Clinical Study Protocol	
Study Intervention	Tezepelumab
Study Code	D5241C00001
Version	7.0
Date	18-Oct-2022
EudraCT/EU CT Number	2019-001363-67

A Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter, Phase 2a Study to Explore the Efficacy and Safety of Tezepelumab in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) (COURSE)

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

IND number: 103031

EudraCT number: 2019-001363-67

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

Version Scope: Global version 7.0, 18 October 2022

Amendment Number: 6.0

Study Intervention: Tezepelumab
Study Phase: 2a

Short Title: Tezepelumab COPD Exacerbation study

Acronym: COURSE

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

Study Physician Name and Contact Information will be provided separately
International Co-ordinating Investigator:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6.0	*18-Oct-2022*
Amendment 5.0	*21-Mar-2022*
Amendment 4.0	*15-Mar-2021*
Amendment 3.0	*11-Aug-2020*
Amendment 2.0	*26-May-2020*
Amendment 1.0	*16-Dec-2019*
Original Protocol	*03-May-2019*

Amendment 6.0 (18-Oct-2022)

This modification is considered to be substantial based on the criteria set forth in article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 3 (13) because it might impacts the safety of participants and the scientific value of the study.

Overall Rationale for the Amendment:

The main reason for this amendment is to update the important potential risks and adverse events of special interests (AESI) to align with Investigator's Brochure (IB) Edition 5.1 (dated 22 July 2022), as well as, to update the scope of the Independent Adjudication Committee assessment.

Other changes are minor and non-substantial, including alignment with regulatory trial requirements, correcting typos, among others.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Protocol title and Section 1.2 Synopsis	Added EudraCT/EU CT Number to Title and Synopsis page.	To align with regulatory requirements related to Clinical Trial Transparency (CTT) language.	Non-substantial
Section 1.1 Schedule of activities, Table 1 and Section 6.5 Concomitant Therapy, Table 6	Restriction for inactive/killed vaccinations (e.g. inactive influenza vaccine) revised from within 7 days to 5 days before or after any IP dosing.	To align with IB Edition 5.1.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.2 Synopsis, Independent Adjudication Committee and Section 8.4.7 Independent Adjudication Committee	The scope of the IAC changed. Added serious cardiac events as an event requiring adjudication. Added that the IAC will assess whether there is a causal relationship between IP use and MACE events, serious cardiac events, and deaths.	To update the scope of the IAC assessment to align with IB Edition 5.1.	Substantial
Section 2.3 Benefit/Risk Assessment, Table 3 – Risk Assessment	New Table 3 – Risk Assessment: "Important potential risks" added including serious infections, malignancies, and serious cardiac events; "Potential risks" added including serious hypersensitivity reactions, and helminth infections; "Study procedures" added including COVID 19. The rationale for risk and mitigation strategy is provided for all risks in Table 3.	To align with IB Edition 5.1.	Substantial
Section 4.1 Overall design, and Section 9.6 Interim Analyses	Revised data cut off for the second interim analysis from 3 months to approximately 1 month after Last Subject Randomized.	The second interim analysis period was shortened as a sufficient amount of data will be available 1 month after the Last Subject Randomized.	Non-substantial
Section 4.4 End-of-study	Added the End of Study Definition under FDA and EU requirements.	To align with regulatory requirements related to Clinical Trial Transparency (CTT) language.	Non-substantial
Section 5.1 Inclusion criteria	Updated Criterion#11: 'Subjects on theophylline or roflumilast prior to Visit 1…' by adding "Note".	To clarify the check of the blood concentration levels of theophylline is a recommendation, not an inclusion criterion.	Non-substantial
Section 5.2 Exclusion criteria, Section 8.1.2.1 General requirements, and section 8.2.11.2 SARS-Cov-2 testing	Updated Criterion #39: 'SARS-COV-2 test during the study conduct' by adding alternative test (approved by local health authorities). Related sections were updated for consistency.	To allow alternative tests approved by local health authorities to confirm SARS-COV-2 infection.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.5 Concomitant Therapy, Table 6	Added COVID-19 vaccination based on the existing section 8.2.10. The COVID-19 vaccination restriction has not been changed.	To align with section 8.2.10 where all this information was in the previous CSP version.	Non-substantial
Section 8.1.1.1 Severity of COPD Exacerbation	Severe COPD exacerbation definition was clarified. Following two bullet points in this section… (severe) • "Hospitalization due to the COPD exacerbation • The subject been admitted for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility (depending on the country and healthcare system) for the COPD exacerbation" …were merged in a single bullet point with the following wording: • "Hospitalization defined as inpatient admission for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility (depending on the country and healthcare system) for the COPD exacerbation."	To clarify the definition of severe COPD exacerbation.	Non-substantial
Section 8.3.7.1 Adverse Events of Pneumonia Requiring a Confirmed Diagnosis	Amended wording to clarify the severe infection pages in eCRFs must 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.	To clarify reporting rules for pneumonia in eCRFs and align with section 8.3.8.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.3.8 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 reactions". Replaced "Severe infections" and "Opportunistic infections" with "Serious infections", and added a footnote clarifying when to complete the eCRF Severe infection pages.	To align with IB Edition 5.1, and to ensure consistent reporting in the eCRF.	Substantial
Section 8.3.10 Medical Devices Deficiencies	Removed "and with third party medical devices". Replaced bullet points - "Device constituent parts of the tezepelumab combination product - the AstraZeneca medical device complaint report will be used to collect the deficiency.' with 'The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be used to collect the deficiency."	To clarify that as only device constituents of combination products are provided for use in the study and to align with Appendix J. To clarify the device constituent deficiency reporting instructions (aligned with the Pharmacy Manual).	Non-substantial
Section 8.3.10.3 Prompt Reporting of Medical Device Deficiencies to Sponsor	Added two bullet points: - "The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be sent to AstraZeneca by email." - "Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.4.1."	To clarify the device constituent deficiency reporting instructions (Aligned with the Pharmacy Manual). To amend instructions on reporting to specify use of the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form and to remove email addresses.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Deleted bullet points: - "The AstraZeneca Report Form will be sent to the sponsor via email. - Medical Device Deficiency with an associated SAE - AEMailboxClinicalTrialTCS@astrazeneca.com - gsqincomingcomplaints@astrazeneca.com NOTE: For SAE's, the eCRF must also be populated - see Section 8.4.1. - Medical Device Deficiency with an associated AE - gsqincomingcomplaints@astrazeneca.com - Medical Device Deficiency without an associated adverse or serious adverse event - GCSCProductComplaintOriginators@astrazeneca.com"		
Section 8.4.4 Medication Error, Drug Abuse and Drug Misuse, and Appendix B 8	Added definition and timelines for reporting drug abuse and drug misuse. Also, added the definition of medication error to align with Appendix B.8	To align with EU regulatory trials regulations.	Non-substantial
Appendix A 1	Added wording related to regulatory requirements for Serious Breaches.	To align with EU regulatory trials regulations.	Non-substantial
Appendix A 6	Added requirements and timelines to submit clinical results to EU Clinical Trial Information System (CTIS).	To align with regulatory requirements related to Clinical Trial Transparency (CTT) language.	Non-substantial

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 – Screening Period – Enrolment, Run-in

Assessment/Activity	Screening		Details in CSP Section or Appendix
	Enrolment	Run-in	
Visit	**1[a]**	**2[a]**	
Day	**-42 to -35**	**-35**	
Visit Window (days)	**0**	**+/- 4[b]**	
Pre-visit Assessments			
Telephone assessment of possible COVID-19 symptoms [k]	**X**	**X**	Section 4.1 and Appendix I
Study Procedures			
Informed Consent Form (ICF) and addendum to ICF (sputum/nasal sub-studies) (if applicable)	**X**		Section 5.1
COVID-19 addendum to ICF (if applicable) [m]	**X**		Appendix A 3 and Appendix I
Inclusion/exclusion criteria	**X**	**X**	Section 5.1 and 5.2
Demography	**X**		Section 5.1
Medical, Surgical and COPD history	**X**		Section 5.1
Concomitant medication	**X**	**X**	Section 6.5
Adverse events	**X**	**X**	Section 8.3 and Appendix B
Assessment of COPD exacerbation	**X**	**X**	Section 8.1.1
Smoking status	**X**	**X**	Section 8.2.2
Fractional Exhaled Nitric Oxide (FeNO) [c]		**X**	Section 8.1.3
Patient Reported Outcome Assessments at Visit			
COPD Assessment Test (CAT)	**X**		Section 8.1.6.6
Site assigns electronic Patient Reported Outcome (ePRO) device and trains subject per the training guidelines		**X**	Section 8.1.6
Patient Reported Outcome Assessments at Home			
Home ePRO daily completion [d]		**X**	Section 8.1.6.1
EXACT-PRO/E-RS™: COPD [d]		**X**	Section 8.1.6.7
Clinical Lung Function Assessments			
Pre-BD spirometry [l]	**X**	**X**	Section 8.1.2
Post-BD spirometry		**X**	Section 8.1.2.2
Routine Safety Procedures [f]			
Complete physical examination [e]	**X**		Section 8.2.4
Weight, Height [e]	**X**		Section 8.2.3
Vital Signs [e]	**X**		Section 8.2.5
Supplemental oxygen (O_2) status [e]	**X**		Section 8.2.7
Oxygen saturation (SpO_2) [e]	**X**		Section 8.2.8
Chest x-ray [eg]	**X**		Section 8.2.9
12-Lead digital Electrocardiogram (dECG)	**X**		Section 8.2.6
Laboratory Assessments			
Clinical chemistry	**X**		Section 8.2.1
Hematology [h]	**X**		Section 8.2.1
Urinalysis	**X**		Section 8.2.1
Serology (Hepatitis B, C; HIV-1; HIV-2)	**X**		Section 8.2.11.1
Serum pregnancy test	**X**		Section 8.2.1.1
FSH [i]	**X**		Section 8.2.1.1
TB Test (if applicable) [e]	**X**		Section 5.2

Pneumococcal and annual influenza vaccination, if applicable	X[j]		Section 8.2.10
SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) [l]	X		Section 8.2.11.2

[a] Screening lung function assessments and ECG can only be done when there are no restrictions to medications (refer to Section 6.5.5 and 8.1.3) and Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is negative. If the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result will not be available on the day of Visit 1, the screening lung function assessments and ECG must be postponed until next visit, the postponed Visit 1, after the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is confirmed negative. At a minimum, the following assessments/activities must be performed at Visit 1: obtain informed consent, temperature measurement, enrolment of subject in IWRS and SARS-CoV-2 naso/oropharyngeal swab test. The remaining Visit 1 assessments can be postponed together with the screening lung function assessments and ECG. At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed. Visit 2 should be scheduled, if the Visit 2 post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result.

