will be followed up closely throughout study.
Malignancies	Given the potential theoretical risk, the long-term treatment intended for a chronic disease, and the nature of malignancy development, malignancy is included as an important potential risk. There is no evidence to suggest an increase in malignancies in the tezepelumab data to-date in either pre-clinical or clinical studies. No causal relationship with tezepelumab could be	Participants with current malignancy or whose curative therapy was completed recently will be excluded from participation based on eligibility criteria. All participants will be closely followed during the study for any adverse events, including malignancies that are considered AESI.

Important Potential Risk	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
	established for cases reported.	
Serious cardiac events	A numerical imbalance in cardiac disorder SAEs was observed in the DESTINATION Long Term Extension study (Investigator's Brochure) with more events in participants treated with tezepelumab versus participants treated with placebo. None of the cardiac disorder SAEs was considered causally related to tezepelumab by investigators or Independent Adjudication Committee. There is no known mechanism by which blocking TSLP would lead to cardiac pathophysiology.	Participants with cardiac disorders that are not stable in the opinion of the investigator or who present meaningful abnormal findings in examination, lab assessments or ECG will be excluded based on eligibility criteria. All participants will be closely followed during the study for any adverse events, including serious cardiac events that are considered AESI.
Potential risks	**Summary of data/rationale for risk**	**Mitigation strategy**
Study intervention		
Serious hypersensitivity reactions	Systemic reactions to large therapeutic molecules can be IgE or non-IgE-mediated and are generally characterised by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnoea, wheezing, bronchospasm, nausea/vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can all be severe or life-threatening. Effects typically occur during or within several hours after study intervention but may be delayed. The administration of a monoclonal antibody can result in the formation of ADA. The occurrence of ADA could result in immune complex disease (Type 3 hypersensitivity reactions) with manifestations such as serum sickness, nephritis, and vasculitis, or altered tezepelumab levels or activity.	To mitigate the potential risk of serious hypersensitivity reactions during and after administration of tezepelumab, specific requirements for observing participants for AEs/SAEs and for monitoring vital signs are included in this CSP. In addition, medical equipment to treat acute anaphylactic reactions will be immediately available and site staff will be trained to recognise and treat anaphylaxis. Participants with sensitivity to any component of the study intervention or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation will be excluded. Participants who have a history of anaphylaxis or documented immune complex disease following any biologic therapy will also be excluded. Serious hypersensitivity reactions are an

Important Potential Risk	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
		AESI and these events will be monitored closely throughout the study.
Helminth infections	Potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to parasitic infestation/infection.	To decrease the risk of parasitic infestation or infection, participants who have a history of clinically significant infection, requiring treatment with systemic antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the run-in period or at randomisation; and participants with a helminth 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 will be excluded. Helminth infections are an AESI. Participants who develop such infections will be monitored closely throughout the study.
Study procedures		
COVID-19 Pandemic, risk of COVID-19 infection	There is the risk of exposure to COVID-19 to participants during site visits	Local guidelines will be followed to mitigate risk of participant's exposure to COVID-19. To identify potential COVID-19 infection during the study a COVID-19-related questionnaire is recommended prior to every visit. Visits will be deferred if abnormalities noted. Sites are recommended to follow local severe acute respiratory coronavirus 2 (SARS-CoV-2) testing guidelines, if applicable. COVID-19 vaccination is allowed during the study (see section 8.2.7 and Table 9). Refer to Appendix H Changes related to

Important Potential Risk	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
		COVID-19 Pandemic.

2.3.2 Benefit Assessment

Benefits for tezepelumab over placebo include a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics.

2.3.3 Overall Benefit: Risk Conclusion

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 and are in development for the treatment of severe asthma.
The benefit/risk assessment for tezepelumab in severe asthma based on the development through Phase 2 and Phase 3 (Menzies-Gow A et al 2021) is favourable.
More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tezepelumab may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints/variables
Primary	
• To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult participants with severe uncontrolled asthma compared with placebo	• Primary endpoint: Annualized asthma exacerbation rate (AAER) • Primary outcome measure: AAER ratio vs placebo over 52 weeks
Key secondary	
• To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo	• Secondary endpoint: change from baseline in pre-dose/pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV1) • Key outcome measure: Mean difference vs placebo at Week 52

• To assess the effect of 210 mg of tezepelumab SC Q4W on health status/health related quality of life compared with placebo	• Secondary endpoint: Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score • Key outcome measure: Mean difference vs placebo at Week 52
• To assess the effect of 210 mg of tezepelumab SC Q4W on asthma control compared with placebo	• Secondary endpoint: Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) Score • Key outcome measure: Mean difference vs placebo at Week 52
• To assess the effect of 210 mg of tezepelumab SC Q4W on asthma symptoms compared with placebo	• Secondary endpoint: Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) score • Key outcome measure: Mean difference vs placebo at Week 52
Other Secondary	
• To assess the effect of 210 mg of tezepelumab SC Q4W on other endpoints associated with asthma exacerbations	• Outcome variable: Time to first asthma exacerbation • Outcome measure: Asthma exacerbation hazard ratio vs placebo over 52 weeks • Outcome variable: Proportion of participants who did not experience an asthma exacerbation • Outcome measure: Difference in proportions vs placebo at Week 52 • Outcome variable: Annualized rate of exacerbations associated with emergency room (ER) visit or hospitalization[a] • Outcome measure: AAER ratio vs placebo over 52 weeks
• To assess the effect of 210 mg of tezepelumab SC Q4W on biomarkers	• Outcome variables: Change from baseline in fractional exhaled nitric oxide FENO (ppb) peripheral blood eosinophils total serum IgE • Outcome measure: Mean difference vs placebo at Week 52

• To assess the effect of 210 mg of tezepelumab SC Q4W on other asthma control metrics	• Outcome variables: Change from baseline in weekly mean rescue medication use weekly mean morning and evening peak expiratory flow (PEF) weekly mean number of nighttime awakenings • Outcome measure: Mean difference vs placebo at Week 52
• To evaluate the effect of 210 mg tezepelumab SC Q4W compared with placebo on health resource utilization due to asthma	• Outcome variables: Asthma specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • Outcome measures: Difference in number of asthma specific resource utilizations vs placebo over 52 weeks
• To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	• PK: Serum trough concentrations • Immunogenicity: Incidence of anti-drug antibodies
• To assess the effect of 210 mg of tezepelumab SC Q4W on general health-related quality of life,	• Outcome variable: European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score • Outcome measure: Mean difference vs placebo at Week 52
Safety	
• To evaluate the safety and tolerability of tezepelumab	• Adverse events (including serious adverse events [SAEs]) • Vital signs • 12-lead electrocardiograms • - Clinical laboratory tests (haematology, clinical chemistry, urinalysis)
CCI [redacted]	
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

[a] Terminology to describe emergency room/department and urgent care visits may differ between countries. All such visits have been captured as emergency room (ER) visits, which will be included in the analyses and outputs.

4 STUDY DESIGN

4.1 Overall Design

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

For details on the efficacy and safety endpoints, see Section 3.

This is a Phase 3, regional, multicentre, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of 210 mg of tezepelumab administered Q4W SC in adult participants with severe uncontrolled asthma.

A total of 396 participants will be randomized in the study in a 1:1 ratio to either tezepelumab or placebo (198 per group), with at least 70% of the participants from China. The rest of the participants will come from other countries. The participants will be stratified by region (China/non-China).

All participants must have been on a medium to high dose ICS for at least 3 months prior to screening (see Appendix F for definitions of medium to high dose ICS) and have been on at least one asthma controller medication with or without OCS in the 3 months prior to date of informed consent as per inclusion criteria 5 and 6.

The total study population will be monitored to ensure a broad participant distribution across 3 different key clinical factors. Approximately 40% of the total study population will be participants who are treated with a total daily dose of medium dose ICS as well as on at least one additional maintenance asthma controller medication with or without OCS in the previous 3 months prior to date of informed consent.

Approximately 40% of participants in the study will be required to have had at least 3 exacerbations in the past 12 months, with the remaining participants having had exactly 2 exacerbations. Details on acceptable documentation is specified in section 8.1.1.

The study will also aim to randomize approximately 55% of participants with <300 eosinophils/µl and approximately 45% of participants with ≥ 300 eosinophils/µl. In addition, a reasonable number of participants is expected to be randomized with < 150 eosinophils/µl and > 450 eosinophils/µl.

The anticipated percentages for the factors of historical exacerbations and blood eosinophils will be applied to the overall population as well as the China/non-China sub-population. The anticipated percentages for the factor of ICS dose will be different between China and non-China sub-population (with approximately 20% medium dose ICS participants in non-China region and approximately 50% medium dose ICS participants in China). When the target

percentage of participants for the ICS, exacerbations or eosinophil subgroup in a region (China or non-China) is reached, consideration will be given to closing the IRT/RTSM randomization for that subgroup within the specific region. Once a subgroup is closed, participants in the screening/run-in period in the closed subgroup will not be allowed to be randomized and will be screen failed.

Section 6.5 (Table 7 and Table 8) provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial.

The study will consist of a screening/run in period between 5-6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. During the treatment period, IP will be administered starting at Day 0 until week 48. IP will not be administered on week 52. Participants who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period. Further information is provided in section 7.1. Any new treatments that are initiated will be recorded in the eCRF.

Participants will complete a 12-week post treatment - follow-up period for the assessment of safety and anti-drug antibodies.

Two database locks (DBLs) are planned in this study. The primary DBL will be conducted after the last participant completes the 52-week double-blind treatment period; and the final DBL will be conducted after the last participant completes the last safety follow-up visit (Week 64). After the primary DBL, the study treatment allocation for participants will become known to the sponsor staff. The blind will be maintained for the investigators, investigational site staff and participants until the final DBL.

During the screening/run-in period the participant must undergo all assessments per Table 1.

Prior to randomization the participants must meet all inclusion /exclusion criteria. If a participant does not meet all inclusion criteria or meets any exclusion criteria as per section 5.1 and section 5.2, the participant will be screen failed. Rescreening is allowed only once. Further details are specified in section 5.4.

4.2 Scientific Rationale for Study Design

The purpose of this study is to provide evidence of the efficacy and safety of 210 mg dose of tezepelumab administered Q4W SC in participants with a history of asthma exacerbations and severe uncontrolled asthma receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS.

The primary (AAER) and key secondary endpoints (lung function and asthma control) are well accepted measures for a study in severe asthma. These endpoints have been shown in the Phase 2b and Phase 3 studies to clearly differentiate the tezepelumab benefit from placebo. In

order to avoid bias the study will be randomized and double blinded. Participant entry will be stratified by region (China/non-China) to ensure equitable distribution for analysis.

Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma. Due to the mechanism of action, it is expected that severe asthmatics irrespective of their phenotype of asthma would benefit from treatment with tezepelumab. Participant entry into the study will be monitored to ensure that there are adequate numbers of participants within different phenotypes (high and low eosinophils, medium and high dose ICS, and number of exacerbations in the previous year) for analysis.

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 20101183, 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 that 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.

The dose of CCI has been selected for evaluation in asthma populations with a body weight of ≥40 kg.

The study is designed to dose participants at Q4W with the last dose given at week 48, EOT visit at week 52, and a 12-week follow-up period.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under Food and Drug Administration (FDA) and European Union (EU) regulatory requirements:

EU requirements define study completion as the last visit of the last participant for any protocol related activity.

FDA requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

In this study, the end of study is defined as when the last participant has completed his/her last scheduled contact.

In this study, a participant is considered to have completed the study when he/she has completed his/her last scheduled contact.

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

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of 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 participants who are at, or over the age of majority (as per local law).

The ICF process is described in Appendix A 3.

Age

2. Participants must be 18 to 80 years of age inclusive at the time of signing the informed consent form.

Type of participant and disease characteristics

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

4. Participants who have received a physician-prescribed asthma controller medication with medium or high dose ICS as per GINA guideline (GINA 2017) for at least 6 months prior to Visit 1.

5. Documented treatment with a total daily dose of either medium or high dose ICS (≥ 500µg fluticasone propionate dry powder formulation equivalent total daily dose) for at least 3 months prior to Visit 1. The ICS can be contained within an ICS/LABA combination product.

   - Equivalent ICS doses as detailed in Appendix F.

6. At least one additional maintenance asthma controller medication is required 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.

7. Morning pre-BD FEV1 <80% predicted normal at either Visit 2 or Visit 2a.

8. Evidence of asthma as documented by either:

   Documented historical reversibility of FEV1 ≥12% and ≥200 mL in the previous 12 months prior to Visit 1.

   OR

   Post-BD (albuterol/salbutamol) reversibility of FEV_1 ≥12% and ≥200 mL during screening (15-30 min after administration of 4 puffs of albuterol/salbutamol) at either Visit 2 or at Visit 2a.

   Note: refer to Appendix I - Clarification on the post-BD spirometry at Visit 2 or Visit 2a.

9. Documented history of at least 2 asthma exacerbation events within 12 months prior to Visit 1, and at least one of the exacerbations should occur during the treatment of medium-to-high dose ICS. These can be as follows:

- An asthma exacerbation is defined as a worsening of asthma that required treatment with systemic corticosteroids for at least 3 consecutive days (a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids).

OR

- An emergency room visit (defined as evaluation and treatment for <24 hours in an ER or urgent care center) that required systemic corticosteroids (as per above).

OR

- An inpatient hospitalisation due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours.

NOTE: For participants receiving a stable maintenance dose of OCS, a temporary increase for at least 3 consecutive days over and above the stable existing maintenance dose qualifies as an exacerbation.

The below defines what is acceptable to document exacerbations in this program:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant 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.
- Participants can provide 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 participant 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 participant 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 participant records have been unsuccessful.

10. ACQ-6 score ≥1.5 at Visit 1

Weight

11. Weight ≥40 kg at Visit 1

Reproduction

12. Negative serum pregnancy test for female participants of childbearing potential at Visit 1.

13. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from screening, and must agree to continue using such precautions for 16 weeks after the final dose of 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 vasectomised sexual partner, Implanon™, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch ™ or Nuvaring™.

    - 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.

14. Inclusion Criterion# 14 removed with Version 3.0 of Clinical Study Protocol.

Inclusion criteria at randomization:

15. ACQ-6 score ≥1.5 on the day of randomization

16. Fulfilment of at least one of the following conditions over the 7 days prior to randomization:

    - ≥ 2 days with a daytime or night-time symptoms score ≥1
    - Reliever SABA use on > 2 days
    - ≥ 1 awakening due to asthma requiring SABA use

17. Minimum compliance of 70% with daily eDiary during the run-in (having a minimum of 15 fully compliant days in the 21 days up to and including the day of randomization - Day 0).

    A compliant day requires completion of evening eDiary and subsequent morning eDiary such that an ASD daily score can be calculated.

    - The run-in period for this criterion is defined as the period between eDiary assignment (evening assessment) and the randomization visit (morning assessment).

18. Minimum of 4 days with complete (Evening and subsequent morning) daily eDiary in the 7 days prior to randomization (Evening assessment Day -7 to Morning assessment Day 0 - randomization visit).

19. Minimum of 70% with background asthma medication(s) as captured in the eDiary during the run-in period (having a minimum of 15 fully compliant days in the 21 days up to and including the day of randomization - Day 0).

    - Days with missing eDiary data treated as non-compliant for this criterion

20. Acceptable inhaler, peak flow meter, and spirometry techniques during the run-in period.

5.2 Exclusion Criteria

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

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 participant throughout the study
   - Influence the findings of the study or the interpretation
   - Impede the participant's ability to complete the entire duration of study

3. History of cancer:

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

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

4. History of a clinically significant infection, including upper (URTI) or lower respiratory tract infection (LRTI), requiring treatment with antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the 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 participants with smoking history ≥ 10 pack-years and participants using vaping products, including electronic cigarettes. Former smokers with a smoking history of <10 pack years and users of vaping or e-cigarette products must have stopped for at least 6 months prior to Visit 1 to be eligible.

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

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

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

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

Prior/concomitant therapy

11. Receipt of any marketed 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 longest) prior to Visit 1.

    Note: Participants on previous biologics treatment are allowed to enter the study provided the appropriate washout period is fulfilled.

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

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

15. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period, and/or receipt of any COVID-19 vaccine within 28 days prior to date of randomization.

16. Participants that have been treated with bronchial thermoplasty in the last 12 months prior to Visit 1.

Prior/concurrent clinical study experience

17. Known history of sensitivity to any component of the IP formulation or a history of drug or other allergy that, in the opinion of the investigator, contraindicates their participation (see section 6.1.1).

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

19. Concurrent enrolment in another clinical study involving an IP.

20. Participant randomization in the current study or previous Tezepelumab studies.

21. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or site staff), or participants employed by or relatives of the employees of the site or sponsor.

Diagnostic assessments

22. Any clinically meaningful abnormal finding in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete the entire duration of the study.

23. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2 times the upper limit of normal (ULN) at Visit 1.

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

Other exclusions

25. Pregnant, breastfeeding, or lactating women.

    A serum β-HCG pregnancy test (by central laboratory) must be drawn for women of childbearing potential at the screening visit. If the results of the serum β-HCG (from central laboratory) cannot be obtained prior to dosing of the IP, a participant may be enrolled on the basis of a negative urine/serum pregnancy test (by local laboratory, following local requirement), though serum β-HCG must be obtained. If either test is positive, the participant should be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant menstrual history and sexual history, including methods of contraception, should be considered. Any participant whose menstrual and/or sexual history suggests the possibility of early pregnancy should be excluded.

26. Unwillingness or inability to follow the study procedures, in the opinion of the investigator.

5.3 Lifestyle Considerations

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

5.3.1 Meals and Dietary Restrictions

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

Participants should not eat or drink 1 hour prior to having FENO assessment.

5.3.2 Caffeine, Alcohol, and Tobacco

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

Current smokers or participants 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 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.

5.3.3 Activity

Participants 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 participants who consent 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 participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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

5.4.1 Re-screening

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

Participants with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to Visit 1or 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), participants may potentially be re-screened. These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF).

Any re-screened participant will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF) 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). If the timeframe between screening and re-screening is more than 30 days, then all Visit 1 assessments should be repeated.

Participants who experience an asthma exacerbation during the screening/run-in period 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.

Rescreened participants should be assigned the same participant number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

IMPORTANT: Re-screening for participants who have screen-failed due to PRO criteria (e.g. ACQ-6 score <1.5, did not meet minimum symptom requirement, or did not report adequate compliance with maintenance medications) is not allowed.

Re-screening of a participant for any other reason will be allowed only upon approval of the AstraZeneca Study Physician. A documented approval for re-screening should be filed in the Investigator Study File (ISF).

6 STUDY INTERVENTION

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

Study intervention in this study refers to tezepelumab or placebo.

6.1 Study Intervention(s) Administered

6.1.1 Study Interventions

Table 5 Study Interventions

Arm name	Treatment 1	Treatment 2
Intervention name	Tezepelumab	Placebo
Type	Drug	Drug
Dose formulation	CCI [redacted]	0.7% (w/v) sodium carboxy methyl cellulose in 10 mM acetate, 250 mM L-proline, 0.01% (w/v) polysorbate 80, pH 5.0
Unit dose strength(s)	210 mg	NA
Dosage level(s)	Refer to section 6.2	Refer to section 6.2
Route of administration	Subcutaneous (SC) Injection	Subcutaneous (SC) Injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study treatment will be provided in 5 mL vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in 5 mL vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

6.1.2 Medical Devices

The MasterScope with integrated ECG (manufactured by eResearchTechnology®) and NIOX VERO (manufactured by Circassia®) are provided for use in this study.

Instructions for medical device use are provided in the device user manuals.

6.2 Preparation/Handling/Storage/Accountability

IP will be supplied to the site in a kit with one vial of either tezepelumab or placebo. Each kit has a unique number that is printed on all labels within the kit (i.e., the outer carton label and the label of each container within the carton).

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Please note: During the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration may be performed at the participant's home by a qualified HCP. Please refer to Appendix H for further details.

Dose Preparation

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

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

To prepare the participant's dose, the IP will be selected for administration according to the kit identification numbers assigned by the IRT/RTSM. One vial of IP will be assigned by IRT/RTSM for each dose.

Dose preparation steps:

1. Allow the vial to equilibrate at room temperature (about 30 minutes to 1 hour). Ensure that the vial is adequately protected from light during the warming process. Gently swirl the vial to ensure the contents are mixed to a clear, homogeneous solution. Do not shake.

2. To prepare IP for administration remove the tab portion of the vial cap and clean the stopper with 70% ethyl alcohol or equivalent.

3. Attach a 21G 1½-inch sterile disposable needle to a 2mL or 3mL sterile syringe.

4. Withdraw 1.9 mL of the IP from the vial.

5. Remove and discard the 21G 1½-inch sterile disposable needle from the syringe.

6. Attach a new 27G ½-inch sterile disposable needle to the same syringe in step 5.

7. Apply the appropriate label to the syringe.

The assigned vial should be used at one time to prepare the dose required at each visit. Unused product in opened and dispensed vials should not be used for subsequent dosing and should be stored for IP accountability. If the opened and dispensed vials must be discarded immediately after dose preparation as per site's SOP, the kit boxes must be retained for IP accountability.

The IP will be administered by one SC injection (see Table 6) and must be prepared using disposable plastic syringes and aseptic technique.

Table 6 Study Intervention Dose Preparation

Dose	Number of vial(s) required	Syringe size required	Total volume administered
CCI	1	2mL or 3 mL	1.9 mL
Placebo	1	2mL or 3 mL	1.9 mL

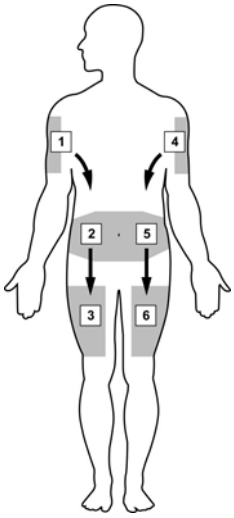
[a] Due to the gradations available on 2mL or 3 mL disposable plastic syringe, dose based on 1.9 mL administered volume is 209 mg.

Dose Administration

IP will be administered by a qualified healthcare professional (e.g., pharmacist or study nurse) at the site. The injection site must be recorded in the source documents at each treatment visit and in the eCRF. The person administering the dose will wipe the skin surface of the upper

arm, anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90 degree angle approximately halfway into the SC tissue. The IP will be slowly injected (at least 5 second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. It is advised that the site of injection of IP be rotated such that the participant receives IP at a different anatomical site at each treatment visit. In cases when rotation of the injection site is not feasible and/or the participant prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents. The suggested injection site rotation sequence is presented below in Figure 2.

Figure 2 Suggested Schema of Rotation of Injection Sites



Participants should be observed for a minimum of 2 hours after administration of the first two IP administrations for the appearance of any acute drug reactions. For the remaining doses, participants will be observed for a minimum of 1 hour after IP administration for any such reaction.

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

- The participant received allergen immunotherapy injection on the same day as scheduled IP administration.
- The participant has an intercurrent illness that in the opinion of the investigator may compromise the safety of the participant in the study (e.g., viral illnesses).
- The participant is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.

The visit should be rescheduled within the allowed visit window and IP should be administered at that visit. If this is not possible the IP administration should be skipped. If a participant skips 2 consecutive IP administrations, the AZ study physician should be contacted to discuss further participation.

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

6.3 Measures to Minimise Bias: Randomization and Blinding

Participant enrolment and randomization

The Investigator(s) will:

1. Obtain signed informed consent from the potential participant before any study specific procedures are performed.
2. Assign the potential participant a unique enrolment number (which begins with an 'E') via the Interactive Web Response System/Interactive Voice Response System (IRT/RTSM).
3. Determine participant eligibility.
4. Assign the eligible participant a unique randomization code via the IRT/RTSM.
5. Participants will be allocated to receive tezepelumab or placebo in a 1:1 ratio. Randomization will be stratified by region (China /non-China). Randomization numbers will be grouped in blocks. If a participant withdraws from the study, then his/her enrolment/randomization code cannot be reused. Withdrawn participants will not be replaced.

Specific information concerning the use of the IRT/RTSM will be provided in a separate manual.

Procedures for handling incorrectly enrolled or randomized participants

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

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the participant from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the participant and AstraZeneca study physician must ensure the decision is appropriately documented. Participants that are discontinued from treatment should be followed up according to the options described in section 7.1.1. 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.

Methods for assigning treatment groups

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

The randomization code will be assigned from a randomization list prepared by a computerized system provided by Parexel Informatics on behalf of AZ (AZRand). All participants will be stratified at randomization by region (China versus non-China). At least 70% of the participants will come from China. The rest of the participants will come from other countries.

Ensuring blinding

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

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

The following personnel will have access to the randomization list:

- Those carrying out the packaging and labelling of IP
- Those generating the randomization list
- Personnel at the IXRS company
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- Bioanalytical lab analyst performing the PK sample analysis

The information in the randomisation list will be kept from other personnel involved in the conduct of the study and in a seure location until agreed to break the blind.

After the primary DBL, the study treatment allocation for participants will become known to the sponsor staff. The blind will be maintained for the investigators, investigational site staff and participants until the final DBL.

Additional procedures to ensuring blinding in case of local laboratory usage can be found in section 8.2.5.2.

Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized participant, will be available to the Investigator(s) and delegate(s) at the study sites from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each site.

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

AstraZeneca retains the right to break the treatment code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and until the primary DBL has been documented.

6.4 Study Intervention 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 ICS asthma medications taken in the 12 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment.

To satisfy inclusion criteria 5, a history of continuous treatment with medium or high dose ICS plus a second controller medication for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF prior to the date of randomization.

In order to satisfy inclusion criterion 6, a history of all asthma controller medications for the 3 months prior to Visit 1 until the end of the study should be documented in source and recorded in the eCRF. No changes are allowed to background asthma medications throughout the duration of the study except during the treatment of an asthma exacerbation.

All other medications taken for conditions other than asthma in the 3 months prior to Visit 1 and COVID-19 vaccine given at any time must be recorded in the eCRF along with reason for treatment by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2).

Maintenance asthma medication is not regarded as an IP, but will be provided/reimbursed by AstraZeneca according to local regulations in order to maintain appropriate oversight and access to this concomitant therapy.

As theophylline has a narrow therapeutic window, please note that participants on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented before Visit 1. If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analysed at the central or local lab as applicable. Investigator can use their time and other factors that may impact the results. 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 participant 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 7 Restricted medications

Medication/class of drug:	Usage
Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. The participants should be instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment (please refer below for long-acting bronchodilator restrictions). Use of SABA should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at Visit 1. Twice daily bronchodilators should be withheld for at least 12 hours prior to the scheduled FENO and spirometry at site. Once daily bronchodilators should be withheld for at least 24 hours prior to the scheduled FENO and spirometry at site. Participants will not need a washout of their asthma medications for unscheduled visits due to asthma worsening.
Short-acting beta-agonists (SABA)	Regular scheduled use of SABA is not allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. PRN use is allowed if needed, however attention should be paid to the following restrictions. SABA should be withheld for at least 6 hours prior to scheduled spirometry, FENO, ECG at site with the exception of any unscheduled visits due to asthma worsening. When possible, home PEF assessments should be taken after the SABA is withheld for at least 6 hours.

Table 7 Restricted medications

Medication/class of drug:	Usage
Additional Maintenance Controllers	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. Once daily LABA or LAMA should be withheld for at least 24 hours prior scheduled spirometry and FENO at site visits with the exception of any unscheduled visits due to asthma worsening. Twice daily LABA or LAMA containing therapies should be withheld for at least 12 hours prior to scheduled spirometry and FENO at site with the exception of any unscheduled visits due to asthma worsening. LTRA should be restricted for at least 24 hours prior to scheduled spirometry and FENO at site with the exception of any unscheduled visits due to asthma worsening. Participants on theophylline should have blood concentration levels within therapeutic range documented before proceeding in the study. Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry and FENO at site with the exception of any unscheduled visits due to asthma worsening. Once daily theophyllines should be withheld for at least 24 hours prior to scheduled spirometry and FENO at site with the exception of any unscheduled visits due to asthma worsening.
Short-acting anticholinergics (e.g. ipratropium)	These are not allowed as a rescue treatment for worsening asthma symptoms from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. They may be used for managing an asthma exacerbation event.
Inactive/killed vaccinations (e.g. inactive influenza)	Allowed provided they are not administered within 5 days before or after any IP dosing visit.
COVID-19 vaccination	Refer to Section 8.2.7

Table 7 Restricted medications

Medication/class of drug:	Usage
Allergen immunotherapy	Allowed, if on stable therapy for at least 2 months prior to date of Visit 1 with no anticipated change during the treatment period. These should not be administered on the same day as IP administration.

Table 8 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 maintenance treatment of asthma, asthma exacerbations in screening/run-in, and protocol defined asthma exacerbations on or after Visit 3)	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.
Any marketed (e.g. omalizumab, mepolizumab, reslizumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of Visit 1, throughout the entire, screening run in period, treatment period (even if the participant has discontinued IP) and until the follow up visit week 64.
Other study interventions (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 until the follow up visit week 64.

Table 8 Prohibited medications

Prohibited medication/class of drug:	Usage
Herbal remedies for the treatment of bronchodilation (refer to the product label)	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.

6.5.1 Rescue Medicine

SABA should be withheld for at least 6 hours prior to scheduled site visit spirometry, FENO, ECG at site with the exception of any unscheduled visits due to asthma worsening. When possible, home lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Albuterol (US)/salbutamol (ex US) rescue medication will be provided by the sponsor and obtained locally.

Regularly scheduled SABA use in the absence of any asthma symptoms is not allowed from enrolment (Visit 1) and throughout the study duration. Prophylactic use of SABA (e.g. prior to planned exercise) or any other use than to curb worsening of asthma symptoms should be documented in medical notes and entered in the eCRF. Any such prophylactic use of SABA must not be recorded in the Asthma Daily Diary.