[b] The run-in phase (35 days) can be shortened by 4 days (to 31 days) or extended by 4 days (to 39 days). In case of a COPD exacerbation or respiratory infection (excluding pneumonia) during the screening phase, the screening period may be extended up to 14 days (including the 4 days i.e., to 49 days) to allow for the completion of the course of systemic corticosteroids and/or antibiotics or antiviral medication or to meet FeNO restrictions (Refer to section 5.4).

[c] The sponsor will be blinded to the FeNO values except at screening visit, at any repeat testing that is performed during the screening period and prior to Investigational Product (IP) administration. The sites will be blinded to the FeNO values for the whole study duration.

[d] Daily Morning Diary: Nocturnal awakening and items related to: rescue medication use, major/minor symptoms; Daily Evening Diary: EXACT-PRO/E-RS™: COPD and items related to: rescue medication and maintenance medication.

[e] These Visit 1 procedures can be performed at any time between Visit 1 and Visit 2 inclusive.

[f] The suggested order of assessments: ePRO, vital signs, ECG, FeNO, spirometry and blood draws.
IMPORTANT: Applicable during COVID-19 pandemic: the suggested order of assessments: Vital signs, ePRO, blood draws and SARS-CoV-2 naso/oropharyngeal swab testing. The lung function assessments and ECG can only be done after Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is negative.

[g] A chest X-ray must be done at Visit 1, or at any time that allows the chest X-ray assessment prior to randomization. Under special circumstances, a recently done historical chest X-ray (anterior-posterior and lateral)/CT/MRI for other reasons (not study related) might be acceptable. The outcome of the X-ray/CT/MRI must be documented in the patients' medical records. Study Physician approval of historical chest X-ray must be obtained prior to randomization.

[h] The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (Visit 1 and Visit 2), any repeat testing that is performed during the screening period and prior to first Investigational Product (IP) administration.

[i] FSH test done only for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month.

[j] Pneumococcal vaccination can be done at Visit 1 or at any time prior to first IP administration. Annual influenza vaccination can be done at any other time throughout the study (except for within ±5 days of IP administration) at the discretion of Investigator. Inactive/killed vaccinations e.g. influenzae should be withheld 3 weeks prior to EOT for patients in the sub study (if no safety concerns) as it might influence exploratory sputum analysis. Refer to Section 8.2.10.

[k] During the COVID-19 pandemic, subjects must be contacted by telephone for COVID-19 screening assessments within 72 hours prior to every study visit (except remote visits). Refer to Appendix I for details.

[l] Central laboratory SARS-CoV-2 nasopharyngeal or locally performed SARS-CoV-2 naso/oropharyngeal swab test result (or rapid test result) must be available and negative prior to performing screening lung function assessments and ECG (refer to footnote a under Table 1, section 1.1).

[m] During re-consenting of subjects during the COVID-19 pandemic, local and regional guidelines must be followed. Refer to Appendix I for further details.

Table 2 – Treatment Period - Randomization, Treatment and Follow-Up

Assessment/ Activity	Treatment Period														Follow-up		IPD	UNS [a]	EXA [b]	Details in CSP Section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**EOT/ 16**	**17**	**18**				
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**				
Visit Window (days)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±5**	**N/A**	**N/A**	
Pre-visit Assessments																				
Telephone assessment of possible COVID-19 symptoms [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix I
Study Procedures																				
COVID-19 addendum to ICF (if applicable) [m]	X																			Appendix A 3 and Appendix I
Inclusion/exclusion criteria	X																			Section 5.1 and 5.2
Concomitant medication [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Adverse events [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3 and Appendix B
Assessment of COPD exacerbation [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Smoking status [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.2
Healthcare resource utilization [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 8.9
FeNO [c]	X	X		X			X				X			X			X			Section 8.1.3
Patient Reported Outcome Assessments at Visit [d]																				
CAT [n, o]	X			X			X			X				X			X			Section 8.1.6.6
SGRQ [n, o]	X			X			X			X			X	X			X			Section 8.1.6.5
ePRO compliance check [n, o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			Section 8.1.6
Patient Reported Outcome Assessments at Home [d]																				
Home ePRO daily completion	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			Section 8.1.6.1
EXACT-PRO/E-RS™: COPD	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			Section 8.1.6.7
Routine Safety Procedures																				
Brief physical examination [n]		X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	Section 8.2.4

Assessment/ Activity	Treatment Period														Follow-up		IPD	UNS [a]	EXA [b]	Details in CSP Section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**EOT/ 16**	**17**	**18**				
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**				
Visit Window (days)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±5**	**N/A**	**N/A**	
Complete physical examination [n]	X													X			X			Section 8.2.4
Weight	X													X						Section 8.2.3
Vital Signs [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5
Supplemental O_2 status [n]	X	X	X		X		X		X		X		X	X			X		X	Section 8.2.7
Oxygen saturation (SpO_2) [n]	X	X	X		X		X		X		X		X	X			X		X	Section 8.2.8
12-lead digital Electrocardiogram (ECG)	X			X			X				X			X			X		X	Section 8.2.6
Lung Function Assessments [e]																				
Pre-BD spirometry	X	X		X			X				X			X			X		X [f]	Section 8.1.2
Post-BD spirometry	X						X							X			X			Section 8.1.2.2
Laboratory Assessments																				
Clinical chemistry [n]	X			X			X			X			X	X			X		X	Section 8.2.1
Hematology [g n]	X			X			X			X			X	X	X	X	X		X	Section 8.2.1
Total Serum Immunoglobulin [g]	X	X		X			X			X				X			X			Section 8.8.2
Urinalysis [n]	X			X			X			X			X	X			X			Section 8.2.1
Urine pregnancy test (dipstick)[h n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 8.2.1.1
Serum for Pharmacokinetics (PK)	X	X		X			X			X				X		X	X			Section 8.5
Serum for Immunogenicity [i]	X	X		X			X			X				X		X	X			Section 8.5.2
Serum/Plasma Biomarkers	X	X		X			X			X				X			X		X	Section 8.8
Urine Biomarkers	X	X		X			X			X				X			X		X	Section 8.8
Blood RNA transcript profiling (PAXgene® tube)	X	X		X			X			X				X			X		X	Section 8.8.3
AstraZeneca (AZ) genetics blood sample (optional)[j]	X																			Section 8.7.1 and Appendix D
SARS-CoV-2 serology test [q]	X																			Section8.2.11.2

Assessment/ Activity	Treatment Period														Follow-up		IPD	UNS [a]	EXA [b]	Details in CSP Section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**EOT/ 16**	**17**	**18**				
Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**				
Visit Window (days)	**0**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±5**	**N/A**	**N/A**	
Subset of Subjects Participating in Sputum and Nasal Lining Fluid/Epithelial Cells Sub Studies Only [k]																				
Sputum post-BD spirometry	**X**													**X**			**X**		**X**	Section 8.1.2.3
Sputum microbiome	**X**													**X**			**X**		**X**	Section 8.8.5
Sputum biomarkers and Exploratory PK	**X**													**X**			**X**		**X**	Section 8.8.5
Sputum cell pellet – cell counts and/or RNA transcriptomic profiling	**X**													**X**			**X**		**X**	Section 8.8.5
Nasal lining fluid (nasal biomarkers and Exploratory PK)	**X**	**X**		**X**			**X**			**X**				**X**			**X**		**X**	Section 8.8.6
Nasal epithelial cells (RNA transcriptome)	**X**													**X**			**X**			Section 8.8.4
Study treatment administration																				
Randomization [r]	**X**																			Section 6.1
Administration of IP [l n]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**							Section 6.1.2

NOTE: The suggested order of assessments to be completed prior IP administration: ePRO, Vital signs, ECG, FeNO, spirometry and blood draws. Applicable during COVID-19 pandemic: Vital signs, ePRO, ECG, FeNO, spirometry and blood draws.

[a] Unscheduled visits may be initiated as needed and additional assessments can be performed at the discretion of the PI.

[b] EXA visit is an optional visit and may be initiated when patient experiences COPD exacerbation. Additional assessments can be performed at the discretion of the PI. If the EXA visit falls within +/- 5 days of the scheduled treatment visit window, the laboratory assessments do not need to be repeated at the next scheduled visit if the same laboratory assessments were already completed at EXA visit, unless at the PI's discretion. Refer to Section 8.1.1.5.

[c] The sponsor will be blinded to the FeNO values except at screening visit, at any repeat testing that is performed during the screening period and prior to Investigational Product (IP) administration.. The sites will be blinded to FeNO values for the whole study duration.

[d] Daily Morning Diary: Nocturnal awakening and items related to: Rescue medication use, major/minor symptoms; Daily Evening Diary: EXACT-PRO/E-RS™: COPD and items related to: rescue medication and maintenance medication. EXACT-PRO/E-RS™: COPD is completed daily via e-diary and checked at visits.

[e] 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. For every other visit, pre-BD spirometry assessments must be performed only after appropriate restrictions are met as per Section 8.1.2, if not this should be rescheduled to the earliest opportunity within the allowed visit window. Applicable for the COVID-19 pandemic: Spirometry should be performed if allowed and according to local regulations and guidance.

[f] Pre-BD spirometry (according to separate instruction manual) will be performed at EXA visit as part of induced sputum procedures during treatment phase if subject is participating in the sputum sub study.

[g] The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (Visit 1 and 2), any repeat testing that is performed during the screen visits, and prior to IP administration.

[h] For WOCBP only, urine HCG test to be done at study site at each treatment visit before the IP administration.