Rescue use of SABA administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation. Occasions where SABA is administered via nebulization will be recorded separately from metered dose inhaler inhalations in the eDiary.

6.5.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.5.3 Bronchial Thermoplasty

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

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Participants who complete week 64 should be given standard of care at the discretion of the investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants may be discontinued from study intervention in the following situations.

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. Participants who discontinue study treatment will be encouraged to remain in the study to complete all remaining study visits during the 48 weeks treatment period.

- Participant decision. The participant is at any time free to discontinue IP treatment, without prejudice to further treatment
- Adverse Event considered to jeopardize the safety of a participant participating in the study
- Pregnancy
- Severe non-compliance with the Clinical Study Protocol
- 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 participants who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins
- Development of one or more of the following:
    - Confirmed ALT or AST increase of ≥ 8 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 intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

Participants 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 the study withdrawal are detailed below in section 7.2. If the participants decide to withdraw consent, then the reason for this must be recorded separately in the eCRF.

A participant 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. Participants 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 64 even if the participant 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 pharmacodynamics effects of tezepelumab reference should be made to the investigator brochure.

All participants who prematurely discontinue IP should return to study center and complete the procedures described for the premature IP Discontinuation visit (IPD) at 4 weeks (+/- 5 days) post last IP administration.

Participants who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessment.

At the IP discontinuation visit the participant will be given three options as to how they will be followed:

1. The participant should be encouraged to return for all regular clinic visit and performed all scheduled assessments until he/she completes a total of 52 weeks treatment period.
2. The participants will be offered follow-up on a monthly basis via telephone calls while continuing ediary and ePEF completion (no further procedures will be performed), until the participants completes 52 weeks in the study. In addition to the PRO assessments that are performed at home, the participant may also complete the other clinic specified PRO assessments (as defined in the SoA) at home as well. The

participants should return for a follow up visit 16 weeks (+/-5 days) (refer to SOA, V19-week64) post last IP administration and for the EOT visit at Week52 (+/- 5 days).

3. If the participants cannot or does not wish to comply with any of the options above, (or any component of them such as only telephone based visits without completion of the ediary and ePET), they will complete a follow-up visit at 16 weeks (+/- 5 days) (refer to SoA, Visit19-week64) post last IP administration. After this visit the Investigator will only contact the participant at 52 weeks post-randomization. No other study assessments will be performed prior to this contact.

If the last IP administration was after week 36 for option 1 or 2, the participant will return to the clinical for an EOT visit at Week52 (+/- 5 days), and for option 3, the investigator will contact the participant at 52 weeks post randomization. The participant for option 1, 2 and 3 will then return for a follow-up visit 16 weeks (+/- 5 days) post last IP administration (refer to SoA, V19-Week 64).

The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2. Participants who do not wish to have any follow-up contacts will be discontinued from the study. All discontinued participants must return the ediary and ePEF devices at the EOT visit.

If the participant choose option 1, all assessments will be completed as per the SoA as indicated in Section 1.3. If the participant chooses 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, health care utilization, and asthma exacerbation information.

Participants who initially choose option 1 or 2 and subsequently cannot or do not wish to comply with the requirements of their option can continue with a less intensive option (i.e. participant initially choosing option 1 can continue with option 2 or 3, participants initially choosing option 2 can continue with option 3).

If a participant discontinues IP due to a study specific discontinuation criterion, this should always be recorded as “Development of study specific discontinuation criteria” on the Discontinuation of Investigational Product form in the eCRF.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, without prejudice to further treatment, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records) as per section 7.1.1

- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant 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 participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.
- A participant who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up participants as medically indicated. A withdrawal visit is essential to collect as much data as possible for the participant as per EOT visit described in SOA, Table 2. The participant will return all study supplied equipment including Home PEF meter and eDiary. Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRFs as well as in the Informed Consent Form (ICF) or assent form.

7.2.1 Withdrawal due to recruitment completion

When the required number of participants are randomized in the study, ongoing participants 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 and eCRF. As with screen failures, no further study related follow-up of these participants is required.

7.2.2 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 participants and if relevant give appropriate medical treatment, take necessary measures and document these in the source notes.

7.3 Lost to Follow up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study. Should the participant be unreachable at the end of the study, the participant 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 participant 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 participant using publicly available sources, if allowed by local regulations.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples

- The investigator will ensure that data are recorded on the electronic Case Report Forms (CRFs). 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 electronic CRFs. A copy of the completed electronic CRFs will be archived at the study site. Additional data to assess the impact of COVID-19 pandemic will be collected.

8.1 Efficacy Assessments

8.1.1 Assessment of asthma exacerbation

Participants enrolled in the study should have had at least 2 or more exacerbations in the prior 12 months before Visit 1. 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 participant 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 participant 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 participant 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 participant records have been unsuccessful.

During the study an asthma exacerbation will be defined as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least consecutive 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.

- An emergency room (ER) or urgent care visit (UC) (defined as evaluation and treatment for <24 hours in an emergency department or UC center) due to asthma that required systemic corticosteroids (as per the above).

- An in-patient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

Note: The protocol defined exacerbations will be recorded on the exacerbation "EXACATE" eCRF page. Terminology to describe ER and UC visits may differ between countries. All such visits have been captured as ER visits on the eCRF page.

The ePRO device will be programmed to alert both the participant and study centre when certain prespecified worsening thresholds are crossed as below. The purpose of the alerts is to trigger a contact between the site and participant for further evaluation if deemed necessary by the investigator.

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or

- An additional nebulized β2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or

- An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criteria should be met on 2 consecutive days), and/or

- An increase in total asthma symptom score (the sum single-item global assessment of daytime symptoms [evening assessment] and single-item global assessment of nighttime [morning assessment] of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days.

Where an alert is triggered as a result of the 2-consecutive day rule, the alert will be reset following activation such that alerts cannot be triggered on consecutive days.

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

The start of an exacerbation is defined as the start date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visits

requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier.

The end date of an exacerbation is defined as the last date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visit, or date of hospital discharge, whichever occurs later.

If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation.

All asthma exacerbations that occur during the treatment period and follow up, must be recorded in the exacerbation eCRF. See section 8.3.5 for additional information recording asthma exacerbations as an AE/SAE during the study.

8.1.2 Spirometry

8.1.2.1 General Requirements

Lung function (FEV_1 and $FEF_{25-75\%}$) will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study center personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important

- Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.
- Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.
- Participants should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below:
-
  - SABAs 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 theophyllines should be withheld for at least 12 hours prior to scheduled spirometry at site.
- Once daily theophyllines for at least 24 hours prior to scheduled spirometry at site.

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

Time of day for scheduled center visit spirometry

Spirometry testing should be done according to the SoA. For adult participants, 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 visit (Visit 3).

All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Detailed procedure for performing spirometry will be described in a separate instruction manual. Details regarding assessment of the quality of spirometry and the best test report (BTR) process will also be detailed in the manual.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the Predicted Normal Values (PNV) and are pre-programmed into the spirometer (Quanjer PH et al 2012).

FEV_1, expressed as percent of the PNV, will be calculated as follows:

$$FEV_1\% \text{ of PNV} = (FEV_1 \text{ measured}/FEV_{1PNV}) \times 100$$

8.1.2.2 Post-BD spirometry and FEV_1 reversibility assessment

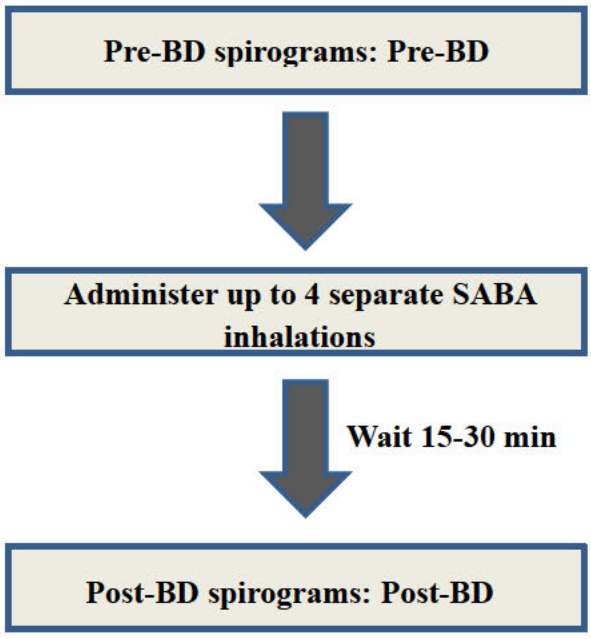
All participants must meet inclusion criteria 8 either by having documented historical reversibility or by demonstrating reversibility either at Visit 2 or Visit 2a.

If documented historical reversibility is available, the post-BD spirometry procedures must be performed at Visit 2 to categorize participants (establish baseline characteristic) prior to randomization. The documented historical reversibility must be recorded in the

eCRF/spirometer prior to randomization. Further details will be provided in a separate instruction manual.

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 participant 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 participant's heart rate, tremor or safety; the reason should be noted in the participant'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.

Visit 2a is an optional visit at which the reversibility testing/ post BD spirometry can be repeated, if the inclusion criteria were not met or the participant was unable to perform good quality spirometry.

The highest technically acceptable pre- and post-BD FEV_1 will be used to determine reversibility.

Reversibility is calculated as follows:

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

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, enrollment 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 participant's charts.

8.1.3 Home PEF testing

An electronic, hand-held spirometer to measure PEF will be provided to the participant after inclusion criteria 7 and 8 has been met. This can be either at Visit 2 or at Visit 2a.

Home PEF testing will be performed by the participant in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home PEF should start from the evening of Visit 2 or Visit 2a until the morning of Visit 17 (Week 52) using an ePEF meter device supplied by the vendor (eResearch Technology Inc.). When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

Participants should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing.

The Investigator/authorized delegate will check participant's adherence to correct use of the peak flow meter at each visit as shown in SoA (or on EOT visit if prematurely discontinued from the study).

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

8.1.5 CompEx

CompEx is defined as follows (Fuhlbrigge et al 2017):

An exacerbation (as defined in section 8.1.1) and/or

An objective deterioration defined as 2 of the following criteria for ≥ 2 consecutive days:

- ≥15% decrease from baseline in morning or evening PEF

AND at least one of the following:

- ≥1.5 puffs increase from baseline in rescue medication morning or evening
- ≥1 score increase from baseline, or the absolute maximal asthma symptom score in the morning or evening

Or one of the criteria above together with all diary variable showing a slope of worsening over at least a 5-day period.

8.1.6 Patient reported outcomes

Patient reported outcomes (PRO) data will be captured electronically using a handheld device at home and at the site. Site personnel will be trained on the use of both devices. Detailed

procedures for using both devices and participant training on use of the handheld device will be described in a separate instruction manual. Participants will be trained on at home use of the eDiary and ePEF meter at Visit 2 or 2a. The site staff will set assessment reminder alarms on the device. Participant training will include explanation of functionality and proper use of the ePEF meter. Training will emphasize the importance of completing the PRO assessments as scheduled to capture the participant's experience and meet the objectives of the study. The participant will be asked to use both devices as part of the training to verify completion of training on the eDiary. The questionnaires will be administered in the handheld device at home in the following order: Asthma Symptom Diary, Rescue medication, Total Asthma symptom score, nocturnal awakening, maintenance medication, peak expiratory flow assessment.

At home PRO assessment will start the evening of Visit 2, if the participant meets inclusion criteria 7 and 8 at this visit. If only one of these criteria are met at Visit 2, the at home ePRO assessment should be deferred to the evening of Visit 2a, after the other criteria is also met. Participants will complete assessments twice daily and at other timepoints specified in the SOA.

The investigator/authorized delegate will check participant’s adherence to the PRO assessment schedule as is necessary to maintain necessary to minimize missing data and at each study visit. Frequent compliance checks between visits will be necessary to ensure sufficient data is available to meet inclusion criteria 17, 18 and 19.

8.1.6.1 Daily Diary

The daily diary will be completed each day from the evening of Visit 2 or Visit 2a to the morning of Visit 17. The morning eDiary will include: Asthma Symptom Diary (ASD) morning items, questions about rescue medication, nighttime awakening, and use of maintenance medications. The evening eDiary will include: ASD evening items and questions about rescue medications. Upon completion of the morning and evening questions the participant will complete the peak expiratory flow assessment.

There will be triggers in the ePRO device to alert the participants to signs of worsening of asthma and to contact their physician, please refer to section 8.1.1. The participant should contact the investigator for evaluation after receiving a diary alert.

ASD

Asthma symptoms will be recorded using the ASD (Globe et al 2015), which comprises 10 items (5 items in the morning; 5 items in the evening). The morning items assess nighttime symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and the frequency of nighttime awakening. The evening items assess symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and activity limitation since

waking. Items are scored from "0" (no symptom, no nighttime awakening, or no activity limitation) to "4" (very severe symptom, unable to sleep, or extreme activity limitation). A daily ASD score is the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. Calculation of a daily ASD score requires data from the evening diary assessment and the subsequent morning diary assessment. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4.

Global asthma symptom items

In addition to the ASD, participants will complete a single item global assessment of asthma symptoms (0-3) each morning and evening. The sum of evening and subsequent morning single global item scores (0-6) will be used for the alerts system.

Rescue medication

The number of rescue medication inhalations (puffs) and nebulizer treatments taken will be recorded by the participant in the Asthma Symptom Diary twice daily (i.e., in the morning and evening) beginning the evening of Visit 2 or Visit 2a until the morning of Visit 17. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and the morning will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the participant in the Asthma Symptom Diary each morning, beginning in the morning after Visit 2 or Visit 2a until the morning of Visit 17, by answering a question as to whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Maintenance medication

Maintenance medication administration will be recorded in the Asthma Symptom Diary once daily in the morning, beginning in the morning after Visit 2 or Visit 2a until the morning of Visit 17.

8.1.6.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and short-acting β2-agonist use via participant-report.

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.

ACQ-6 will be completed at the beginning of site visits using an eDiary in accordance with the SoA.

8.1.6.3 Standardised asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma participants. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Participants are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline. The AQLQ(s)+12 will be completed using the eDiary in accordance with the SoA.

8.1.6.4 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Based on empirical data and interviews with participants, a mean change score of 4 units is associated with a minimum clinically important difference (MCID). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009). SGRQ will be completed at the beginning of site visit using eDiary in accordance with the SoA.

8.1.6.5 European quality of life-5 dimensions-5 levels (EQ-5D-5L)

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems,

slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The participant will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the participant will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The EQ-5D-5L will be completed using the eDiary in accordance with the SoA.

8.1.6.6 Sino-nasal Outcome Test (SNOT-22)

The SNOT-22 is a 22-item health-related outcomes assessment for sinonasal conditions (Hopkins et al 2009). The tool is a modification of the SNOT-20 (Piccirillo et al 2002) where items related to nasal blockage and loss of sense of tastes and smell have been added and the importance rating has been removed. The 22-question SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110 (higher scores indicate poorer outcomes); a MCID of 8.90 has been established (Hopkins et al 2009).

The SNOT-22 will be completed at the site visits in accordance with the SoA.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 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 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 8.3.5 for details.

8.2.2 Weight and height

Weight and height will be measured in accordance with the SoA. The participant's weight will be recorded in kilograms, and height will be recorded in centimeters. Weight and height measurements will be performed in light clothing and with shoes off.

8.2.3 Vital Signs

Vital signs (i.e. pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with 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 participant in a quiet setting without distractions (e.g., television, cell phones).

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

Respiration rate will be obtained after participant 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 ECG will be taken in supine position, prior to blood draw, spirometry, BD administration and IP administration.

The investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. In case of discrepancy between the investigator's interpretation and that provided by the ECG machine (if applicable), the investigator's interpretation will take precedence and should be noted on the printout and recorded in the eCRF. A copy of the ECG will be produced and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine is used for assessment throughout the participant's participation in the study.

ECG data and evaluation will be recorded in the eCRF.

8.2.5 Clinical Safety Laboratory Assessments

See Table 9 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

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

Table 9 Laboratory safety variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S-Alkaline phosphoatase (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
B-Mean Corpuscular Volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Chloride
Urinalysis	S-Creatinine
U-Hb/Erythrocytes/Blood	S-Creatinine kinase (CK)
U-Protein/Albumin	S-CRP
U-Glucose	S-Gamma-glutamyl transpeptidase (GGT)
U-Microscopy and culture as required*	S-Glucose
	S-Phosphorus
	S-Potassium
	S-Sodium
	S-Total cholesterol
	S-Uric acid

*Urine samples will be analysed by the central laboratory only when a positive urinalysis result for any parameter is observed.

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

8.2.5.1 Pregnancy Test

The following tests are applicable to female participants only, and will be conducted in accordance with the schedule provided in section 1.3.

- Serum ß-human chorionic gonadotropin (ß-HCG) – the test done at enrolment (Visit 1) only, for WOCBP (analysed at central laboratory).
- FSH – the test done at enrolment (Visit 1) only, for female participants to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months.
- Urine or Serum HCG* – the test will be performed locally at the study site for WOCBP at each treatment visit before IP administration. Positive test result must be confirmed with serum β-HCG by central lab.
- Note: * the study site can perform urine HCG or Serum HCG before IP administration, which source documentation (test report) should meet local regulatory requirements.

8.2.5.2 CCI [redacted]

The sponsor and site will be blinded to the CCI [redacted] from the central laboratory reports after randomization. However if the global central laboratory kit shortage and/or other logistical factors limit access to the central laboratory, investigators could be unable to perform central lab assessments and in these situations they may use local laboratory for safety assessments.

To mitigate the risk of unblinding in case of a need to perform local safety laboratory assessments, the requested tests should be restricted to the relevant test(s) required, where possible. For example, if hemoglobin is desired, the investigator should avoid ordering a complete blood cell count with a differential count. In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice.

AstraZeneca should be notified of all local safety laboratory assessments that are required by the investigator, without being revealed the eosinophil, basophil or monocyte counts.

To maintain the blind in case of local laboratory results use, site staff who are directly involved in the participant's management should remain blinded to any blood eosinophil, basophil and monocyte counts results included as part of an outside laboratory report or electronic medical record. Similarly, CCI [redacted] results must be redacted from all communications with the adjudication committee and the sponsor.

8.2.6 Other Safety Assessments

8.2.6.1 Serology

Hepatitis B surface antigen, hepatitis C antibody will be tested in Central lab, HIV-1 and HIV-2 antibodies will be performed in local lab. All these testing will be assessed at enrolment (Visit 1) only. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

8.2.7 COVID-19 vaccination

COVID-19 vaccines are either nucleic acid vaccines (which can include DNA plasmid and mRNA), recombinant vector vaccines (non-replicating viral vectors) or inactivated virus vaccines. DNA plasmid and mRNA vaccines are considered an inactivated vaccine. Recombinant vector candidates potentially may be in a new category. Based on available publications on mRNA and virus vector anti-SARS CoV-2 vaccines, the immune response developed rapidly after vaccination administration. No live attenuated COVID-19 vaccines are currently available. For vaccines that are currently approved under emergency use authorization (EUA) or approved in the future, please refer to relevant health authority websites for further guidance.

Please note that any live attenuated vaccine is prohibited during study conduct (see Table 8).

Given the limited long term safety data of COVID-19 vaccines and the potential to confound the interpretation of safety results in the study, the following COVID-19 vaccination guidance (Table 10) should be followed depending on the study period.

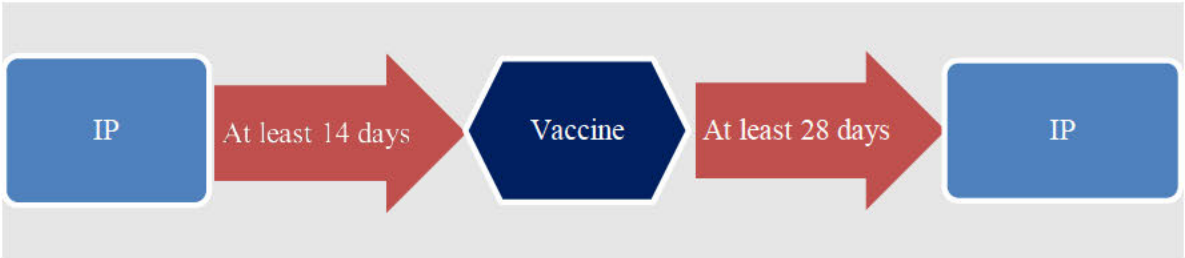
Table 10 COVID-19 Vaccination guidance

Study Period	Vaccine usage
Participants at screening/run-in period	• If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated or scheduled to be vaccinated before the screening or run-in visit, the randomization visit should be scheduled to ensure that the first IP dose is administered at least 28 days after any vaccination dose. As these intervals might change, please discuss with the study physician for most current recommended time interval prior to any vaccine dose. See exclusion #15 in section 5.2.
Participants in treatment period	• If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated during the study, **IP dosing can continue but IP should not be administered within 14 days before or 28 days after a dose of vaccine.** As these intervals might change, please discuss with study physician for the most current recommended time interval prior to any vaccine dose. • If participant receives COVID-19 vaccine less than 14 days from the

	last IP dose, the next IP administration should be rescheduled or skipped to ensure the next IP dose is at least 28 days after the vaccine administration. • COVID-19 vaccination schedule should follow country specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the IP dosing/COVID-19 vaccination intervals are maintained • Study visits should still be conducted within the protocol specified time window even if a participant receives a COVID-19 vaccine dose. However, even if IP is not administered at a study visit because of COVID-19 vaccination restrictions, other site visit assessments should still be performed according to the SoA (Table 2). • At every study visit during the treatment period, the investigator must ask if the participant has received or is planning to receive a COVID-19 vaccination. This is to ensure that the required time interval for IP dosing (mentioned above) is maintained. • If it is anticipated that a participant will miss two consecutive IP administrations, the AstraZeneca study physician should be contacted to discuss further participant participation in the study. • The reason for skipping IP administration should be recorded with "COVID-19" prefix in medical records and COVID-19 related eCRF modules.
Participants in Follow-up period	• If COVID-19 vaccination is in the best interest of the participant, COVID-19 vaccination could be administered. Participant should follow schedule of assessments listed in Table 2; no special adjustments are needed. It is advised that participant wait for 14 days after the last IP dose.

The suggested IP dosing/COVID-19 intervals are also summarized in Figure 4. As these intervals might change, please consult the Study Physician to confirm the most current recommended time interval, prior to any vaccine dose.

Figure 4 COVID-19 Vaccination Between IP dosing



Reporting of COVID vaccination:

COVID-19 vaccine details including vaccine's name/manufacturer, route of administration, and vaccination date should be entered into the eCRF CM module.

If a participant experiences an AE/SAE associated with COVID-19 vaccination, the investigator should record this in source document and determine whether the IP should be continued, skipped or permanently discontinued in accordance with section 7.1

8.3 Adverse Events and Serious Adverse Events

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

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

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised 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 8.3.2.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

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

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

8.3.2 Follow-up of AEs and SAEs

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

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

Adverse event variables

'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
- Maximum Intensity
- Investigator causality rating against the Study Intervention(s) (yes or no)
- Action taken with regard to Study Intervention(s)
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

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

8.3.3 Causality Collection

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

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

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

Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant 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 eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (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, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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

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

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

- The sign or symptom is serious according to definitions, see Appendix B
- The participant discontinues IP due to the sign or symptom

- The sign or symptom is new to the participant or not consistent with the participant's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfils any of the above criteria

8.3.6 Hy's Law

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

8.3.7 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:

- Serious hypersensitivity reactions
- Malignancy
- Helminth infections
- Serious infections[a]
- Guillain Barre Syndrome
- Serious cardiac events

[a]eCRF 'Severe infections' pages to be completed for infections which are defined as SAE, or requiring treatment with systemic antiviral medications, intravenous antibiotics or medications for helminth parasitic infection, or requiring a permanent discontinuation of study drug.

8.3.8 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative will work with the investigator to ensure that all

the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Once the investigators or other site personnel indicate an AE is serious in the web-based data capture (WBDC) system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

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

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

8.3.9 Pregnancy

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

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

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.9.1 Maternal Exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be

reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.9.2 Paternal Exposure

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

8.3.10 Medication Error, Drug Abuse and Drug Misuse

If an event of medication error, drug abuse, or drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.8) and **within 30 days** for all other events.

8.3.10.1 Medication Error

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

The full definition and examples of medication error can be found in Appendix B4.

8.3.10.2 Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.10.3 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.11 Management of IP-related toxicities

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. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix E .

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifest 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

Participants will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 3 and 5, participants should be observed for a minimum of 2 hours

after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, participants will be observed for a minimum of 1 hour after IP administration for any such reaction.

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

8.3.12 Independent Adjudication Committee (IAC)

An independent adjudication committee is constituted to provide an external independent assessment of blinded data during the Phase 3 trials to confirm the diagnosis and causality of MACE events (defined in the IAC charter), serious cardiac events, deaths, as well as the diagnosis of malignancies that occur from randomization until the end of the follow up period.

This independent adjudication committee, also evaluates cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of follow up period, to evaluate whether any such event is due to a worsening of asthma. The committee includes specialists in pulmonology, cardiology, neurology and oncology and operates in accordance with dedicated Adjudication Committee Charter/Manual of Operations.

8.3.13 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 participant is the preferred method to inquire about AE occurrences.

8.4 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 on IMP or AstraZeneca NIMP and possible symptoms of an overdose are not established.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the Study Clinical Lead, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
    - An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics and immunogenicity

8.5.1 Collection of samples and drug concentration

Serum samples for determination of tezepelumab will be collected pre-dose according to the SoA (Table 2).

Samples will be collected, labeled, 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.

8.5.2 Collection of samples to measure the immunogenicity of tezepelumab

The immunogenicity of tezepelumab will be assessed in serum samples according to the SoA (section 1.3).

Samples will be measured for the presence of ADAs and neutralizing antibodies (nAb) 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 with confirmed positive ADA will be analyzed for the presence of ADA-neutralizing antibodies.

Samples will be analysed by designated third party on behalf of AstraZeneca. Samples will be disposed of after the Clinical Study Report finalization.

8.5.3 Storage and destruction of pharmacokinetic/immunogenicity samples

The residual pharmacokinetic/immunogenicity samples aliquots may be retained for the purposes of reanalysis at AstraZeneca or designee for a maximum of 5 years after publication of the Clinical Study Report or as per local regulation, after which they will be destroyed. This is intended to allow AstraZeneca to investigate any anomalous results or respond to regulatory

authority questions. Samples will only be re-analysed according to the original purpose for which they were collected (eg pharmacokinetic / immunogenicity analysis).

8.5.4 Pharmacodynamics

Pharmacodynamic parameters will be evaluated using biomarkers (see section 8.6).

8.6 Biomarkers

Serum samples will be collected according to the schedule in Table 2 to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to asthma.

Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to the centers.

8.6.1 Storage, re-use and destruction of biomarker samples

Samples will be stored and disposed according to local laws and regulations. Summaries and analyses for biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving tezepelumab to generate hypotheses to be tested in future research.

8.6.2 Serum Immunoglobulins

The levels of total CCI [redacted] will be tested by a central laboratory in accordance with the SoA. Instructions for sample collection, processing, storage and shipment will be provided in a separate laboratory manual.

8.6.3 Other Study Related Biomarker Research

Not Applicable

8.7 Optional Genomics Initiative Sample

Not applicable

8.8 Healthcare Resource Utilization and Health Economics

Healthcare resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. At randomization, Healthcare Resource Utilization (HRU) information will be collected with a 'one year' recall period. All the subsequent visits will collect HRU information with a recall period of 'since the last scheduled visit'. The data may be used as input to health economic analysis for example cost utility analysis or cost effectiveness analysis. Protocol-mandated procedures, tests, and encounters are excluded. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The following two-sided hypotheses will be evaluated in this trial. The nominal significance levels and methodology for accounting for multiplicity in testing these hypotheses is described in Section 9.4.

Primary endpoint

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

versus

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

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

Key secondary endpoints

H02: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) = 0

versus

H12: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means greater than 0.

H03a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) = 0

versus

H13a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means greater than 0.

H03b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) = 0

versus

H13b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means less than 0.

H04: Difference in mean change from baseline in weekly mean daily ASD score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14: Difference in mean change from baseline in weekly mean daily ASD score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means less than 0.

9.2 Sample Size Determination

Approximately 396 participants will be randomly assigned to study treatment using 1:1 allocation between the two treatments. The sample size is estimated based on the primary endpoint (AAER) only.

198 participants per arm are planned to be randomized assuming a 10% dropout rate to obtain 178 completers. With 178 participants per treatment group, it is estimated that for the primary endpoint (AAER), assuming a placebo rate of CCI and a shape parameter of CCI (over-dispersion), there will be 90% power to detect a rate reduction of CCI at a 2-sided significance level of 5%. The methodology used is described in Keene et al (2007) and Zhu and Lakkis (2014). The minimum detectable rate reduction with the above assumptions is CCI.

The study is powered based on the primary endpoint (AAER) only and not for the subsequent multiple testing procedures of the key secondary endpoints described in Section 9.4.

China will contribute at least 70% of the 396 participants. The remaining participants will be contributed by other countries.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All participants analysis set	All enrolled participants who sign the ICF.
Randomised participants analysis set	All participants randomized to study treatment (irrespective of whether study treatment is subsequently taken).
Full Analysis Set (FAS)	All participants randomized to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.

Safety Analysis Set	All participants who received at least one dose of IP.
Pharmacokinetic (PK) Analysis Set	All participants in the full analysis set who received active (tezepelumab) treatment and had at least one detectable serum concentration from a PK blood sample collected post first dose which is assumed not to be affected by factors such as protocol deviations.