[i] In case of anaphylaxis additional samples will be taken for serum for immunogenicity.
[j] The ICF must be signed by the subject prior to the collection of optional pharmacogenetic sample.
[k] Induced sputum and nasal sampling will be performed in a subset of subjects only and selected sites that are participating in the sub-study will consent subjects to participate in both induced sputum and nasal sample collection. Induced sputum is preferred however spontaneous sputum is acceptable if subjects that cannot induce sputum. If sputum and nasal collections occur at the same visit, nasal sampling should occur before spontaneous/induced sputum collection. If patient is not able to produce sputum (spontaneous or induced) at Visit 3, the patient should then be withdrawn from the sub-study, but can continue in the main study, and the nasal samples should be discarded. Sputum sampling at IPD visit and at EOT visit can be performed up to 5 days after the IPD visit and EOT visit. During the COVID-19 pandemic, sputum and nasal samples will only be collected if allowed per local Health and Safety regulations or guidance and if sub-study laboratory test kits are available.
[l] IP must be administered only after all other assessments have been completed on a scheduled visit. During the COVID-19 pandemic, IP administration can be performed at the subject's home or alternative location. Also, laboratory assessments can be completed post IP administration. Please refer to Appendix I.
[m] During re-consenting of subjects during the COVID-19 pandemic, local and regional guidelines must be followed with regard to verbal informed consent. Refer to Appendix I for further details.
[n] During the COVID-19 pandemic for at home IP administration visits, where possible study assessments should be conducted according to the SoA 1.1. However, the qualified HCP is expected to collect this information as a minimum. If possible, it is preferred that the HCP collects urine samples, safety and other blood samples as well. For further details, please refer to Appendix I.
[o] These assessments can be replaced by a phone visit during COVID-19 pandemic. Please refer to Appendix I.
[p] During the COVID-19 pandemic, subject must be contacted by telephone for COVID-19 screening assessment within 72 hours prior to every study visit (except remote visits). Refer to Appendix I for details.
[q] SARS-CoV-2 serology test at Visit 3 is applicable for newly enrolled subjects. For remaining ongoing active subjects (in treatment or in follow-up), the test should be done as soon as possible but preferably at the next site visit.
[r] Randomization transaction in IWRS should be completed after confirmation of subject eligibility.

(EOT) - End of treatment; (EXA) - COPD exacerbation visit; (FU) - Follow-up; (IPD) - IP discontinuation visit; (UNS) - Unscheduled visit

1.2 Synopsis

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Parallel Group, Multicenter, Phase 2a Study to Explore the Efficacy and Safety of Tezepelumab in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) (COURSE)

Brief Title: Tezepelumab COPD Exacerbation study

Regulatory Agency Identifying Number(s):
IND number: 103031
EudraCT number: 2019-001363-67

Rationale: The purpose of this global study is to evaluate the efficacy and safety of tezepelumab 420 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) in adults with moderate to very severe COPD receiving triple inhaled maintenance therapy (inhaled corticosteroid/long-acting β2 agonist and long acting muscarinic antagonist [ICS/LABA/LAMA]) who have had ≥2 documented COPD exacerbations in the 12 months prior to study start. The study will evaluate the incidence of COPD exacerbations and other efficacy parameters such as lung function and quality of life and will provide adequate safety information in order to characterize the benefit-risk profile of tezepelumab treatment in subjects with COPD.

Primary Objective	**Outcome Measure**
To evaluate the effect of tezepelumab as compared with placebo on COPD exacerbations in subjects with moderate to very severe COPD	**Primary endpoint:** Rate of moderate or severe COPD exacerbations **Primary outcome measure:** Moderate or severe COPD exacerbation rate ratio (tezepelumab vs placebo) **Supportive endpoint:** Rate of moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbations **Supportive Measure:** Moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbation rate ratio (tezepelumab vs placebo)

Secondary Objectives	Outcome measure
To evaluate the effect of tezepelumab compared with placebo on time to first moderate/severe exacerbation	**Outcome variables:** • Time to first moderate or severe COPD exacerbation • Proportion of subjects with ≥1 moderate or severe COPD exacerbation **Outcome Measures:** • Hazard Ratio (tezepelumab vs placebo) • Odds Ratio (tezepelumab vs placebo)
To evaluate the effect of tezepelumab as compared with placebo on severe COPD exacerbations	**Secondary outcome variable:** Rate of severe COPD exacerbations **Outcome measure:** Rate ratio (tezepelumab vs placebo) **Supportive outcome variables:** • Time to first severe COPD exacerbation • Proportions of patients experiencing a severe COPD exacerbation **Supportive outcome measures:** • Hazard ratio (tezepelumab vs placebo) • Odds ratio (tezepelumab vs placebo)
To evaluate the effect of tezepelumab as compared with placebo on pre-bronchodilator (BD) lung function	**Outcome variable:** Change from baseline in pre-BD forced expiratory volume in 1 second (FEV_1) at Week 52 **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52

To evaluate the effect of tezepelumab as compared with placebo on respiratory health status/health-related quality of life	**Outcome variables:** • Proportion of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 52 • Change from baseline in SGRQ at Week 52 • Change from baseline in COPD assessment tool (CAT) at Week 52 **Outcome Measures:** • Odds Ratio (tezepelumab vs placebo) • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentration Immunogenicity: Incidence of anti-drug antibodies (ADA)
Safety Objectives:	**Safety Variables:**
To assess the safety and tolerability of tezepelumab as compared with placebo in subjects with moderate to very severe COPD	Adverse events/serious adverse events (AEs/SAEs) Vital signs Laboratory assessments Electrocardiograms (ECG)
Exploratory Objectives:	**Exploratory Variables:**

To explore the effect of tezepelumab on COPD Composite Exacerbations (COPDCompEx) event	**Outcome variable:** • Time to COPDCompEx event • Rate of COPDCompEx events **Outcome Measure:** • Hazard Ratio (tezepelumab vs placebo) • Rate ratio (tezepelumab vs placebo) over first 12 weeks treatment period
To explore the effect of tezepelumab on time to a Clinically Important Deterioration (CID) event	**Outcome variable:** Time to CID event **Outcome Measure:** Hazard Ratio (tezepelumab vs placebo)
To explore the impact of tezepelumab on blood eosinophil and neutrophil levels	**Outcome variable:** Change from baseline in blood eosinophil and neutrophil levels **Outcome measure:** Change from baseline at Week 52
To explore the effect of tezepelumab on post-BD lung function (FEV_1)	**Outcome variable:** Change from baseline in post-BD forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52

To evaluate the effect of tezepelumab on respiratory symptoms and on the frequency, duration and severity of EXACT-PRO defined events	**Outcome variable:** • Change from baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (EXACT-PRO/E-RS™: COPD) • Rate of EXACT-PRO defined exacerbations **Outcome measure:** • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52 • EXACT-PRO defined exacerbation rate ratio (tezepelumab vs placebo)
To evaluate tezepelumab's effect on COPD-related healthcare resource utilization	**Outcome variable:** Rate of COPD-specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other COPD medications) **Outcome measure:** Difference in rate of COPD-specific resource utilizations (tezepelumab vs placebo) over 52 weeks
To assess the effect of tezepelumab on airway inflammation	**Outcome variable:** Fractional exhaled nitric oxide (FeNO) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To assess the effect of tezepelumab on total serum immunoglobulins	**Outcome variable:** Total Immunoglobulins (IgE, IgA, IgM, IgG) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52

To assess the effect of tezepelumab on blood biomarkers	Serum and plasma biomarkers including markers of remodeling and inflammation
To evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome, in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations during treatment phase	• Sputum biomarkers of inflammation and remodeling • Sputum cell counts and cell differentials from cytospins • Sputum microbiome
To explore the effect of tezepelumab on the blood and/or nasal epithelial cell and/or sputum cell transcriptome for pharmacodynamic (PD) markers of exposure or response to tezepelumab and pre-and post-dose predictive markers of clinical response	Transcriptomic biomarkers (may include but not limited to): RNA-Seq and RNA microarray profiling and microbiome profiling. Transcriptomics analysis may be carried out on blood cells, and/or nasal epithelial cells and/or sputum cells
To evaluate the effect of tezepelumab on nasal lining fluid biomarkers	Nasal biomarkers including but not limited to inflammation and remodeling
To evaluate the effect of tezepelumab on urine biomarkers	Urine biomarkers including but not limited to inflammation and remodeling
To explore the relationships between pharmacogenomic DNA markers and response/exposure to tezepelumab	Optional AZ genomics blood sample. Pharmacogenomic biomarkers may include (but not limited to): SNP and epigenetic
To explore the PK of tezepelumab in respiratory tract fluid	Tezepelumab concentrations in nasal lining fluid and/or sputum

Note: Some exploratory analyses may be reported separately from the CSR.

Overall design:

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of tezepelumab 420 mg administered by SC injection Q4W in subjects with moderate to very severe COPD receiving triple inhaled maintenance therapy (ICS, LABA and LAMA), and having had ≥2 documented COPD exacerbations in the 12 months prior to visit 1. Approximately 40% of subjects will have had ≥3 exacerbations in the 12 months prior to Visit 1 and approximately 30% of subjects will have had at least 1

severe exacerbation (an exacerbation resulting in hospitalization) in the 12 months prior to Visit 1.

The study will randomize approximately 338 subjects 1:1 to either tezepelumab or placebo, stratified by region, and number of prior exacerbations. Approximately 20% of the subjects will be targeted to have ≥300 eosinophils/μL, 40% of the subjects between ≥150 to <300 eosinophils/μL and a maximum of approximately 40% of the subjects with <150 eosinophils/μL at enrolment.

Induced sputum analyses will be performed in a subset of subjects and in a limited number of sites globally. The aim of the induced sputum subset analysis is to explore the mechanisms by which tezepelumab might reduce COPD exacerbations. In these same selected subjects, analysis of nasal lining fluid and epithelial transcriptomics will also be performed.

The screening period which consist of enrolment and run-in, will be approximately 6 weeks to allow adequate time for all the eligibility criteria to be evaluated. At the end of the run-in period, subjects must continue to have a CAT score ≥15 and 70% compliance with the maintenance therapy and acceptable compliance with the eDiary to be randomized. Subjects who meet the eligibility criteria will be randomized to treatment.

After randomization subjects will be treated at monthly intervals with the last treatment administered at Week 48. The end-of-treatment (EOT) visit (Week 52) will occur at 4 weeks after last treatment administered at Week 48 and follow-up visits will occur at Week 58 and Week 64. Subjects will be maintained on their currently prescribed maintenance therapies from enrolment throughout the run-in and treatment period.

Study Period:

Estimated date of first patient enrolled Q3 2019.
Estimated date of last patient completed Q1 2024.

Number of Subjects:

Approximately 338 subjects will be randomized to either tezepelumab or placebo (1:1) globally from at least 90 sites. The subjects will be stratified by region and prior number of exacerbations (2 vs ≥3). Since the primary analysis of the primary endpoint will include all available data, including after treatment discontinuation, no need is envisaged to adjust the number of subjects planned to be randomized to obtain a number of evaluable subjects.

Treatments and Treatment Duration:

The study will consist of a screening period for approximately 6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. Subjects will be randomized in a

1:1 ratio to either 420 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. Subjects that complete the 52-week study visit will complete a 12 week off-treatment follow-up period for assessments. Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period (see Section 7.1.1).

Independent Adjudication Committee:

An Independent Adjudication Committee (IAC) will assess blinded data to confirm the diagnosis and causality of major adverse cardiac events (MACE; defined in the IAC charter), serious cardiac events, and deaths, as well as the diagnosis of malignancies, that occur from randomisation until the end of the follow-up period.

The IAC will 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 COPD.

Details on the adjudication process, including scope of adjudication and the committee membership, will be included in the Adjudication Committee Charter/Manual of Operations.

Independent Data Monitoring:

An Independent Data Monitoring Committee (IDMC) will be tasked with two major responsibilities. First, it will be responsible for assessing all safety related data collected during the study, including serious adverse events (including deaths and all hospitalizations), non-serious adverse events and laboratory values. The IDMC will periodically review unblinded safety summary tables and listings and evaluate for subject safety and make appropriate recommendations. The committee will operate in accordance with an IDMC Charter.

Second, the IDMC will be responsible for overseeing the two unblinded interim analyses based on the primary endpoint that will be conducted in this study (see Section 4.1).

Statistical Methods:

Efficacy analyses will be performed using the full analysis set (FAS), which consists of all subjects randomized and receiving any dose of IP. All subjects in the FAS will be included in the main efficacy analyses, including subjects 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).

The primary efficacy variable is the annual COPD exacerbation rate. The exacerbation rate in the tezepelumab dose group will be compared to the exacerbation rate in the placebo group

using a negative binomial model including covariates of treatment group, region and the number of exacerbations in the year before the study (2 vs ≥3). The logarithm of the follow-up time will be used as an offset variable in the model.

Secondary efficacy variables include the time to first COPD exacerbation, proportion of subjects with at least one COPD exacerbation, annual rate of severe COPD exacerbations, change from baseline in Pre-BD FEV1 and SGRQ, and proportion of subjects with at least 4 units decrease in SGRQ. These endpoints will be compared to the placebo group using appropriate models (Cox proportional hazards for time to event endpoint, logistic regression for proportion endpoints, Negative Binomial regression for annual rate endpoints, Mixed effect Model Repeated Measures (MMRM) for change from baseline endpoints.)

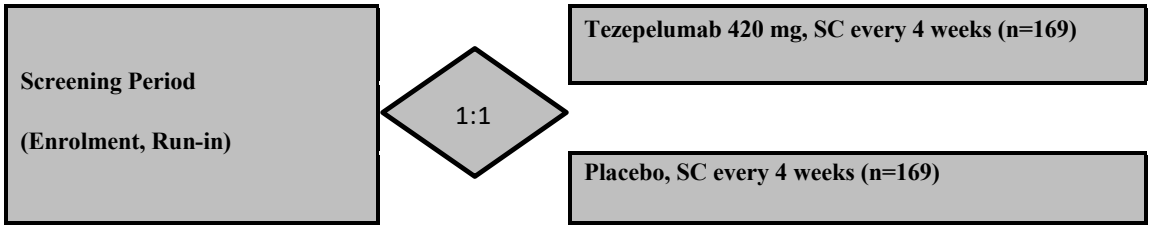
All safety parameters will be analyzed descriptively. Safety analyses will be based on the safety analysis set, defined as all subjects who received at least 1 dose of IP.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 - Study Flow Chart

V1	V2	R/V3	V4-V15	EOT/V16	V17, V18
Week -6	Week -5	Week 0	Week 4-48	Week 52	Week 58, 64
Enrolment	**Run-in**	**Treatment Phase**			**Follow-up**
Screening					



V: Visit, R: Randomization

2. INTRODUCTION

2.1 Study Rationale

2.2 Background

Chronic obstructive pulmonary disease (COPD) is a progressive disease and a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third leading cause of death and disability worldwide by 2020 (Global Initiative for Chronic Obstructive Lung Disease [GOLD 2019]).

Acute exacerbations of COPD (AECOPD) are responsible for a large portion of the economic burden of COPD. In addition to a substantial economic burden, AECOPDs are also responsible for much of the morbidity and mortality from COPD. Patients with frequent AECOPD show associated increased airway inflammation and accelerated decline in lung function compared with patients with infrequent exacerbations (Donaldson et al 2002).

Thymic stromal lymphopoietin (TSLP) is an upstream pleiotropic cytokine which is released by airway epithelial cells in response to either allergens or non-specific stimuli such as viruses, bacteria, and cigarette smoke, all of which are known to be associated with COPD exacerbations (Ziegler et al 2013). In response to an allergen or non-specific stimuli, TSLP activates dendritic cells, which stimulate Type 2 helper T (Th2) cells to differentiate and produce the Type 2 cytokines interleukin (IL)-4, IL-5, and IL-13 (Watson and Gauvreau 2014). TSLP can also drive Th17 cell expansion through activation of dendritic cells, which will increase neutrophil recruitment (Ziegler et al 2013).

TSLP, along with the other epithelial “alarmins”, IL-25 and IL-33, activates Type 2 innate lymphoid cells (ILC2) and other inflammatory cell (including mast cells, basophils, and macrophages), thus promoting T2 inflammation by up-regulating Type 2 cytokines in response to an epithelial insult (e.g., pollutants, microbes, cigarette smoke, bacterial and viral infections, mechanical injury, trauma and pro-inflammatory cytokines etc.) (Camelo et al 2017).

TSLP protein is released from COPD epithelium following toll-like receptor (TLR) viral (Calvern et al 2012) and pro-inflammatory cytokine stimulation (Kato et al 2007, Lee and Ziegler 2007). TSLP protein has been detected in nasal secretions from healthy subjects undergoing natural rhinovirus infection (Perez et al 2014) as well as in the bronchoalveolar lavage (BAL) fluid and sputum of non-exacerbating COPD subjects (Ying et al 2008), and sputum (Anzalone et al 2018). TSLP mRNA expression is seen in airway epithelial cells in patients with COPD (Ying et al 2008).

Tezepelumab is a fully human immunoglobulin G (IgG) monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with the TSLP receptor (TSLPR). The hypothesis for the mechanism of action of tezepelumab in COPD is two-fold. First, because TSLP is one of the earliest responses to airway damage caused by a range of stimuli, inhibition of TSLP is expected to prevent the acute response to epithelial damage and prevent COPD exacerbations. Secondly, given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is anticipated to have broad impact on the spectrum of acute and chronic airway inflammatory responses seen in COPD. Both effects are expected to reduce COPD exacerbations and improve COPD symptoms (Camelo et al 2017).

Thus, it is hypothesized that inhibition of upstream TSLP by tezepelumab will be effective in reducing airway inflammation in patients with COPD and reducing annualized COPD exacerbation rates. The purpose of the present study is to investigate the ability of tezepelumab versus placebo to enable reduction of the annualized COPD exacerbation rate in subjects with moderate to very severe COPD receiving standard maintenance therapy.

2.3 Benefit/Risk Assessment

COPD is a progressive disease which is characterized by exacerbations and health related quality of life loss (GOLD 2019). Despite being treated with double and triple inhaled therapy, many COPD patients continue to have exacerbations (Wedzicha et al 2013).

It has been shown that tezepelumab, as add-on therapy to standard-of-care (SoC), significantly reduces asthma exacerbations, including exacerbations associated with hospitalization or ER visit, and improves lung function, asthma control, and quality of life in patients with severe uncontrolled asthma. Moreover, clinical improvements were seen irrespective of patient phenotype or biomarker status (Corren et al 2017). In the same study, tezepelumab was shown to decrease blood eosinophil counts, FeNO, and IgE levels, suggesting that multiple pathways are being impacted by blocking TSLP.

No clinical data are available to show the effect of tezepelumab in COPD. However, efficacy and safety data obtained in asthma supports clinical development of tezepelumab in COPD.

Use of tezepelumab has been demonstrated to show an important benefit in asthma in a phase 2b and phase 3 study. 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 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.

A detailed assessment of the overall risk/benefit of tezepelumab in patients with COPD is given in the Investigator's Brochure.

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 by safety blood work throughout the study; and through standard AE/SAE reporting. Participants will be excluded if they received systemic immunosuppressive or immunomodulating drugs within 3 months prior to Visit 1; 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 finalised < 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. Serious infections are an AESI and participants who develop serious

		infection will be followed up closely throughout study.
Malignancies	Given the potential theoretical risk due to the mechanism of action of tezepelumab, 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 established for cases reported.	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/serious adverse event, including malignancies that are considered AESI.
Serious cardiac events	A numerical imbalance in cardiac disorder SAEs was observed in the DESTINATION Long Term Extension study (see 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	To mitigate the potential risk of serious hypersensitivity reactions during and after administration of tezepelumab, specific requirements

	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.	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. To mitigate the potential risk of immune complex disease participants will be monitored for confirmed immune complex disease through routine monitoring of AEs/SAEs. 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 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.	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 Table 6). Refer to Appendix I Coronavirus (COVID 19) Pandemic Guidance.

3. OBJECTIVES AND ENDPOINTS

Table 4 - Study Objectives

Primary Objective	**Outcome Measure**
To evaluate the effect of tezepelumab as compared with placebo on COPD exacerbations in subjects with moderate to very severe COPD	**Primary endpoint:** Rate of moderate or severe COPD exacerbations **Primary outcome measure:** Moderate or severe COPD exacerbation rate ratio (tezepelumab vs placebo) **Supportive endpoint:** Rate of moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbations **Supportive Measure:** Moderate (excluding exacerbations treated only with antibiotics) or severe COPD exacerbation rate ratio (tezepelumab vs placebo)
Secondary Objectives	**Outcome measure**
To evaluate the effect of tezepelumab compared with placebo on time to first moderate/severe exacerbation	**Outcome variables:** • Time to first moderate or severe COPD exacerbation • Proportion of subjects with ≥1 moderate or severe COPD exacerbation **Outcome Measures:** • Hazard Ratio (tezepelumab vs placebo) • Odds Ratio (tezepelumab vs placebo)
To evaluate the effect of tezepelumab as compared with placebo on severe COPD exacerbations	**Secondary outcome variable:** Rate of severe COPD exacerbations

	Outcome measure: Rate ratio (tezepelumab vs placebo) **Supportive outcome variables:** • Time to first severe COPD exacerbation • Proportions of patients experiencing a severe COPD exacerbation **Supportive outcome measures:** • Hazard ratio (tezepelumab vs placebo) • Odds ratio (tezepelumab vs placebo)
To evaluate the effect of tezepelumab as compared with placebo on pre-bronchodilator (BD) lung function	**Outcome variable:** Change from baseline in pre-BD forced expiratory volume in 1 second (FEV_1) at Week 52 **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the effect of tezepelumab as compared with placebo on respiratory health status/health-related quality of life	**Outcome variables:** • Proportion of subjects achieving an MCID of 4 units or more in SGRQ total score at Week 52 • Change from baseline in SGRQ at Week 52 • Change from baseline in COPD assessment tool (CAT) at Week 52 **Outcome Measures:** • Odds Ratio (tezepelumab vs placebo) • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52