For analysis of efficacy variables, participants will be assigned to the FAS (defined above) according to their randomized treatment.

Safety presentations and anti-drug antibodies (ADA) presentations will be based on the safety analysis set, with participants assigned according to their actual treatment. Further details of how actual treatment will be determined for analysis in the event of treatment dispensing errors etc. will be specified in the statistical analysis plan (SAP). Any important deviations from the randomized treatment assignment, and any participants that have received study intervention without being randomized, will be listed and considered when interpreting the safety data.

Summaries of PK will be based on the PK analysis set.

9.4 Statistical Analyses

Two DBLs are planned in this study. The primary DBL will be conducted after the last participant completes the 52-week double-blind treatment period. The final DBL will be conducted after the last participant completes the last safety follow-up visit (Week 64).

After the primary DBL, the study treatment allocation for participants will become known to the sponsor staff. The blind will be maintained for the investigators, investigational site staff and participants until the final DBL. All personnel involved with the analysis of the study will remain blinded until the primary DBL. Important protocol deviations will be identified prior to unblinding at the primary DBL.

All analyses of the primary and secondary endpoints will be performed based on the primary DBL data. Additional summaries based on the final DBL data will be produced as appropriate. Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be prepared prior to review of any potential treatment-revealing data is undertaken and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data at the primary DBL. The SAP will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. 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.

Frequency and percentages of participant disposition and reasons for discontinuation of IP will be presented. Participants who prematurely discontinue the IP will be listed along with

the reason for discontinuation. In addition, frequency and percentages of withdrawal from the study together with reasons will be presented.

Demographics and participant characteristics will be summarized by treatment group using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) using the FAS.

Relevant medical history/current medical conditions will be summarized by treatment group, system organ class and preferred term of the MedDRA dictionary using frequency and percentage of participants for each treatment group.

Prior and concomitant medications, categorized according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarized by treatment group as frequency and percentage of participants reporting usage. Prior medications are defined as those which stopped before first dose of IP. Concomitant medications are defined as those which either started or continued after first dose of IP.

Important protocol deviations will be defined at participant level prior to unblinding at the primary DBL and will be summarized by treatment group. With the exception of the PK analysis set, participants will not be excluded from analysis sets on the basis of any important protocol deviations. The definitions of each category of important protocol deviation will be fully specified in the study Non-compliance Handling Plan and will include (but may not be limited to): participants who were randomized to study treatment without fulfilling key entry criteria; participants who received prohibited or restricted concomitant medications during IP treatment, participants who received the incorrect study treatment or study dose at any time during the 52-week double-blind treatment period.

9.4.1 General Considerations

9.4.1.1 Multiple testing procedures

The overall Type 1 error rate will be strongly controlled at the 0.05 level across the primary and key secondary endpoints. The following hierarchical testing strategy will be applied, ordered by clinical relevance, with the hypotheses to be tested as defined in Section 9.1:

Level 1

The null hypothesis H01 will be tested at a 2-sided 5% significance level with regard to the primary endpoint (AAER).

Level 2

If H01 is rejected at the 2-sided 5% significance level, then the null hypothesis H02 will be tested at a 2-sided 5% significance level with regard to change from baseline in pre-BD FEV_1.

Level 3

If H02 is rejected at the 2-sided 5% significance level, then the null hypotheses H03a and H03b will be simultaneously tested at an overall 2-sided 5% significance level with regard to:

- change from baseline in AQLQ(S)+12 total score
- change from baseline in ACQ-6 score

using a truncated Hochberg approach. In general, under this approach, the highest of the two ordered p-values within Level 3 will be evaluated at a $\gamma\alpha + (1-\gamma)\alpha/2$ significance level (2-sided), and the lowest of the 2 ordered p-values within Level 3 will be evaluated at a $\gamma\alpha/2 + (1-\gamma)\alpha/2$ significance level (2-sided), where $\alpha = 0.05$, and where γ is the truncation parameter ($0 \leq \gamma \leq 1$).

It is noted an intermediate choice $0 < \gamma < 1$ of the truncation parameter represents a choice between these extremes of regular Hochberg (corresponding to $\gamma = 1$) and Bonferroni approaches ($\gamma = 0$), balancing considerations of how stringent hypothesis testing should be in Level 3 in order to claim significance, versus the ability to subsequently claim significance from formal hypothesis testing in Level 4. In this trial γ will be set to 0.5.

Using this choice of truncation parameter, the highest of the two Level 3 p-values will be evaluated at a 3.75% significance level (2-sided). If it is significant at the 3.75% level, then both hypotheses H03a and H03b will be rejected, and testing will proceed to Level 4. If it is not significant at the 3.75% level, then the lowest of the 2 Level 3 p-values will be evaluated at a 2.5% significance level (2-sided). If it is significant, then the relevant null hypothesis (either H03a or H03b) will be rejected, and testing will proceed to Level 4. If it is (also) not significant, then formal testing will stop at Level 3. The significance levels for subsequent evaluation in Level 4 for each of these scenarios are given below.

Level 4

The null hypothesis H04 will be tested at the significance level retained from Level 3, which depends on the outcomes in Level 3 as follows:

- Case 1: If both comparisons in Level 3 exhibit statistical significance, then H04 will be tested at a 2-sided 5% significance level with regard to change from baseline in weekly mean daily ASD score.
- Case 2: If only one of the comparisons in Level 3 exhibits statistical significance, then H04 will be tested at the 2-sided significance level $\alpha - [\gamma\alpha + (1-\gamma)\alpha/2]$ retained from Level 3, where $\alpha = 0.05$.

Using the proposed choice of $\gamma = 0.5$, if both H03a and H03b were rejected in Level 3, then H04 in Level 4 will be tested at a 2-sided 5% significance level (Case 1). If only one of H03a and H03b was rejected in Level 3, then H04 in Level 4 will be tested at a 2-sided 1.25% significance level (Case 2).

9.4.1.2 Definition of baseline

In general, the last measurement on or prior to the date of randomization will serve as the baseline measurement for efficacy endpoints while the last measurement prior to the first dose of study treatment will serve as the baseline measurement for safety endpoints. If there is no value on or prior to randomization (or the first dose of study treatment, depending on the endpoint), then the baseline value will not be imputed and will be set to missing.

For weekly means derived from participant diaries, baseline is defined as the mean of the available data in the most recent week prior to the date of randomization. If more than 3 days are missing, then the baseline weekly mean will be set to missing. The "most recent week" starts with the evening measurement one week prior to the date of randomization and ends with the morning measurement on the day of randomization.

Further details regarding baseline definitions will be provided in the SAP.

Change from baseline is defined as the absolute difference between the measurement at the relevant post-baseline time point and the baseline value.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary analysis of the primary efficacy endpoint (AAER over 52 weeks) will quantify the effect of the initially randomized treatment, regardless of the treatments that participants actually received, or whether the participants received other controller therapy/rescue medications post IP discontinuation. This analysis will therefore include all available data after treatment discontinuation until the end of the planned treatment period. Participants will be encouraged to continue to undergo applicable study related visits/procedures for the full 52-week period even after premature discontinuation of IP. Consequently, participants lost to follow-up and participants who withdraw their consent will be the only source of missing information for the primary analysis. Missing data will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to perform the statistical test specified in Section 9.1, and to estimate the treatment effect and its 95% confidence intervals. The response variable in the model will be the number of asthma exacerbations experienced by a

participant over the 52-week study period (or shorter duration if not followed up for the full 52 weeks). Treatment, region (China or non-China) and history of exacerbations (≤2 or >2 in previous 12 months) will be included as factors in this model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable in the model, to adjust for participants having different follow-up times during which the events occur. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, will not be included in the calculation of time at risk for exacerbation.

Descriptive summaries of the asthma exacerbations will also be presented.

Annualized rates for the individual exacerbation criteria (emergency room visits due to asthma that required systemic corticosteroids, hospitalization due to asthma, or use of systemic corticosteroids) will be summarized descriptively. The exacerbations associated with emergency room visits or hospitalisations and the exacerbations associated with hospitalisations only will be analyzed using a similar model as for the primary endpoint, respectively.

Subgroup analyses, and exact definition of all relevant categories where needed, will be pre-specified in the SAP.

Sensitivity analyses on the primary endpoint will be performed and will be fully specified in the SAP. These may include, but not necessarily be limited to:

- Analysis which makes provision for data to be missing-not-at-random (MNAR) and which makes different assumptions regarding those participants who discontinue treatment or study prior to 52 weeks.
- Analysis which uses the exacerbation data captured whilst receiving study treatment only
- Analysis in which adjudication outcomes of the ER or urgent care visits, hospitalizations and all deaths are considered.

9.4.2.2 Secondary Endpoint(s)

The main analysis of the key secondary endpoints (changes from baseline to Week 52 for each of pre-BD FEV_1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean daily ASD score) will quantify the effect of the initially randomized treatment at Week 52, regardless of the treatments that participants actually received, or whether the participants received other controller therapy/rescue medications, including participants who discontinued study treatment prior to Week 52. This analysis will therefore include all available data after treatment discontinuation until the end of the planned treatment period. Missing data will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

Change from baseline for the key secondary endpoints in the tezepelumab group will be compared to that seen in the placebo group using a linear model for repeated measures. In this model, inference will be based on the restricted maximum likelihood estimation. This model will be used to perform the statistical tests specified in Section 9.1, and to estimate the treatment effect at Week 52 and its 95% confidence interval for each endpoint. The response variable in the model will be change from baseline at each scheduled post-randomization visit up to and including Week 52, and irrespective of whether the participant remained on treatment and/or took other treatments. Treatment, visit, region (China or non-China) and treatment by visit interaction will be included as factors in this model. Baseline of the corresponding endpoint will also be included in the model as a continuous linear covariate. Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant. If this model fails to converge with unstructured covariance, the SAP will pre-specify the approach for selecting a simpler covariance structure. The Kenward-Roger approximation to estimating the degrees of freedom will be used for tests of fixed effects derived from this model.

Descriptive summaries of the key secondary endpoints will also be presented. Adjusted means from the repeated measures model above will be displayed graphically over time and used to evaluate time of onset of effect.

Subgroup analyses, and exact definition of all relevant categories where needed, will be pre-specified in the SAP.

Sensitivity analyses on the key secondary endpoints will be performed and will be fully specified in the SAP. These may include, but not necessarily be limited to, the same items considered for the primary endpoint in Section 9.4.2.1.

As a supportive analysis to the analysis of change from baseline in ACQ-6, the main ACQ-6 analysis described above will be repeated for change from baseline in ACQ-5 and ACQ-7 score using a similar repeated measures model. Similar descriptive and graphical summaries will also be produced.

As further supportive analyses to the analyses of change from baseline in ACQ-6 and AQLQ(S)+12, responders/non-responders (as defined in Sections 8.1.6.2 and 8.1.6.3) will be summarized descriptively and analyzed using a generalised linear model for repeated measures, using a logit link function. In this model, inference will be based on generalised estimating equations using the method of Liang and Zeger (1986). The response variable in this model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 52, irrespective of whether the participant remained on treatment and/or took other treatments. Treatment, visit, region (China or non-China) and treatment by visit interaction will be included as factors in the model. Baseline of the corresponding endpoint

will also be included in the model as a continuous linear covariate. Further details will be specified in the SAP.

9.4.2.3 Analysis of other efficacy endpoints

Annualized rates for other relevant endpoints will be summarized descriptively and analyzed using a similar model as for the primary endpoint (Section 9.4.2.1).

Other binary endpoints will be summarized descriptively and analyzed using a logistic regression model with factors which will include treatment, region (China or non-China). Baseline of the corresponding endpoint will also be included in the model (where relevant) as a continuous linear covariate.

Other continuous endpoints will be summarized descriptively and analyzed using a repeated measures model analogous to that specified for key secondary endpoints (Section 9.4.2.2). Log transformation of endpoints prior to implementing the repeated measures model will be considered for continuous endpoints which do not meet the distributional assumptions, and this will be pre-specified in the SAP where possible.

Time to first asthma exacerbation will be summarized graphically using Kaplan-Meier estimates, and analyzed using a Cox proportional hazards model with factors for treatment, region (China or non-China) and history of exacerbations (≤2 or >2 in previous 12 months).

Further details of statistical models for other efficacy endpoints will be specified in the SAP, including details of how missing data and data collected after premature discontinuation of study treatment will be handled.

Sensitivity and subgroup analyses will not be performed on other efficacy endpoints, unless specified otherwise in the SAP.

9.4.3 Safety

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in force at the primary DBL. The definition of on-treatment and on-study for AE analyses will be given in the SAP.

The number and percentage of participants with on-treatment and on-study AEs will be tabulated separately by preferred term and system organ class. An event that occurred one or more times during a period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all participants in the safety analysis set. On-treatment AEs will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a participant report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the participant's worst occurrence (most severe/most related) will be tabulated.

Serious AEs, AEs leading to discontinuation from IP, and commonly occurring AEs will be summarized in a generally similar manner. AEs, SAEs, AEs leading to death, and AEs leading to discontinuation of IP will be summarized for each treatment group as applicable.

An overall summary of on-treatment AEs will be presented by treatment group adjusted for participant exposure to treatment.

AEs of Special Interest (AESIs), as defined in Section 8.3.7 will also be summarized descriptively by treatment group.

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

Vital signs data will be summarized by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital signs abnormalities will be summarized. Abnormal ECGs as per Investigator's overall interpretation will be summarized.

9.4.4 Other Analyses

Tezepelumab serum concentrations will be summarized using descriptive statistics by visit. Observed serum concentrations of tezepelumab for each individual will be listed by visit.

The prevalence and incidence of ADA will be reported by treatment group. ADA data will be summarized using descriptive statistics at each visit by treatment group. Samples confirmed positive for ADA will be tested for neutralizing antibodies (nAb) and the nAb status will be summarized by treatment group. The potential effects of ADA status and ADA titer on PK of tezepelumab will be evaluated. The potential association of immunogenicity with efficacy and safety may be evaluated if appropriate.

Additional analyses assessing the impact of COVID-19 will be specified in the SAP.

9.5 Interim Analyses

No interim analyses are planned in this trial.

9.6 Data Monitoring Committee

Not applicable

10 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 (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- 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

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

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical

investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
    - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

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 participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised 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 centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened 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 authorised designee will explain to each participant the objectives of the exploratory research. Participants 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 participant will give a separate agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will indicate this in the ICF. If a participant 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 analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

During the COVID-19 pandemic, re-consent may be obtained remotely and/or verbally if local/regional guidelines allow in order to reduce the risk of participants of COVID-19 exposure during clinic visits. For further details please refer to **Appendix H**.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised 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://astrazenecagrouptrials.pharmacm.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 participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan; Non-compliance handling plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved 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 participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the monitoring plan

A 9 Study and Site Start and Closure

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

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

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

Reasons for the early closure of a study site by the sponsor or investigator may include but are

not limited to:

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

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

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

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

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

Life-threatening

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

Hospitalisation

Outpatient treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, 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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific 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 jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

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

Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of

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

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another 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 recognised feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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 recognised that could have led to an error

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

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

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

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)

- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route

- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

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

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

The investigator:

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

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

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

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. 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 participant meets potential Hy's Law (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 Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× Upper Limit of Normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN 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 ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, 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 (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

D 3 Identification of potential Hy's Law cases

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

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

Central laboratories being used:

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory 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 participant meets PHL criteria (see section 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the 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.