To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentration Immunogenicity: Incidence of anti-drug antibodies (ADA)
Safety Objectives:	**Safety Variables:**
To assess the safety and tolerability of tezepelumab as compared with placebo in subjects with moderate to very severe COPD	Adverse events/serious adverse events (AEs/SAEs) Vital signs Laboratory assessments Electrocardiograms (ECG)
Exploratory Objectives:	**Exploratory Variables:**
To explore the effect of tezepelumab on COPD Composite Exacerbations (COPDCompEx) event	**Outcome variable:** • Time to COPDCompEx event • Rate of COPDCompEx events **Outcome Measure:** • Hazard Ratio (tezepelumab vs placebo) • Rate ratio (tezepelumab vs placebo) over first 12 weeks treatment period
To explore the effect of tezepelumab on time to a Clinically Important Deterioration (CID) event	**Outcome variable:** Time to CID event **Outcome Measure:** Hazard Ratio (tezepelumab vs placebo)
To explore the impact of tezepelumab on blood eosinophil and neutrophil levels	**Outcome variable:** Change from baseline in blood eosinophil and neutrophil levels **Outcome measure:** Change from baseline at Week 52

To explore the effect of tezepelumab on post-BD lung function (FEV_1)	**Outcome variable:** Change from baseline in post-BD forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To evaluate the effect of tezepelumab on respiratory symptoms and on the frequency, duration, and severity of EXACT-PRO defined events	**Outcome variable:** • Change from baseline in Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (EXACT-PRO/E-RS™: COPD) • Rate of EXACT-PRO defined exacerbations **Outcome measure:** • Mean difference in change from baseline (tezepelumab vs placebo) at Week 52 • EXACT-PRO defined exacerbation rate ratio (tezepelumab vs placebo)
To evaluate tezepelumab' s effect on COPD-related healthcare resource utilization	**Outcome variable:** Rate of COPD-specific resource utilization (e.g., unscheduled physician visits, unscheduled phone calls to physicians, use of other COPD medications) **Outcome measure:** Difference in rate of COPD-specific resource utilizations (tezepelumab vs placebo) over 52 weeks
To assess the effect of tezepelumab on airway inflammation	**Outcome variable:** Fractional exhaled nitric oxide (FeNO) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52

To assess the effect of tezepelumab on total serum immunoglobulins	**Outcome variable:** Total Immunoglobulins (IgE, IgA, IgM, IgG) **Outcome measure:** Mean difference in change from baseline (tezepelumab vs placebo) at Week 52
To assess the effect of tezepelumab on blood biomarkers	Serum and plasma biomarkers including markers of remodeling and inflammation
To evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome, in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations during treatment phase	• Sputum biomarkers of inflammation and remodeling • Sputum cell counts and cell differentials from cytospins • Sputum microbiome
To explore the effect of tezepelumab on the blood and/or nasal epithelial cell and/or sputum cell transcriptome for pharmacodynamic (PD) markers of exposure or response to tezepelumab and pre-and post-dose predictive markers of clinical response	Transcriptomic biomarkers (may include but not limited to): RNA-Seq and RNA microarray profiling and microbiome profiling. Transcriptomics analysis may be carried out on blood cells, and/or nasal epithelial cells and/or sputum cells
To evaluate the effect of tezepelumab on nasal lining fluid biomarkers	Nasal biomarkers including but not limited to inflammation and remodeling
To evaluate the effect of tezepelumab on urine biomarkers	Urine biomarkers including but not limited to inflammation and remodeling
To explore the relationships between pharmacogenomic DNA markers and response/exposure to tezepelumab	Optional AZ genomics blood sample. Pharmacogenomic biomarkers may include (but not limited to): SNP and epigenetic
To explore the PK of tezepelumab in respiratory tract fluid	Tezepelumab concentrations in nasal lining fluid and/or sputum

Note: Some exploratory analyses may be reported separately from the CSR

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 6.1.

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

This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of tezepelumab 420 mg administered by SC injection Q4W in subjects with moderate to very severe COPD receiving triple inhaled maintenance therapy (ICS, LABA and LAMA), and having had ≥2 documented COPD exacerbations in the 12 months prior to visit 1. Approximately 30% of subjects will have had at least 1 severe exacerbation (an exacerbation resulting in hospitalization) within the 12 months prior to Visit 1. Approximately 40% of subjects will have had ≥3 exacerbations within the 12 months prior to Visit 1.

The study will randomize approximately 338 subjects 1:1 to the treatment arms, stratified by region, and number of prior exacerbations. Approximately 20% of the subjects will be targeted to have ≥300 eosinophils/µL, 40% of the subjects between ≥150 to <300 eosinophils/µL and a maximum of approximately 40% of the subjects with <150 eosinophils/µL at enrolment. When the target percentage of subjects for the prior exacerbations or eosinophil subgroup in a region or overall is reached, consideration will be given to closing the Interactive Web Response System (IWRS) randomization for that subgroup [by region or overall]. Once a subgroup is closed, subjects in the screening period in the closed subgroup will not be allowed to be randomized and will be screen failed.

Induced sputum analysis will be performed in a subset of subjects and in a limited number of sites globally. The aim of the induced sputum subset analysis is to explore the mechanisms by which tezepelumab might reduce COPD exacerbations. In these same selected subjects, analysis of nasal lining fluid and epithelial transcriptomics will also be performed.

Pre-visit assessment during COVID-19 pandemic

Subjects must be contacted by telephone for assessment of possible COVID-19 symptoms within 72 hours prior to every study visit (except remote visits). Please refer to Appendix I for details.

Screening Period (Enrolment and Run-in)

After the initial enrolment period and confirmation of the eligibility criteria at Visit 1, subjects will proceed to the run-in period at Visit 2 for approximately 5 weeks to allow adequate time for all the eligibility criteria to be evaluated, refer to Table 1. Visit 1 and Visit 2 assessments can be combined.

Screening lung function assessments and ECG can only be done when there are no restrictions to medications (refer to Section 6.5.5 and 8.1.3) and Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is negative. If the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result will not be available on the day of Visit 1, the screening lung function assessments and ECG must be postponed until next visit, the postponed Visit 1, after the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is confirmed negative.

At a minimum, the following assessments/activities must be performed at Visit 1: obtain informed consent, temperature measurement, enrolment of subject in IWRS and SARS-CoV-2 naso/oropharyngeal swab test. The remaining Visit 1 assessments can be postponed together with the screening lung function assessments and ECG. At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed.

Visit 2 should be scheduled, if the Visit 2 post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result.

Subjects who have a blood eosinophil count <300 at enrolment Visit 1 can be re-tested at an unscheduled visit, upon approval of the AstraZeneca Study Physician. It is recommended that any re-test for blood eosinophils is performed not earlier than 4 weeks from the previous testing. In case of recent treatment with systemic corticosteroids, an interval of ≥6 weeks from the last dose is recommended.

The 35 day run-in can be extended by:

- 4 days for all patients (maximum run-in duration is then 39 days) or
- 14 days (including 4 days for all patients) for patients with exacerbation or respiratory infection (excluding pneumonia) during screening (maximum run-in duration is then 49 days) (Refer to section 5.4).
- waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result
- 28 days for patients receiving COVID-19 vaccine during screening

- 28 days for waiting time required to receive central lab kits
- Extension of the screening/run-in for any other reason will be allowed only upon approval of the AstraZeneca Study Physician (Refer to section 5.4).

The 35 day run-in can be shortened by:

- 4 days for all patients (run-in duration is then 31 days)

At the end of the run-in period, subjects must continue to have a CAT score ≥15, 70% compliance with maintenance therapy and acceptable compliance with the eDiary in order to be randomized. Subjects who meet the eligibility criteria will be randomized to treatment.

Acceptable Documentation for COPD disease state and Historical COPD Exacerbations and Background Therapy

A patient's verbal history suggestive of COPD symptoms and/or COPD exacerbation(s) in the previous year, but without supporting documentation, is not sufficient to satisfy these inclusion criteria. The below defines what is acceptable documentation for COPD disease and historical COPD exacerbations (inclusion criterion 6) in this program:

- COPD disease state and COPD exacerbation(s) in the previous year:
  - Clinic visit (primary or specialist healthcare provider [HCP]) notes or emergency room/hospital records listing COPD as a current diagnosis and providing evidence of ≥2 moderate or severe exacerbations in the previous year (52 weeks prior to enrolment)
  - Documented prescription of systemic corticosteroids of at least 3 days duration (or 1 injection of depot formulation) and/or antibiotics for treatment of exacerbation
  - Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a subject was hospitalized or treated with systemic corticosteroids for a COPD exacerbation

NOTE: In case of re-screening, moderate to severe COPD exacerbations from screening period are considered as historical COPD exacerbations within 2 to 52 weeks prior to re screening Visit 1 (Inclusion 6) and should be entered in eCRF module COPDEXH and included in total number of historical COPD exacerbation during IWRS stratification transition at re-screening visit. Refer to section 5.4

The below defines what is acceptable documentation for background COPD therapy (inclusion criterion 7) in this program:

- Use of triple (ICS/LABA/LAMA) background therapy for COPD throughout the previous year (52 weeks prior to enrolment), including assessment of patient's compliance and any identified gaps in treatment or periods of double/monotherapy during the previous year:

  - Recent, active medication list as per HCP note
  - Filled prescriptions based on a pharmacy record
  - Another acceptable medical record as per local clinical practice

During the screening period the subject must undergo all assessments per Table 1.

Randomization, Treatment and Follow-up

After randomization subjects will be treated at monthly intervals with the last treatment administered at Week 48. The end-of-treatment (EOT) visit (Week 52) will occur at 4 weeks after last treatment administered at Week 48. Follow-up visits will occur at Week 58 and Week 64 to allow for determination of immunogenicity and evaluation of safety. Subjects will be maintained on their currently prescribed maintenance therapies from enrolment throughout the run-in and treatment period. During the treatment period the subject must undergo all assessments per Table 2.

During the COVID-19 pandemic, a phone call visit can replace an on-site visit and on-site IP administration can be replaced with home/alternative location IP administration. Patient must sign the COVID-19 addendum to informed consent prior to starting the alternative options of on-site IP administration. If obtaining signed addendum is not feasible, patient can follow alternative options after verbal consenting. Please refer to Appendix I for details.