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

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

As soon as possible after the biochemistry abnormality was initially detected, the 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 participant 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

D 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 (18 December 2018)

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA 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 E Anaphylaxis: signs and symptoms, management

E 1 Introduction

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

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

E 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that participant (minutes to several hours): Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that participant's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigenantibody 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.

E 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

E 4 Management of Acute Anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

a. Place participant in recumbent position and elevate lower extremities.
b. Establish and maintain airway.
c. Administer oxygen.
d. Establish venous access.
e. Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

a. Consider epinephrine infusion.
b. Consider 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 participant taking b-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.

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Appendix F Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	**Medium**	**High**
Beclomethasone dipropionate (non HFA)	1000	>1000
Beclomethasone dipropionate (HFA)	400	>400
Ciclesonide	320	>320
Triamcinolone acetonide	2000	>2000
Flunisolide	2000	>2000
Fluticasone furoate (e.g. Arnuity® Ellipta®)	n.a.	200
Fluticasone propionate	500	>500
Fluticasone propionate HFA	440-500	>500
Budesonide	800	>800
Mometasone furoate	440	>440
Inhaled Corticosteroid in ICS/LABA combination[a]	**Medium**	**High**
Beclomethasone dipropionate (e.g. Fostair®)	400	>400
Fluticasone propionate HFA (e.g. Seretide®, Advair®)	500	>500
Fluticasone furoate (e.g. Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (e.g. Symbicort®)	640	>640
Mometasone Furoate (e.g. Dulera®)	400	>400

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

Appendix G Abbreviations

Abbreviation or special term	Explanation
AAER	Annuallized Asthma Exacerbation Rate
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AERR	Asthma Exacerbation Reduction Rate
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATS	American Thoracic Society
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
ASD	Asthma Symptom Diary
AST	Aspartate Aminotransferase
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
CGIC	Clinical – Global Impression of Change
CO_2	Carbon Dioxide
CompEx	Composite Endpoint for Exacerbations
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Event

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions 5 Level
EU	European Union
FEIA	Fluorescent Enzyme Immunoassay
$FEF_{25\%-75\%}$	Forced expiratory flow over 25-75% of the vital capacity
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
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IgG	Immunoglobulin G

Abbreviation or special term	Explanation
IL	Interleukin
IL-13	Interleukin-13
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IUO	Investigational Use Only
IVRS	Interactive Voice Response System
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
IXRS	Interactive Voice/Web Response System
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LAR	Late Asthmatic Response
LIMS	Laboratory Information Management System
LRTI	Low Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit
MAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimum Clinically Important Difference
MNAR	Missing-Not-at-Random
nAb	Neutralizing Antibodies
NIMP	Non-investigational Medicinal Product
OCS	Oral Corticosteroids

Abbreviation or special term	Explanation
OAE	Other Significant Adverse Event
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PEO	Performance Evaluation Only
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
PT	Preferred Term
Q4W	Every 4 Weeks
RTSM	Randomisation and Trial Supply Management
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SOA	Schedule of Assessment
SOC	System Organ Class
SDV	Source Data Verification
Th2	T Helper 2 Cells
TLC	Total Lung Capacity
TSLP	Thymic Stromal Lymphopoietin
TSLPR	Thymic Stromal Derived Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

Appendix H Changes Related to COVID-19 Pandemic

Appendix H Changes Related to COVID-19 Pandemic

During the COVID-19 pandemic, AZ will approve the continuation of the enrolment and randomization or if those activities will need to be temporarily placed on hold until the pandemic stabilizes in the area.

Participants who were screen failed due to a temporary recruitment pause due to the COVID-19 pandemic may be allowed to re-screen even if the participants have already been re-screened once before. A documented approval by study physician for re-screening due to COVID-19 should be filed in the Investigator Study File (ISF).

Screening visit, all run-in and randomization visits must be conducted on-site to complete the required assessments according SoA in order to confirm eligibility criteria.

If central laboratory kits are unavailable at the site due to production issues related to the COVID-19 pandemic, the visit window according to SoA may be extended in order to have the scheduled test conducted upon documented confirmation from AZ Study Physician.

The clinical safety laboratory tests according to SoA can be performed at a local laboratory if clinically indicated at the discretion of the Investigator. However, all laboratory assessments for Visit 1, Visit 3 and EoT or IPD Visit (as per SoA) must be analysed at the central laboratory.

Please Note: Changes below should only be implemented during the COVID-19 pandemic and if allowable by local/regional guidelines.

H 1 Home Visits to Replace On-Site Visits (where applicable)

Due to local travel restrictions and/or site restrictions, participants may not wish to or may not be able to go to the study site for study visits and related procedures. If an on-site visit is not possible, it is recommended to have a home visit with home administration of IP by a qualified HCP (up to Visit 16) or without administration of IP for EOT Visit and Visits 18 and 19, provided this is acceptable within local regulation/guidance. Additional information related to the visit can be obtained remotely by phone call and/or video conference. This is to ensure safety of the study participants and minimum disruption to IP administration that may occur during the COVID-19 pandemic.

Home IP administration will apply to participants that have completed at least two IP administrations on-site.

Study assessments, where possible to be performed at home, should be conducted according to the SoA. At minimum, during home visit the qualified HCP is expected to:

- Collect information on healthcare resources utilization
- Perform a physical examination
- Collect vital signs
- Collect adverse events
- Collect information on asthma exacerbation
- Review concomitant medications
- If possible, collect blood and urine sample according to the SoA
- Conduct urine pregnancy test (dipstick), prior to IP administration, if applicable
- eDiary data completion/review
- Administer IP
- Observe the participant for one hour after IP administration for the signs or symptoms of any acute drug reactions
- Document the visit

Please refer to the separate IP Home (or Alternative Site) Administration Instructions for more information.

H 2 Visits at an Alternate Location (where applicable)

Study visits including administration of IP and study assessments according to the SoA can take place at an alternative location away from infection risk zones, or closer to the participant's home, provided this is acceptable within local regulation/guidance and agreed with AstraZeneca Study Team.

Please refer to the separate IP Home (or Alternative Site) Administration Instructions for more information.

H 3 Remote Visits to Replace On-Site Visits (where applicable)

During the COVID-19 pandemic, on-site visits may be replaced by a remote visit (phone call and/or video conference) if participants cannot attend the visits at the study site, at an alternate site or have home visits and if allowed by local/regional guidelines.

Having a phone call and/or a video conference with the participant will allow conduct of study procedures including reporting of adverse events, concomitant medication, information on asthma exacerbation, e-Diary compliance and healthcare resource utilization while minimizing the risk to participants of COVID-19 exposure.

H 4 End of Treatment Visit

If the EOT visit at Week 52 cannot be performed on-site, at an alternate site or at the participant's home, the EOT visit should be conducted as a remote visit.

H 5 Re-consenting of Participants During the COVID-19 Pandemic

COVID-19 addendum to ICF must be obtained prior to starting any procedures according to Appendix H. If a participant is unable to travel to the site due to the COVID-19 pandemic, it is necessary to obtain re-consent remotely and/or verbally for the implementation of the new urgent changes in the study during the COVID-19 pandemic. This will minimize the risk to the participant of COVID-19 exposure with clinic visits. Confirmation of participant's re-consent needs to be documented in the source documents. Applicable local guidelines and regulations on re-consenting process should be followed.

Appendix I Clarification on the post-BD spirometry at Visit 2 or Visit 2a

All participants must perform Post BD spirometry assessment at Visit 2 or Visit 2a to demonstrate reversibility. The historical reversibility will be used for eligibility unless the participant demonstrates reversibility at either Visit 2 or Visit 2a.

1. **It is mandatory to perform a post-BD spirometry at Visit 2 (V2)** even if documented historical reversibility is available (refer to SoA, Table 1 footnote d and section 8.1.2.2).

2. The **historical reversibility data will not be used for eligibility** if **one** of the following options is met:

a. Post-BD **reversibility** of FEV1 ≥12% and ≥200 mL demonstrated **at V2**
b. Post-BD **reversibility** of FEV1 ≥12% and ≥200 mL failed V2 but demonstrated **at V2a**

As a reminder, if the reversibility was met at V2, it does not need to be repeated at V2a (refer to SoA, Table 1 footnote b)

3. **If reversibility test failed at V2 and:**

a. no documented historical reversibility in the previous 12 months prior to visit 1 is available, **it must be demonstrated at V2a**. If the post-BD test at V2a is not positive or performed, the inclusion criteria #8 will not be demonstrated and the participant will have to be screen failed.

b. documented historical reversibility in the previous 12 months prior to visit 1 is available, **it is allowed to conduct a post-BD test at V2a.** If the post-BD test at V2a is not performed, no protocol deviations will be reported as that is not a mandatory requirement and inclusion criteria #8 will be confirmed based on the historical data.

Appendix J Protocol Amendment History

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

Version 6.0, 10 Oct2022

The main reasons for this amendment include:
a) Updating the scope of assessment of the pre-specified events by the Independent Adjudication Committee,
b) Adding important potential risks and serious cardiac events as a new adverse event of special interest,
Other changes are minor non-substantial changes such as updating standard wording using the latest CSP template and correcting typos among others.

Changes to the protocol are summarized below.

Section 1.1 Synopsis & Section 3 Objective and endpoints:

- Added safety objective and endpoint into the table of objective and endpoint in Section 1.1
- Added wording 'Key' to the title of 'Secondary Objectives' and deleted 'Key' which prior to each
- secondary objective.
- Wording 'endpoint' was added to each secondary objectives
- Replaced 'Outcome measure' with' Endpoint/variable' in Section 1.1
- Added 'variables' in Section 3

Section 1.1 Synopsis, Independent Adjudication Committee and Section 8.3.12 Independent Adjudication Committee

- Updated language regarding Independent Adjudication Committee to amend the scope of the performed assessments.

Section 2.3 Benefit/Risk Assessment

- Added Table 3 Risk Assessment table: New category of "Important potential risks" including serious infections, malignancies and serious cardiac events added, "Potential risks of clinical significance" updated to "Potential risks" and text on risk of serious infections updated.

Section 1.1 Synopsis; Section 4.1 Overall design; Section 6.3 Measures to minimize bias:randomization and blinding; Section 9.2 Sample size determination

- The percentage of China participants has changed from approximately 70% to at least 70%.

Section 4.4 End of study definition

- Added clinical trial transparency information Added wordings 'In this study'

Section 6.2 Preparation/Handling/Storage/Accountability

- Remove the sentence 'The subject received COVID-19 vaccination or is planning to receive COVID-19 vaccination where the required time interval between IP dosing and COVID-19 vaccination as specified in section 8.2.7, Table 9'

Section 6.3 Measures to Minimise Bias: Randomization and Blinding

- Remove the capping specification

Section 6.5 Concomitant Therapy, Table 7

- Restriction for inactive/killed vaccinations (e.g. inactive influenza) revised from '5 days before or after any study visit' to '5 days before or after any IP dosing'.

Section 8.1.4 FENO

- Revised reference: 'Airway inflammation will be evaluated using a standardized single-breath FENO test in accordance with the SoA. The standard single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017).'
- Correction of reference Non-substantial Section 8.3.7 Adverse Events of Special Interest

Section 8.3.7 Adverse Events of Special Interest

- Added new AESI: 'Serious cardiac events'.
- Removed 'Injection Site reactions'.
- Replaced 'Anaphylactic reactions' and 'Immune complex disease (Type III hypersensitivity reactions' with 'Serious Hypersensitivity reaction'.
- Replaced 'Severe infections and Opportunistic infections' with 'Serious infections', and added a footnote clarifying when to complete the eCRF 'Severe infection' pages

Section 3, section 6.1, section 6.2, section 6.5, section 8.2.5 and section 8.2.7

- Updated table number from' Table 3, Table 4, Table 5, Table 6, Table7, Table 8, Table 9' to 'Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10'

Section 8.3.10 Medication error, drug abuse and drug misuse and Appendix B 4

- Added information about drug abuse and drug misuse
- Updated 'AstraZeneca study intervention' to 'IMP or AstraZeneca NIMP'

Section 8.4 Overdose

- Added information about investigator should evaluate and closely monitor the participants in an overdose event

Section 9.4.1.2 Definition of baseline

- Clarified the definition for change from baseline: replaced "postrandomization time point" by "postbaseline time point"

Appendix A1

- Added Regulatory Reporting Requirements for Serious Breaches

Appendix G Abbreviations

- Added abbreviations and explanation of IMP and NIMP Removed abbreviation and explanation of DAE

Section 11 References

- Added reference 'Alving et al 2017' and removed reference 'Dweik et al 2011'

Version 5.0, 17 May 2022

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 1-

- For routine safety measurements "Vital signs", detail in CSP section or Appendix changed from "Section 8.2.2" to "Section 8.2.3".
- For routine safety measurements "Weight, Height", details in CSP section or Appendix changed from "Section 8.2.1.1" to "Section 8.2.2".

- For routine safety measurements "12-lead ECG", details in CSP section or Appendix changed from "Section 8.2.3" to "Section 8.2.4".
- For laboratory assessments "Pregnancy or FSH test", details in CSP section or Appendix changed from "Section 8.2.4.1" to "Section 8.2.5.1".

Section 1.1, SoA, Table 2-

- For routine safety measurements "Vital signs", details in CSP section or Appendix changed from "Section 8.2.2" to "Section 8.2.3".
- For procedures "Weight", details in CSP section or Appendix changed from "Section 8.2.1.1" to "Section 8.2.2".
- For routine safety measurements "12- lead ECG", details in CSP section or Appendix changed from "Section 8.2.3" to "Section 8.2.4".
- For laboratory assessments "Pregnancy test", details in CSP section or Appendix changed from "Section 8.2.4.1" to "Section 8.2.5.1".

Section 1.1, Section 8.3.12- Added Cardiac SAEs into adjudication event, added "the causality relationship between IP and those events will be assessed by independent adjudication committee as well"

Section 1.1 Synopsis; Section 9.4.2.2 Secondary Endpoint(s); Section 9.4.2.3 Analysis of other efficacy endpoints- The model terminology for the main analysis of the key secondary endpoints changed to "a linear model for repeated measures", instead of "a mixed model for repeated measures (MMRM)".

Section 1.1 Synopsis: Section 1.1, SoA, Table 2; Section 9 Statistical Considerations- General update for abbreviation and clarification.

Section 2.2 Background- Updated to reflect new information based on Investigator's Brochure (IB) V 5.0.

Section 2.2 Background; Section 11 References- Summaries of Product Characteristics (SmPC) and United States Prescribing Information (US PI) for several asthma marketed products references were updated to the current versions.