The subject will enter the optional COPD exacerbation visit (EXA) and complete the assessments according to Table 2 if he/she experiences a COPD exacerbation during the treatment period, if deemed necessary by Investigator (refer to Section 8.1.1.5).

The subject can also return to the site to complete an unscheduled visit (UNS) for the following reasons but not limited to, missed assessment(s) at last scheduled visit, safety follow up, issues with equipment, or other reasons that the site deems necessary. The UNS visit should not be used for a COPD exacerbation as there is an EXA visit for this reason. In addition to the assessments listed in Table 2, other assessments may be performed at the PI's discretion.

Section 6.5 (Table 6) provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial.

Interim Analyses

Two interim analyses will be performed. The first interim analysis will occur when subjects with at least 3 months of follow-up represent approximately 30% of all potential follow-up data and will be a futility analysis to potentially stop the study early if lack of efficacy observed.

The second interim analysis will be conducted approximately 1 month after all subjects have been randomized. This interim analysis will be used to guide an 'Early Go' decision by the sponsor to begin planning activities for the next stage of development. Both interim analyses will be carried out using pre-defined rules by the IDMC while the study team remains blinded to ensure the integrity and blinded nature of the study. After the second interim analysis, the study will continue, regardless of whether the criteria for 'Early Go' was met.

4.2 Scientific Rationale for Study Design

The purpose of this global study is to provide evidence of the efficacy and safety of a 420 mg dose of tezepelumab administered Q4W SC in adults with a history of COPD exacerbations and moderate to very severe COPD receiving triple inhaled maintenance therapy with ICS/LABA/LAMA.

The primary endpoint (COPD exacerbation) is a well-accepted measure for a study in COPD. In order to avoid bias the study will be randomized and double blinded. Subject entry will be stratified by region and prior number of exacerbations (2 vs ≥3) to ensure equitable distribution for analysis.

Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is anticipated to have impact on the broad spectrum of inflammatory responses seen in COPD. Subject entry into the study will be monitored to ensure that there are adequate numbers of patients within different phenotypes (level of blood eosinophils and number of exacerbations in the previous year) for analysis.

Induced sputum analysis will be performed in a selected group of sites. The aim of this subset analysis is to further help to answer mechanistic and conceptual questions regarding the effect of tezepelumab in COPD exacerbations. Sputum biomarkers may be measured to evaluate the pharmacology of tezepelumab, exploratory PK, airway microbiome and biomarkers related to COPD, inflammation and the TSLP pathway. Key understandings are believed to come from sputum samples obtained at the time of COPD exacerbation. In these same subjects, analyses of nasal lining fluid and nasal epithelial transcriptomics will be performed to complement the sputum analyses.

4.3 Justification for Dose

A 420 mg Q4W dosing regimen was selected for this Phase 2a study in COPD based on the efficacy, safety, and exposure-response relationships found with tezepelumab treatment in patients with severe asthma, as well as safety data from the Phase 1 studies.

Based on the efficacy and safety data, as well as exposure-response analysis, of the Phase 2b asthma study CD-RI-MEDI9929-1146, 210 mg Q4W SC was selected as the optimal dose of tezepelumab for adult and adolescent patients with severe asthma and is confirmed in the Phase 3 studies in severe asthma. Given the uncertainty in the exposure-response relationship in COPD compared to asthma patients, a higher dose of 420 mg Q4W was selected to ensure maximum efficacy in this proof-of-concept study in COPD patients.

The safety of 420 mg SC dose has been demonstrated in the Phase 1 single ascending dose study 20070620, in which doses up to 420 mg SC and 700 mg IV were evaluated in healthy subjects and subjects with AD and well tolerated. In addition, repeated doses up to 700 mg Q4W IV have been evaluated and well tolerated in healthy subjects in the Phase 1 multiple ascending dose study 20080390 as well as the allergen challenge study 20101183 in patients with mild asthma. Further, in study CD-RI-MEDI9929-1146, repeated dosing at 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W SC for 52 weeks were well tolerated in subjects with severe asthma, and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship in treatment-emergent adverse events. Based on population PK model simulation, the predicted area under the concentration-time curve (AUC) of serum tezepelumab concentration at steady state was CCI lower and the predicted maximum concentration (C_{max}) at steady state was CCI lower at 420 mg Q4W compared to 280 mg Q2W SC. Therefore, the dose of 420 mg Q4W SC CCI [redacted]

4.4 End of Study Definition

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

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines 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.

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

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

5.1 Inclusion Criteria

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

Informed consent:

1. Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

2. Provision of signed and dated written addendum to informed consent form for sputum/nasal sub studies prior to collection of sputum/nasal samples (if applicable).

3. Provision of signed and dated written genetic informed consent prior to collection of optional samples for genetic analysis (if applicable).

   The ICF process is described in Appendix A 3.

Age:

4. Female or male subjects aged ≥40 to 80 years inclusive at the time of enrolment (Visit 1).

Type of subject and disease characteristics:

5. History of moderate to very severe documented physician-diagnosed COPD for at least 12 months prior to enrolment with a post-bronchodilator FEV1/FVC<0.70 and a post-bronchodilator FEV_1 ≥20% and ≤80% of predicted normal value at Visit 2 (or Visit 1 if Visit 1 and 2 are combined).

6. History of at least 2 documented moderate to severe COPD exacerbations, within 2 to 52 weeks prior to enrolment (Visit 1) or re-screening Visit 1. See Section 4.1 for required source documentation for this inclusion.

   – A moderate COPD exacerbation is defined as an exacerbation that required treatment with systemic corticosteroids for at least 3 days duration (or 1 injection of depot formulation) and/or antibiotics.

   – A severe COPD exacerbation is defined as an exacerbation that required hospitalization (defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system).

   – Prior use of antibiotics alone does not qualify as a moderate exacerbation unless the antibiotic was specifically prescribed for the treatment of worsening COPD symptoms.

   – Previous exacerbations should be confirmed to have occurred while patient was on stable triple (ICS/LABA/LAMA) background therapy for COPD and not as a result of a step down in therapy, i.e. change from triple to dual therapy.

     NOTE: In case of re-screening, moderate to severe COPD exacerbations from screening period are considered as historical COPD exacerbations within 2 to 52 weeks prior to re-screening visit and should be included in total number of historical COPD exacerbations. Refer to section 5.4

7. Documented treatment with medium or high dose ICS at a total daily dose corresponding to >250µg fluticasone propionate dry powder formulation equivalent and LABA and LAMA for COPD throughout the year prior to enrolment (Visit 1). The dose of ICS should be stable for 3 months prior to Visit 1. See Section 4.1 for required source documentation for this inclusion criterion. See Appendix F for ICS dose conversion table.

- Patient could have switched therapies during the previous year and/or stepped down for short periods of time, although the total cumulative duration that the patient was not using triple (ICS/LABA/LAMA) background therapy must not exceed 2 months.
- If an Investigator decides to switch a subject who is on an ICS in a separate single device to a fixed-dose combination device therapy, this should be done at Visit 1 and the ICS component must remain at the same dose and schedule as used in the 3 months prior to Visit 1 (provided dose and regimen are locally approved for COPD).

8. CAT score ≥15 at Visit 1 (only based on ePRO questionnaire).

9. Current smoker or ex-smoker with a tobacco history of ≥10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year). Never smokers are not eligible for study entry.

10. If on allergen-specific immunotherapy, subjects must be on a maintenance dose and schedule for at least 2 months prior to Visit 1.

11. If on theophylline or roflumilast, subjects must be on maintenance treatment for at least 12 months prior to Visit 1 and on stable dose 3 months prior to Visit 1.
Note: Subjects on maintenance treatment with theophylline should have blood concentration levels within the therapeutic range documented within 8 weeks prior to 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 (see Section 6.3 and Table 6.

12. Inclusion criterion 12 removed with version 4.0 of Clinical Study Protocol and replaced with Exclusion criterion 40.

Weight:

13. Weight ≥40 kg at Visit 1.

Reproduction:

14. Negative serum pregnancy test for female subjects of childbearing potential.

15. Women of childbearing potential (WOCBP) who are sexually active must use a highly effective form of birth control from enrolment 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.

- An 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 birth control methods include: sexual abstinence [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception], a vasectomized partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, 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 amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

  (a) Women <50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the subject as WoCBP.

  (b) Women ≥50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

Additional criteria to be checked prior to randomization (Visit 3):

16. Compliance with the eDiary completion during the run-in period defined as completing at least 8 EXACT-PRO/E-RS assessments in the 12-day period prior to Visit 3.

17. At least 70% compliance with the subject's maintenance therapy (defined as taking all maintenance medication as scheduled for the day) during the run-in period from Visit 2 (or Visit 1 if Visit 1 and 2 are combined) to Visit 3 based on the eDiary.

18. A CAT score of ≥15 (only based on ePRO questionnaire).

19. Stable FEV_1 during the screening period, defined as a change in pre-BD FEV_1 ≤400 mL and/or ≤25% compared to baseline pre-BD (Visit 1) assessment. If a patient demonstrates significant change (>400 mL and/or >25% in either direction) in pre-BD FEV_1 during the screening period, the AZ study physician must be consulted to determine the patient's disposition; randomization may not occur without consultation and agreement with AZ study physician/delegate.

20. Acceptable inhaler and spirometry techniques according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005) during the run-in period.

5.2 Exclusion Criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

Medical conditions:

1. Clinically important pulmonary disease other than COPD, as judged by Investigator, (e.g., active lung infection, main clinical feature is bronchiectasis or emphysema, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis (ABPA)/mycosis, eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome) and/ or radiological and/or laboratory findings suggestive of a respiratory disease other than COPD that is contributing to the subject's respiratory symptoms.

2. Current asthma diagnosis according to the Global Initiative for Asthma (GINA) guidelines (GINA 2018) or other accepted guidelines. Patients with a history of asthma, including paediatric asthma or asthma-COPD Overlap Syndrome (ACOS), are not eligible for the study.

3. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious (including risk factors for pneumonia), endocrine, metabolic, haematological, immune, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and/or could:

   (a) Affect the safety of the subject throughout the study

   (b) Influence the findings of the study or their interpretation

   (c) Impede the subject's ability to complete the entire duration of study

   Note: Subjects who have epilepsy must be on a stable dose of medication for 28 days prior to randomization.

4. Unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, renal failure, uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator or any ECG abnormality obtained during the screening period that in Investigator's judgement may put the patient at risk or negatively affect the outcome of the study.

5. Treatment with systemic corticosteroids and/or antibiotics, and/or hospitalization for a COPD exacerbation within 14 days prior to enrolment (Visit 1), based on last dose of corticosteroids or last date of hospitalization, whichever occurred later.