Section 2.3 Benefit/Risk Assessment- Previous wording "More detailed information about the known and expected benefits and potential risks of tezepelumab may be found in the IB" changed to "More detailed information about the known and expected benefits and risks and safety profile of tezepelumab may be found in the IB".

Section 2.3.1 Risk Assessment- Previous wording "Tezepelumab has been well tolerated with no safety signals identified in studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 2 program. " changed to "Tezepelumab has been well tolerated with an acceptable safety

profile and no safety signals in subjects with severe, uncontrolled asthma identified in the completed studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 2 and Phase 3 studies "

Section 3 Objectives and endpoints; Section 9.4.2.1 Primary Endpoint(s)-

- Removed "urgent care visit" in outcome variable of Table 3 Objectives and Endpoints. Added a footnote in Table 3 for clarification.
- Removed "urgent care visit" in the statistical analyses for the individual exacerbation criteria.

Section 4.2 Scientific Rationale for Study Design- Updated "these endpoints have been shown in the Phase 2b study" to "These endpoints have been shown in the Phase 2b and Phase 3 studies".

Section 9.3 Populations for Analyses- Replaced "Enrolled" by "All subjects analysis set"; replaced "Randomly Assigned to Study Treatment" by "Randomised subjects analysis set".

Section 9.3 Populations for Analyses- Updated the definition of PK analysis set: replaced "concentration from a sample collected post-dose" by "concentration from a PK blood sample collected post-first dose which is assumed not to be affected by factors such as protocol deviations".

Section 9.4.1.2. Definition of baseline- Updated the definition of baseline for subject diaries endpoints: replaced "prior to the first dose of study treatment." by "prior to the date of randomization".

Section 9.4.2.1 Primary Endpoint(s)- Clarified that the exacerbations associated with the use of systemic corticosteroids alone would only be summarized descriptively and would not be analyzed by the negative binomial model.

Section 9.4.2.3 Analysis of other efficacy endpoints- Replaced "a logistic regression model" by "a generalised linear model for repeated measures using a logit link function" for the supportive responder analyses of ACQ-6 and AQLQ(S)+12.

Version 4.0, 25 August 2021

Changes to the protocol are summarized below.

Protocol Amendment Summary of Changes Table - Replaced VERSION HISTORY section. Instructional Text includes guidance for providing a clean version of the protocol, a track-changes version of the protocol, and a tabular listing detailing initial wording and amended or new wording for substantial amendments.

Synopsis. Number of Participants of Section 4.1 Overall design, Section 6.3 Measures to Minimise Bias: Randomization and Blinding. Methods for assigning treatment groups,

Section 9.2 Sample Size Determination - The percentage of China participants has changed from approximately 80% to approximately 70%.

Synopsis - For Tertiary/Exploratory objectives and outcome measures, move to Section 3" OBJECTIVES AND ENDPOINTS"

Synopsis - Clarifying definition of an enrolled participant

Section 2.3, Benefit/Risk Assessment - TransCelerate Level 3 sub-headings added with instructional text: 2.3.1 Risk Assessment – includes example table, 2.3.2 Benefit Assessment, 2.3.3 Overall Benefit: Risk Conclusion

Section 2.3.3, Overall Benefit: Risk Conclusion - This section is revised to include a reference to Phase 3 results. The benefit/risk assessment remains favourable.

Section 4.1, Overall design, Section 6.3, Measures to Minimise Bias: Randomization and Blinding. Methods for assigning treatment groups - The percentage of participants receiving a total daily dose of ICS classed as 'medium dose' has changed from approximately 20% to approximately 40% of the total study population, and will be approximately 50% of subjects in China.

Section 4.1, Section 6.2, Section 6.3, Appendix G- Replaced IVRS/IWRS with IRT/RTMS

Section 4.1, Overall design, Section 6.3 Measures to Minimise Bias: Randomization and Blinding. Methods for assigning treatment groups.- The distribution of participants between eosinophils <300 and ≥ 300 is changed from "a similar percentage" (50:50) to approximately 55% and 45% respectively.

Section 5.1, Inclusion criterion #8 - revised to provide reference to Appendix I. There have been no changes to the inclusion criterion requirements.
Section 5.2, Exclusion criterion #15 - revised to add that subjects who receive a COVID-19 vaccine within 28 days of randomization should be excluded from the study.

Section 6.2, Dose administration - This section has been revised to clarify how to handle subjects who received or plan to receive COVID-19 vaccination where recommended interval between IP dosing and vaccine administration cannot be followed.

Section 6.5, Concomitant Therapy - added the requirement for collection of COVID-19 vaccine information at any time in eCRF to align with the revisions in Table 5.

Section 6.5, Table 6 Restricted Medications - A reference has been added to this section for clarification about 'COVID-19 vaccination'.

Section 8.2.5.2, maintaining the blind to the subject's blood eosinophil, basophil and monocyte counts in cases of local laboratory usage - A new sub-section has been added to guide the sites on maintaining blind in case of local laboratory usage.

Section 8.2.7, COVID-19 vaccination - A new sub-section has been added to include COVID-19 vaccination recommendations during the study. These recommendations provide guidance to the sites on how to handle subject's vaccination during the study. This sub-section includes a new table (table 9 - COVID-19 Vaccination guidance) and a new figure(Figure 4 – COVID-19 Vaccination Between IP dosing).

Section 8.3 –

- Added the wording regard SAE after the end of study in 8.3.
- Moved "8.3.4 Adverse event data collection" into "8.3.2 Follow-up of AEs and SAEs"
- Added a new wording in 8.3.5, "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."
- Moved "Reporting of serious adverse events" to 8.3.8, add a new wording" For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol." In 8.3.8
- Moved "Pregnancy" to 8.3.9
- Moved "Medication error" to 8.3.10
- Moved "Management of IP-related toxicities" to 8.3.11
- Moved "Independent Adjudication Committee" to 8.3.12
- Moved "Method of detecting AEs and SAEs" to 8.3.13

Section 8.4 - Changed from Level 3 (8.4.3) to Level 2 heading. Add "one or 5 calendar days" requirement for providing information to the AstraZeneca Patient Safety data entry site.

Appendix A.1, Regulatory and Ethical Considerations - New safety language 'Regulatory Reporting Requirements for SAEs'

Appendix A.3, Informed Consent Process - Added Instructional text to include ethical concerns for the study (if any) and to consider the key elements of the Informed Consent process

Appendix A.4, Data Protection - Added common text that the participant will be required to give consent for their data to be used as described in the informed consent

Appendix A6, Dissemination of Clinical Study Data - Updated to correct web link: http://astrazenecagrouptrials.pharmacm.com

Appendix A7, Data Quality Assurance - Delete "physically".

Appendix A8, Source Documents - Delete "reported on the eCRF".

Appendix A.9, Study and Site Start and Closure - Added Suggested Text for study start date and the first act of recruitment， Added Common Text regarding sponsor responsibilities on premature termination/suspension of the study.

Appendix B2, Definitions of serious adverse event - New language about malignancy reporting.

Appendix H, Changes Related to COVID-19 Pandemic - These changes have been made to provide instructions for visit window extensions upon AZ study physician confirmation on a case-by case basis if central laboratory kits are unavailable at site due to COVID-19 pandemic issues and to clarify that all laboratory assessments at Visit 1, Visit 3 and EoT or IPD visit (as per SOA) must be analysed at the central laboratory

Appendix I, Clarification on the post-BD spirometry at Visit 2 or Visit 2a - These changes provide additional information about the requirement of collection of the post-BD spirometry at Visit 2 or Visit 2a and documented historical reversibility availability.

Version 3.0, 10 August 2020

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 1 – Due to a typographical error, incorrect inclusion criteria were listed in footnotes "e" and "f". Inclusion criteria 7 and 8 are now included for correctness.

Section 1.1, SoA, Table 2 – To correct the typo for footnote e and f. It should be "e, ECG must be collected prior to any blood draws, spirometry, BD administration and IP administration", "f, All blood sampling should be done prior to IP administration."

Section 1.1, SoA Table 2 – In case of re-screening, PK and immunogenicity assessments do not need to be repeated if already collected at the original Visit 3 so a clarification is added to footnote "p".

Section 1.1, SoA, Table 2 – Under Table 2 added guidance on how to proceed with respect to Schedule of Activities during the COVID-19 pandemic to ensure the safety of the study subjects, to maintain compliance with GCP and to minimize risks to data integrity.

Section 1.2, Synopsis – Objectives and Endpoints – Other Secondary Objectives;
Section 3, Objectives and Endpoints – Other Secondary Objectives – Revised outcome variable "Proportion of subjects with ≥1 asthma exacerbation" to "Proportion of subjects who did not experience an asthma exacerbation". This is considered to be a more relevant variable for the question of interest.

Section 1.2, Synopsis – Objectives and Endpoints – Exploratory objectives;
Section 3, Objectives and Endpoints – Exploratory Objectives – Replaced "patients" to "subjects" for consistency in use of the term "subjects" throughout protocol.

Section 1.2, Synopsis – Treatments and treatment duration - Added a note to refer to Appendix H for further guidance if subjects are unable to come to the site during the

COVID-19 pandemic. This change is to reduce the risk of COVID-19 exposure for subjects.

Section 1.2, study period – changed according to study progress.

Section 5.1, Inclusion criterion #8 – added a note to clarify that all subjects must perform Post BD spirometry assessment at Visit 2. In the absence of historical reversibility, the subject must demonstrate reversibility at either Visit 2 or Visit 2a as stated in Table 1 SoA.

Section 5.1, Inclusion criteria, removed criterion #14 – "Nonsterilized males who are sexually active with a female partner of childbearing potential must use a condom plus spermicide from Day 1 through 16 weeks after receipt of the final dose of IP. In those countries where the above-mentioned method for contraception is not available, a condom can be used alone. Male subjects must not donate or bank sperm during this same time period." To align with version 4.2 and 4.3 of the IB.

Section 5.1, Inclusion criterion #16 – use of SABA is required to meet the awakening condition due to asthma, therefore "requiring SABA use" is added for clarification.

Section 5.2, Exclusion criterion # 6 – revised criteria to add in restrictions related to the usage of vaping products "Current smokers or subjects with smoking history ≥10 pack-years and subjects using vaping products, including electronic cigarettes. Former smokers with a smoking history of <10 pack years and users of vaping or e-cigarette products must have stopped for at least 6 months prior to visit 1 to be eligible." To clarify the required timeframe for stopping of e-cigarettes prior to screening since its use is prohibited during the study.

Section 5.4, Screen Failures – Added "If the timeframe between Screening and re-screening is more than 30 days, then all Visit 1 assessments should be repeated." To reduce the risk of not identifying the status change in HIV 1, HIV 2, Hepatitis B, Hepatitis C and FSH prior to rescreening, if initial screening visit 1 was more than 30 days ago.

Section 6.1.2, Medical Devices – add the description of study medical device.

Section 6.2, Preparation/handling/storage/accountability – Added a note to clarify that during the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration may be performed at the subject's home by a qualified HCP. This change is to reduce the risk to subjects of COVID-19 exposure with clinic visits.

Section 6.2, Preparation/handling/storage/accountability – Dose preparation steps – Table 5 – Added that a 2 mL sterile syringe can be attached to a 21G 1½ -inch sterile disposable needle during IP dose preparation and subsequently used for IP administration. This change allows for use of a 2 mL syringe in addition to 3 mL syringe because it meets the requirements for IP dose preparation and dosing.

Section 6.2, Preparation/handling/storage/accountability – Dose preparation steps – clarified that the vial labels along with the vials can be discarded immediately post IP preparation as per site's SOP. The statement now reads "If the opened and dispensed vials must be discarded immediately after dose preparation as per site's SOP, the kit boxes must be retained for IP accountability."

Section 6.2, Preparation/handling/storage/accountability – Dose administration – Removed wording "The subject, in the opinion of the investigator, is experiencing an acute or emerging asthma exacerbation" from the list of scenarios when IP should not be administered. An exacerbation per se is not a contraindication for IP administration. Reasons for not administering IP are well covered by the remaining bullets.

Section 6.3, Measures to minimise bias: randomisation and blinding – Procedures for handling incorrectly enrolled or randomized subjects – Revised text to clarify that if subject is discontinued from IP they should still follow the IPD discontinuation procedures as defined in section 7.1.1.

Section 6.3, Measures to minimise bias: randomisation and blinding –Ensuring blinding– removed "Bioanalytical lab performing the PK sample analysis" from the personnel that will have access to the randomization list. The statement now reads: "bioanalytical lab analyst performing the PK sample analysis" The reason for this change is that the laboratory does not require the randomization list for performing PK analysis.

Section 6.3, Measures to minimise bias: randomisation and blinding – Methods for unblinding – replaced "pharmacists" with "delegate(s)" to clarify that the Investigator delegate(s) in addition to the Investigator will be provided access to unblinding the treatment for individuals in medical emergencies. This change allows alignment with the IXRS setup for this study.

Section 6.5, Table 7, Prohibited medications – For any immunomodulators or immunosuppressives, revised the text "(except for OCS used in the maintenance treatment of asthma/asthma exacerbations)" to "(except for OCS used in the maintenance treatment of asthma, asthma exacerbations in screening/run-in, and protocol defined asthma exacerbations on or after Visit 3)". This is to clarify the wording "except for OCS used in the treatment of asthma" is applicable for subjects on OCS maintenance treatment for asthma and "asthma exacerbation" is applicable if it was a protocol defined exacerbation occurring on or after Visit 3.

Section 6.5, Table 7, Prohibited medications – For other investigational products (including investigational use of an approved drug), revised the text "preferably 4 weeks after the last dose of IP" to "until the follow up visit week 64" to clarify that other investigational products cannot be used during the entire duration of the study.

Section 6.5.1, Rescue medication – Added "Regularly scheduled SABA use in the absence of any asthma symptoms is not allowed from enrolment (Visit 1) and throughout the study duration. Prophylactic use of SABA (e.g. prior to planned exercise) or any other use than to curb worsening of asthma symptoms should be documented in medical notes and entered in the eCRF. Any such use of SABA must not be recorded in the Asthma Daily Diary. " This change further clarifies that regularly scheduled SABA use in the absence of any asthma symptoms is not allowed and that the occasional prophylactic use of SABA is not to be recorded in the eDiary.

Section 7.1, Discontinuation of study treatment – Under "Development of any study specific criteria for discontinuation, any malignancy", added the following statement "except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins." This change allows subjects who have had excision of their lesions, which is considered curative, to continue study treatment.

Section 7.1.1, Procedures for discontinuation of study treatment – Replaced "withdrawal" with "discontinuation criteria" to reflect the corresponding eCRF module. The statement now reads: "If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific discontinuation criteria 'This change allows alignment with eCRF design.

Section 8, Study Assessments and Procedures – For clarification added "Additional data to assess the impact of COVID-19 pandemic will be collected."

Section 8.1.6.2, Asthma Control Questionnaire (ACQ-6) – Revised ACQ-6 score from "≤1.5" to "<1.5" to indicate partly controlled asthma and from ">1.5" to "≥1.5" to indicate uncontrolled asthma. This change aligns with the thresholds for partly controlled/uncontrolled asthma established by Juniper et al 2006.

Section 8.2.4, Vital Signs –Revised text to specify that the pulse rate will be obtained before blood pressure only if the manual measurement technique is used. This is to reflect that when the automated device is used the pulse and blood pressure measurements are taken simultaneously.

Section 8.3.8, Adverse Events of Special Interest – Added "systemic" in front of antiviral medications. The revised text reads: "Requiring treatment with systemic antiviral medications, intravenous antibiotics or medications for helminth parasitic infection". To clarify that infections treated with local antivirals are not considered as adverse events of special interest.

Section 8.4.2.2, Paternal exposure – Removed "Male subjects should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose." To align with version 4.2 and 4.3 of the IB.

Section 8.4.2.2, Paternal exposure – Added "in the Pregnancy Report Form" to clarify where outcome of all pregnancies will be reported.

Section 8.4.2.2, Paternal exposure – Added "Consent from the partner must be obtained before the Pregnancy Report Form is completed." To clarify that consent is being obtained from the pregnant partner prior to completing the Pregnancy Report Form.

Section 8.5.2, Collection of samples to measure the immunogenicity of tezepelumab – text is updated to clarify that samples with confirmed positive ADAs will not be archived and will be analyzed for the presence of ADA-neutralizing antibodies, analysis will be completed by a third party and samples will be disposed after Clinical Study Report finalization.

Section 9.3 Populations for analyses - Replaced "All subjects in the full analysis set who received at least one dose of tezepelumab (based on actual treatment received)." by "All subjects in the full analysis set who received active (tezepelumab) treatment and had at least one detectable tezepelumab serum concentration from a sample collected post-dose" to clarify the definition of PK analysis set.

Section 9.3, Populations for analyses - Replaced "All PK summaries will be based on the PK analysis set." by "Summaries of PK will be based on the PK analysis set and will include PK blood samples which are assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received)." to clarify the data included in the PK summaries.

Section 9.4, Statistical Analyses - Replaced "All personnel involved with the analysis and conduct of the study will remain blinded until database lock and Clinical Study Protocol deviations identified" with "All personnel involved with the analysis and conduct of the study will remain blinded until database lock. Important protocol deviations will be identified prior to unblinding". Because important protocol deviations will be identified prior to database lock and study unblinding.

Section 9.4, Statistical Analyses - Replaced "A comprehensive statistical analysis plan (SAP) will be prepared prior to first patient randomized" with "A comprehensive statistical analysis plan (SAP) will be prepared prior to review of any potential treatment-revealing data is undertaken" for clarification and to be consistent with AZ Standard Operating Procedure.

Section 9.4, Statistical Analyses - Replaced "The definitions of each category of important protocol deviation will be fully specified in the SAP." with "The definitions of each category of important protocol deviation will be fully specified in the study Non-compliance Handling Plan." for clarification.

Section 9.4.3, Efficacy analysis - Replaced "history of exacerbations (2 or >2 in previous 12 months)" with "history of exacerbations (≤2 or >2 in previous 12 months)" in the analysis model for efficacy endpoints. No subjects are permitted to be randomised with a history of

fewer than 2 exacerbations according to the eligibility criteria. However, the definition "≤2" is used for analysis purposes, to prevent exclusion of a subject from the analysis in the unlikely event of an important protocol deviation in this regard.

Section 9.4.4, Safety analyses - Replaced "post-treatment" with "on-study", to clarify the periods of interest.

Section 9.4.5, Other analyses - Replaced "Samples confirmed positive for ADA will be archived for possible testing for neutralizing antibodies (nAb)" with "Samples confirmed positive for ADA will be tested for neutralizing antibodies (nAb) and the nAb status will be summarized by treatment group" to reflect nAb will be tested and analyzed.
Section 9.4.5, Other analyses – For clarification added "additional analyses assessing the impact of COVID-19 may be included in the SAP".

Appendix A 3 – Added "During the COVID-19 pandemic, re-consent may be obtained remotely and/or verbally if local/regional guidelines allow in order to reduce the risk to subjects of COVID-19 exposure during clinic visits. For further details please refer to Appendix H" to accommodate the changes made in the protocol.

Appendix A 9 – Added "study and site start and close" section.

Appendix B 2 – Important medical event or medical treatment – Added "Examples of such events are" to clarify that the examples listed in this section can be considered as an important medical event or medical treatment.

Appendix D – Actions required in cases of increases in liver biochemistry and evaluation of Hy's law –minor changes in conjunction with sponsor's routine pharmacovigilance activities/processes.

Appendix E - Anaphylaxis: signs and symptoms, management - Added a reference that was missing from the appendix.

Appendix G, Table of Abbreviations – For clarification, added 1) COVID-19 and 2) HCP

Appendix H – Added Appendix H to describe in more detail the changes made during the COVID-19 pandemic. These changes were made to reduce the subject risk of exposure to COVID-19 during the study.

Version 2.0, 18 February 2019

Changes to the protocol are summarized below.

Version History, Version 1.0, 28 November 2017

Removed adolescents in the protocol and all adolescent related description in the protocol. Defined adult aged 18-80 years old. It is required by CFDA CTP approval letter to exclude adolescents from this study.

Regulatory Agency Identifying Number(s) – added CFDA CTP Number

Section 1.1, SoA, Table 1– Moved SNOT-22 questionnaire from Patient Reported Outcome assessments at home section to Patient Reported Outcome assessments at Visit section. Also added a timepoint at Visit 2a on Table 1 SoA.

Section 1.1, SoA, Table 1– Moved SNOT-22 footnote 'i' to corresponding Visit 2 and Visit 2a timepoints on the SoA and updated footnote to state that SNOT-22 at Visit 2 on the handheld device should only be confirmed once both inclusion criteria 7 and inclusion criteria 8 have been met at either Visit 2 or at Visit 2a as per CSP. ePRO assessments (SNOT-22 and practice diary) need only to be collected once, either at Visit 2 or at Visit 2a if applicable. SNOT-22 questionnaire will only be triggered for subjects that have a medical history of current/ongoing nasal polyposis at Visit 2 or Visit 2a as applicable.

Section 1.1, SoA, Table 1- CCI [redacted] CCI [redacted]

Section 1.1, SoA, Table 1– Added footnote 'n' to clarify that ECG is to be performed prior to blood draw.

Section 1.1, SoA, Table 1– Added footnote 'o' to clarify that eosinophils, basophil and monocyte counts will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

Section 1.1, SoA, Table 1– Added footnote 'p' to clarify that if Visit 1 is conducted more than 35 days in advance of Visit 3, the Visit 2 and Visit 2a visit window is adjusted to complement the preceding visit date (Visit 1).

Section 1.1, SoA, Table 2– Removed Height, CCI [redacted] for biomarker analysis from the table 2.

Section 1.1, SoA, Table 2– Timepoint for Health Care Resource Utilization at Visit 4 was added.

Section 1.1, SoA, Table 2– Scheduled timepoint for SNOT-22 will be moved from Visit 18 (Week 58) to Visit 17 (Week 52). An additional timepoint for SNOT-22 was added to IPD visit.

Section 1.1, SoA, Table 2– Updated footnote 'g' to clarify that CCI [redacted] will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

Section 1.1, SoA, Table 2– Changed Urine pregnancy test, dipstick to Pregnancy test. Updated footnote 'h' to: For WOCBP, urine or serum pregnancy test (HCG) will only be performed at treatment visits, prior to IP administration

Section 1.1, SoA, Table 2– Updated footnote 'i' to clarify that total CCI [redacted] results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

Section 1.1, SoA, Table 2– Added footnote 'q' to clarify that at unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed in the SoA is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

Section 1.2, Synopsis, Exploratory objectives – CCI [redacted]

Section 1.2, Synopsis, Exploratory objectives – CCI [redacted]

Section 1.2 and 8.4.6, Independent Adjudication Committee – Clarified that the independent adjudication committee will evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of treatment period, as well as all deaths, MACE, and malignancies that occur from randomization until the end of the follow up period

Section 1.2, Number of Subjects –Clarified that approximately 80% of the subjects (318 subjects: 159 subjects per group) will come from China and the rest of the subjects will come from other countries.

Section 3, Objectives and Endpoints, Table 3– Updated the endpoint/variable column that change in sinonasal specific HRQoL in patients with co-morbid nasal polyposis will occur at Week 52.

Section 3, Objectives and Endpoints, Table 3– CCI [redacted] CCI [redacted]

Section 4.1, Overall design – Removed adolescent population from application of the anticipated percentages for the recruitment factors.

Section 4.3, Justification for dose – Removed paragraphs describing dose selection for adolescent population

Section 5.1, Inclusion criteria #1 – Removed description of informed assent procedure.

Section 5.1, Inclusion criteria #2 – Change subject age to 18-80 years of age

Section 5.1, Inclusion criteria #5 – Added "(GINA 2017)" reference to provide additional details of medium to high ICS doses.

Section 5.1, Inclusion criteria #6 – Removed "as per GINA guidelines (GINA 2017)" and only reference Appendix F.

Section 5.1, Inclusion criteria #9 – Defined at least one of the historical exacerbations should occur during the treatment of medium-to-high dose ICS.

Section 5.2, Exclusion criteria #12 – Replaced "except stable OCS" with "except for OCS use in the treatment of asthma/asthma exacerbations."

Section 5.2, Exclusion criteria #16 – Changed period of patients treated with bronchial thermoplasty prior to Visit 1from 24 months to 12 months. The rationale is, that there are more and more patients receiving this treatment, and China physicians think 12 months prior to study would be accepted, therefore the change was made.

Section 5.2, Exclusion criteria #23 – Clarified that evidence of active liver disease will include jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2 times the upper limit of normal (ULN) at Visit 1.

Section 5.2, Exclusion criteria #17 and Section 6.2, Dose Preparation – Removed medical monitor.

Section 5.2, Exclusion criteria #25 – Added central lab or local lab to the corresponding test.

Section 5.4, Screen failures – Added 5.4.1 Re-screening

Section 5.4.1, Re-screen – Updated that 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.

Section 5.4.1, Re-screen – Added details pertaining to re-screening of a subject for other reasons.

Section 6.2, Dose Preparation – Updated equilibration time of vial to about 30 minutes to 1 hour at room temperature.

Section 6.2– Dose Preparation – Added the wording, "If the opened and dispensed vials must be discarded immediately after dose preparation as per site's SOP, the vial labels along with the kit boxes must be retained for IP accountability."

Section 6.3, Measures to minimise bias: randomization and blinding – Added further procedures for handling subjects where continued treatment poses a safety risk.

Section 6.3, Measures to minimise bias: randomization and blinding - Added clarified paragraph describing the ICS, exacerbations or eosinophil subgroup closure for overall population, as well as the China/non-China sub-population.

Section 6.3 Measures to minimise bias: randomization and blinding – Clarified that the subjects will be stratified by region (China/non-China).

Section 6.5, Concomitant therapy – Added the word "asthma" to clarify specificity of background medications

Section 6.5, Concomitant therapy – Added description of theophylline testing to 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 analysed 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.

Section 6.5, Concomitant therapy – Removed bullet point "Dosage information including dose and frequency."

Section 6.5, Table 6, Restricted medications – Removed "(unless there is a medical need as judged by the Investigator)" where applicable.

Section 6.5, Table 6, Restricted medications – For maintenance treatment with ICS/LABA, clarified that patients should be instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at Visit 1.

Section 6.5, Table 7, Prohibited medications – Removed "(unless there is a medical need as judged by the Investigator)" where applicable.

Section 6.5, Table 7, Prohibited medications – For Any immunomodulators or immunosuppressives, replaced "(other than prior, stable OCS for the maintenance treatment of asthma)" with "(except for OCS use in the treatment of asthma/asthma exacerbations)." On the corresponding Usage column, also replaced "prior to Visit 1" with "prior to randomization."

Section 6.5, Table 7, Prohibited medications – For medications not currently licensed for use in the treatment of asthma, updated the Usage column to remove "and for the duration of the study."

Section 6.7, Treatment after the end of the study – Clarified that subjects who complete week 64 should be given standard of care at the discretion of the investigator.

Section 7.1, Discontinuation of study treatment – Replaced bullet point "An adverse event" with "An adverse event considered to jeopardize the safety of a subject participating in the study."

Section 7.1.1, Procedures for discontinuation of study treatment – For IPD Option 2, added, "In addition to the PRO assessments that are performed at home, the subject may also complete the other clinic specified PRO assessments (as defined in the SoA) at home as well."

Section 8.1.1, Assessment of Asthma Exacerbations – For one of the prespecified worsening threshold, clarified that the alert will trigger if there is an increase of "2 or more nights" with awakenings due to asthma requiring rescue medication over a 7-day period.

Section 8.1.2.1, Spirometry, General Requirements – Clarified that 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 visit (Visit 3).

Section 8.2.1, Table 8, Laboratory safety variables – Removed dipstick. Updated footnote '*' to Urine samples will be analysed by the central laboratory only when a positive urinalysis result for any parameter is observed. The reason to remove dipstick is it cannot be

kept as source document. To meet the requirement of China authority for source document in the clinical study, urinalysis will be tested in the central lab without using dipstick.

Section 8.2.5, Electrocardiograms – Updated that only a copy of the ECG will be produced and filed.

Section 8.2.6.1, Serology – Updated that Hepatitis B surface antigen, hepatitis C antibody will be tested in Central lab, HIV-1 and HIV-2 antibodies will be performed in local lab.

Section 8.3.4, Adverse event data collection – Added Description of AE to the variables collected for SAE

Section 8.4.6, Independent Adjudication Committee – Clarified that the independent adjudication committee will evaluate all deaths, MACE, and malignancies that occur from randomization until the end of the follow up period.

Section 8.5.3, Storage and destruction of pharmacokinetic/ADA samples – updated to The residual pharmacokinetic/ADA samples aliquots may be retained for the purposes of reanalysis at AstraZeneca or designee for a maximum of 5 years after publication of the Clinical Study Report or as per local regulation, after which they will be destroyed. This is intended to allow AstraZeneca to investigate any anomalous results or respond to regulatory authority questions. Samples will only be re-analysed according to the original purpose for which they were collected (eg pharmacokinetic / ADA/nAb analysis).

Section 8.7, CCI [redacted]

Section 8.7.1, Storage, re-use and destruction of biomarker samples – updated the storage time to a maximum of 5 years after publication of the Clinical Study Report or as per local regulation.

Section 8.7.2, CCI [redacted]

Section 9.4.2, Definition of baseline - Clarified that for efficacy endpoints baseline measurement is on or prior to randomization, and for safety endpoints baseline measurement is prior to the first dose.

Section 9.4.4, Safety analyses – Replaced “AEs leading to study discontinuation” with “AEs leading to discontinuation of IP”.

Section 9.4.5 CCI [redacted]
CCI [redacted]

Initial Version, 28 Nov 2017

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