   Note: Refer to Exclusion criteria 19 for restriction with maintenance systemic steroid treatment.

6. History of clinically significant infection (excluding pneumonia), acute upper or lower respiratory infection, requiring antibiotics or antiviral medication within 14 days prior to enrolment (Visit 1) based on the last day of antibiotic/antiviral treatment or hospitalization date, whatever occurred later.

7. History of pneumonia requiring antibiotics or antiviral medication within 28 days prior to enrolment (Visit 1) or during the screening period, based on the last day of antibiotics or hospitalization date, whatever occurred later or during the enrolment and screening period.

8. Known history of allergy or reaction to any component of the investigational product formulation.

9. History of anaphylaxis to any other biologic therapy.

10. Donation of blood, plasma, or platelets within the past 90 days prior to Visit 1.

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

12. History of alcohol or drug abuse within the past year, which may compromise the study data interpretation as judged by Investigator or Study Physician.

13. History of cancer:

    – Subjects 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.

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

14. Subjects who in the opinion of the Investigator have evidence of active tuberculosis (TB), either treated or untreated, or latent TB without completion of an appropriate course of treatment. Evaluation will be according to the local standard of care as determined by local guidelines and may consist of medical history and physical examinations, chest x-ray, sputum stain and/or culture, and/or TB test (e.g., purified protein derivative or QuantiFeron test).

15. 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:

16. Subjects currently receiving background therapy that is not locally approved for COPD are not eligible for the study (refer to Section 6.5.1)

17. Long term oxygen therapy (LTOT) with signs and/or symptoms of cor pulmonale and/or right ventricular failure, or subjects receiving LTOT >4.0 litres/minute (L/min), or saturation <89% despite LTOT.

18. Use of any non-invasive positive pressure ventilation device (NIPPV). Note: Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

19. Use of systemic immunosuppressive medication (including but not limited to methotrexate, cyclosporine, maintenance systemic steroid treatment, any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1) or throughout the screening period. Use of systemic steroids for treatment of exacerbations is allowed (see exclusion criterion 5).

20. Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1).

21. Receipt of any investigational non-biologic product within 30 days or 5 half-lives whichever is longer, prior to Visit 1.

22. Receipt of any marketed (e.g., omalizumab) or any investigational monoclonal or polyclonal antibody therapy (e.g., gamma globulin) taken for any reason within 4 months or 5 half-lives prior to Visit 1, whichever is longer.

23. Receipt of live attenuated vaccines 30 days prior to first IP administration.

24. Chronic use of macrolide or other antibiotics for prophylactic use of COPD exacerbation if duration of treatment is < 9 months prior to enrolment (Visit 1) or re-screening visit. If the patient was previously on prophylactic treatment but is no longer taking it, the patient cannot be randomized until 6 weeks after the last dose.

    Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on a stable dose/regimen for ≥ 9 months prior to enrolment (Visit 1) or re-screening visit and have had at least 2 historical COPD exacerbations while on prophylactic treatment.

    Note: Patients who received ≥6 months of antibiotics treatment in the previous year must have a hearing assessment performed as per local standard of care within 3 months prior to randomization. These patients must be interviewed for potential

hearing issues/tinnitus at enrolment; any reported issues will be recorded as part of medical history.

25. Influenza vaccination within 3 weeks before sputum collection (Visit 3) for subset of subjects only. Vaccination prior to that or after that time is acceptable.

26. Subjects with lung volume reduction surgery within the 6 months prior to Visit 1. Subjects with history of partial or total lung resection (single lobe or segmentectomy is acceptable).

27. Subjects that have been treated with bronchial thermoplasty or received endobronchial valves in the last 12 months prior to Visit 1.

Prior/concurrent clinical study experience:

28. Subjects participating in, or scheduled for, an intensive (active) COPD rehabilitation program (however subjects who are in the maintenance phase of a rehabilitation program are eligible to take part).

29. Employees of the clinical study centre or family members (first-degree relatives) of such individuals or anyone involved in the planning and/or conduct of the study.

30. Previous treatment with tezepelumab (MEDI9929/AMG157).

Diagnostic assessments:

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

32. Evidence of active liver disease (with or without ongoing treatment), including jaundice or aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase (ALP) > 2 times the upper limit of normal (ULN) at Visit 1.

33. Subjects are excluded if they have any of the following:

    – A history of known immunodeficiency disorder including a positive test for human immunodeficiency virus, HIV-1 or HIV-2 at Visit 1.

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

Other exclusions:

34. Pregnant, breastfeeding, or lactating women.

    - A serum β-HCG pregnancy test must be drawn for women of childbearing potential at the screening visit. If test result is positive, the subject 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 subject whose menstrual and/or sexual history suggests the possibility of early pregnancy should be excluded.

35. Judgment by the Investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements or for safety reasons.

Genetic Research exclusion criteria:

36. Previous allogeneic bone marrow transplant.

37. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

COVID-19 pandemic exclusion criteria:

38. Judgment by the Investigator that the subject should not participate in the study based on assessment of COVID-19 symptoms for active COVID-19 infection or is febrile (≥ 38°C; ≥ 100.4°F) suspected due to COVID-19 infection.

39. Positive SARS-CoV-2 naso/oropharyngeal swab test, positive rapid antigen test or positive alternative test (approved by local health authorities) for active infection at Visit 1.

40. Chest X-ray performed during the screening period which shows abnormalities or evidence of COVID-19 pneumonia that precludes the patient's ability to complete the study.

    Note: Under special circumstances, a recently done historical chest X-ray (anterior-posterior and lateral)/CT/MRI for other reasons (not study related) might be acceptable. The outcome of the X-ray/CT/MRI must be documented in the patients' medical records. Study Physician approval of historical chest X-ray must be obtained prior to randomization.

41. Receipt of any COVID-19 vaccine within 28 days prior to date of randomization.

5.3 Lifestyle Restrictions

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

5.3.1 Meals and Dietary Restrictions

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

Subjects should not eat or drink 1 hour prior to having FeNO assessment.

5.3.2 Alcohol, Tobacco and Other

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

Current tobacco smokers or subjects with smoking history ≥ 10 pack-years (1 pack year = 20 cigarettes smoked per day for 1 year) at Visit 1 are allowed. Never smokers are not allowed to enter the study. Smoking status will be captured on the eCRF throughout the study. See Section 8.2.2.

The use of e-cigarettes (e.g., JUUL) is allowed during the course of the study.

Subjects should not smoke on the assessment day prior to all lung function assessments at the site.

5.3.3 Activity

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

5.4 Screen Failures and Re-screening

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

These subjects should have the reason for study withdrawal recorded as ‘Screen Failure’ (i.e., subject does not meet the required inclusion/exclusion criteria) in the electronic case report

form (eCRF). This reason for study withdrawal is only valid for screen failures, and not randomized subjects.

In following situations, the screening may be extended without prior approval from AstraZeneca Study Physician:

- Subjects that experience a **COPD exacerbation** during the screening period: May remain in screening and the screening period may be extended up to 14 days to allow for the completion of the course of systemic corticosteroids and/or antibiotics if deemed suitable by the Investigator.

  Note: Enrolment: Subjects treated with systemic corticosteroids and/or antibiotics and/or hospitalization for a COPD exacerbation within 14 days prior to enrolment (Visit 1 or re-screening Visit 1), should be delayed allowing patient to be eligible for the study (exclusion criterion 5).

- Subjects with **respiratory infection** (excluding pneumonia) requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the screening period: May remain in screening and the screening period may be extended up to 14 days to allow for the completion of therapy if deemed suitable by the Investigator.

  Note: Subjects treated with antibiotics or antiviral medications for respiratory infection within 14 days prior to enrolment (Visit 1 or re-screening Visit 1) should be delayed allowing patient to be eligible for the study (exclusion criterion 6).

- Subjects with **respiratory infection** (excluding pneumonia) NOT requiring antibiotics or antiviral medication during the screening period:
  May remain in screening and the screening period may be extended up to 14 days to allow subject to meet FeNO restrictions.

  Note: Subjects without antibiotics or antiviral medications for respiratory infection within 14 days prior to enrolment (Visit 1 or re-screening Visit 1) should be delayed allowing patient to meet FeNO restrictions.

Extension of the screening period for any other reason will be allowed only upon approval of the AstraZeneca Study Physician.

In following situation, subject must be screen failed:

- Subjects who experience **pneumonia** during the screening period should be screen failed. They may be re-screened but no sooner than 28 days after the last day of antibiotic treatment or the last date of hospitalization, whatever occurred later (exclusion criterion 7).

- Judgment by the Investigator that the subject should not participate in the study **based on assessment of COVID-19 signs and symptoms for active infection.** Subject can be re-screened within 2 to 4 weeks, upon approval of the AZ Study Physician (exclusion criterion 38).

- Subject who had **positive SARS-CoV-2 naso/oropharyngeal test (or rapid test) at Visit 1** for active infection during screening should be screen failed. They may be re-screened once recovered from the infection, upon approval of the AZ Study Physician (exclusion criterion 39).

Re-screening:

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, etc), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca study physician and documented in the Investigator Study File (ISF).

Re-screening for subjects who have screen-failed due to ePRO criteria (e.g., did not meet minimum EXACT-PRO/E-RS™: COPD requirement or did not report adequate compliance with maintenance medications) is not allowed.

Re-screening of a subject for any 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).

Any re-screened subject will be re-enrolled and reassigned their originally assigned subject number after signing a new ICF and addendum to ICF (if applicable) and after all Visit 1 assessments have been performed as listed in Table 1 (with the exception of testing for HIV-1 and HIV-2, hepatitis B and C, and FSH). If the timeframe between Screening and Re-screening is more than 30 days, then all Visit 1 assessments should be repeated.

In case of re-screening, moderate to severe COPD exacerbations from screening period are considered as historical COPD exacerbations within 2 to 52 weeks prior to re-screening Visit 1 (Inclusion 6) and should be entered in eCRF module COPDEXH and included in total number of historical COPD exacerbation during IWRS stratification transition at re-screening Visit 1.

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

Subjects who were screen failed when the recruitment was temporarily paused due to the COVID-19 pandemic may be allowed to re-screen even if the subjects have already been re-

screened once before. A documented approval for re-screening due to COVID-19 should be filed in the Investigator Study File (ISF).

6. STUDY TREATMENTS

Study treatment is defined as an IP (including placebo) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to tezepelumab or placebo.

6.1 Treatments Administered

6.1.1 Investigational Products

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

Each subject will receive two SC injections at each dosing interval to receive a total dose of 420 mg tezepelumab, or placebo.

Table 5 - Study Treatments

	Treatment 1	**Treatment 2**
Study treatment name:	Tezepelumab	Placebo
Dosage 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
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions:	Refer to Section 6.1.2	Refer to Section 6.1.2
Packaging and labelling	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each APFS will be labelled in accordance with GMP Annex 13 per country regulatory requirement. The labels will be translated into local language where applicable.	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each APFS will be labelled in accordance with GMP Annex 13 per country regulatory requirement. The labels will be translated into local language where applicable.

APFS – Accessorised Pre-Filled Syringe

The accessorized pre-filled syringe (APFS) is a single use, disposable system that is designed to deliver the labelled dose to the subcutaneous space during one injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system.

The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 1 mL long prefilled syringe barrel with a 1/2-inch 27-gauge thin wall staked in needle, rigid needle shield, plunger stopper) and a safety device.

6.1.2 Medical Devices

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

- Accessorised pre-filled syringe (APFS)

Instructions for medical device use are provided in IP Handling Instructions and Pharmacy Manual.

All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the Investigator throughout the study (see Section 8.3.10) and appropriately managed by the manufacturer.

6.2 Preparation/Handling/Storage/Accountability

IP will be supplied to the site in a kit containing APFS tezepelumab or matching 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 APFS within the carton).

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

The IP is to be stored at the study centre in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log while IP is stored at the study centre. The IP must be kept in the original outer container and under conditions specified on the label (between 2°C to 8°C [36°F to 46°F], protected from light). Only subjects randomized in the study may receive study treatment. Only authorized site staff may supply or administer study treatment.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The centre staff should not administer the affected IP and should immediately contact an AstraZeneca representative for further guidance if the following cases are met:

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

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

Please Note: If allowed by local and regional guidelines, IP preparation and administration may be performed at the subject's home/alternative location by a qualified HCP. Before initiating consent for home IP administration visit, the subject must have received at least the first 2 IP administrations at the site. Please refer to Appendix I for further details.

Dose preparation

Each APFS should be visually inspected prior to dose preparation. The IP will be provided to the study sites as a clear to slightly opalescent, colorless to slightly yellow clear solution contained in a pre-filled syringe to be stored between 2°C to 8°C [36°F to 46°F] 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, Investigator, or nurse) 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 removal of the IP from the refrigerator to start of administration should not exceed 8 hours. If storage time exceeds this limit, a new dose must be prepared with a new IP kit.

To prepare the subject's dose, two IP kits will be selected for administration according to the kit identification numbers assigned by IWRS.

Dose preparation steps:

1. Allow the IP to equilibrate to room temperature 68°F to 77°F (20°C to 25°C) for at least 60 minutes prior to dose administration. Ensure that the APFS is adequately protected from light during the warming process.
2. To prepare IP for administration remove the syringe from the carton by holding the middle of the syringe body.
3. Unwrap, but do not detach, the wrap-around label attached to syringe body to view the syringe contents.
4. Look at the liquid through the viewing window. The liquid should be clear and colorless to slightly yellow. Do not inject IP if the liquid is cloudy, discolored, or contains large particles.
5. Re-wrap the label around the syringe body.

Unused product in opened and dispensed IP kits should not be used for subsequent dosing and should be stored for IP accountability. If the opened and dispensed IP kits must be discarded immediately after dose preparation as per site's Standard Operating Procedures (SOP), the syringe labels along with the kit boxes must be retained for IP accountability.

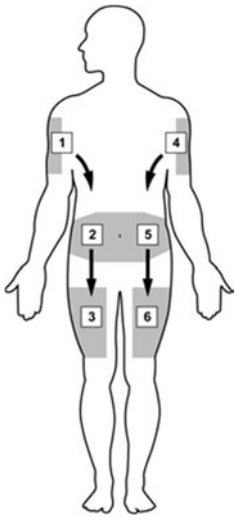
Dose administration

The IP will be administered by the Investigator/authorized delegate. Two injections are required and will be administered at the same anatomical site with a distance of at least 1 inch (3 cm) between the two injections. The injection site must be recorded in the source documents at each treatment visit and recorded 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 fully inserted at a 45-degree angle approximately into the SC tissue. The injection site should not be rubbed after each injection. The second injection should be administered immediately after the first one.

It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. Injection site must be documented on the eCRF and in the source documents at each treatment visit. In cases when rotation of the injection site is not feasible, and/or the subject 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



Further details on IP administration are provided in the IP Handling Instructions document. IP administration must be carried out according to these instructions.

Subjects should be observed for a minimum of 2 hours after administration of the first two IP dosing visits for the appearance of any acute drug reactions. For the remaining doses, subjects 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 subject received allergen immunotherapy injection on the same day as scheduled IP administration.
- The subject has an intercurrent illness that in the opinion of the Investigator and/or medical monitor may compromise the safety of the subject in the study (e.g., viral illnesses).
- The subject is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.
- The subject is confirmed to have an active COVID-19 infection based on positive SARS-CoV-2 test results.
- The subject is suspected to have an active COVID-19 infection based on assessment of COVID-19 symptoms.
- 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 8.2.10, Table 8 cannot be followed.

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 the subject is suspected to have an active COVID-19 infection or fever (≥ 38°C; ≥ 100.4°F) suspected due to COVID-19 infection, the visit should be rescheduled (and IP administration

deferred) and subject should be re-assessed for symptoms of COVID-19 prior to re-scheduled visit.

AZ Study Physician should be contacted to discuss further subject participation in the following situations:

- The subject has been diagnosed with an active COVID-19 infection.
- The subject skips 2 consecutive IP administrations.

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

The subject may remain in the study after an exacerbation and continue to receive IP if the investigator judges that it is medically appropriate for the subject to do so.

6.3 Measures to Minimise Bias: Randomization and Blinding

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign the potential subject a unique enrolment number (which begins with an 'E') via IWRS.

3. Determine subject eligibility.

4. Assign the eligible subject unique randomization code via IWRS.

5. Subjects will be allocated to receive tezepelumab or placebo in a 1:1 ratio and according to the stratification factors listed in Section 4.1. Randomization numbers will be grouped in blocks. If a subject withdraws from the study, then his/her enrolment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

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

Procedures for handling incorrectly enrolled or randomized subjects

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

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the subject from treatment. Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient and AstraZeneca study physician must ensure the decision is appropriately documented. Subjects 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 also be clearly documented.

Methods for assigning treatment groups

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

The randomization code will be assigned from a randomization list prepared by a computerized system provided by PPD on behalf of AZ (AZRand). All subjects will be stratified at randomization by region and number of exacerbations in the 12 months prior to Visit 1 (or re-screening Visit 1) (2 vs ≥ 3).

In order to achieve the assumed exacerbation rates used to determine sample size, it is expected that approximately 30% of subjects will have had at least 1 severe exacerbation (an exacerbation resulting in hospitalization) within 12 months prior to Visit 1 (or re-screening Visit 1) and approximately 40% of subjects will have had ≥3 exacerbations within 12 months prior to Visit 1 (or re-screening Visit 1). (Refer to Section 4.1)

Consideration will be given to closing the Interactive Web Response System (IWRS) randomization for a subgroup [by region or overall] to ensure that approximately 20% of the subjects will be targeted to have ≥300 eosinophils/µL, 40% of the subjects between ≥150 to <300 eosinophils/µL and a maximum of approximately 40% of the subjects with <150 eosinophils/µL at enrolment.

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 subject nor any of the Investigators or sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the subjects 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 subject becomes known to the Investigator or other study staff involved in the management of study subjects or needs to be known to treat an individual subject 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 IWRS company
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- Bioanalytical lab performing the PK sample analysis
- Those involved in the reporting and reviewing the unblinded IDMC presentations

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

No other member of the extended study team at AstraZeneca, or any Contract Research Organization (CRO) handling data, will have access to the randomization scheme during the conduct of the study until after the primary database lock.

Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) and delegate(s) at the study sites from the IWRS. Routines for this will be described in the 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 subject requires knowledge of the treatment randomization. The Investigator should document and report the action to AstraZeneca, without revealing the treatment given to subject to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to 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 subject have been made and documented and until primary database lock after last subject completes week 52 has been documented.

6.4 Compliance to IP

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 with the reason for drug interruption, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant Therapy

Information about all COPD medications given within the 12 months prior to Visit 1, all medications for other indications given in the 3 months prior to Visit 1, COVID-19 vaccine given at any time, and all concomitant medications given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit (as shown in Table 1 and Table 2) and recorded in the eCRF.

The subject's usual pre-study triple inhaled therapy (medium to high dose ICS/LABA/LAMA) formulation, dose and regimen, and any other additional allowed COPD medications that may have been taken prior to enrolment, should be continued without any change throughout the enrolment, run-in, treatment and follow-up period as outlined below.

As theophylline has a narrow therapeutic window, please note that subjects on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented within 8 weeks prior to Visit 1 (see Table 6). If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analyzed at the central or local lab as applicable. Theophylline blood levels greater than 12mg/dl should be managed according to local standards of care and the Investigator's judgment and discussed with AZ study physician prior to randomization. It is recommended that additional increments in dose are evaluated with blood levels. Investigator can use their clinical judgement about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

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

- Reason for use
- Dates of administration including start and end dates

Table 6 - Allowed, Restricted and Prohibited Medications

Medication	Allowed/ Restricted/ Prohibited	Details
Background (maintenance) COPD medication (ICS/LABA/LAMA)	**Allowed**	Documented treatment with medium or high dose ICS at a total daily dose corresponding to >250µg fluticasone propionate dry powder formulation equivalent and a LABA and LAMA for COPD throughout the year prior to enrolment (Visit 1) and throughout the study. The dose of ICS should be stable 3 months prior to V1 and throughout the study. See inclusion criterion 7. ICS in a separate, single device is permitted if all the following criteria are met: - it is administered at the same dose and schedule as in the fixed dose combination product; - it is not given in combination with a LAMA alone. If an Investigator decides to switch a subject who is on an ICS in a separate single device to a fixed-dose combination device therapy, this should be done at Visit 1 and the ICS component must remain at the same dose and schedule as used in the 3 months prior to Visit 1 (provided dose and regimen are locally approved for COPD). Nebulized budesonide is accepted as part of maintenance therapy if the dosing regimen is equivalent to that of budesonide approved as part of a combination product for COPD (e.g., for budesonide/formoterol combination 320mcg/9mcg BID equivalent dose of nebulized budesonide is 0.5mg BID [GOLD 2019]

Medication	Allowed/ Restricted/ Prohibited	Details
		Nebulized LABA is accepted as part of maintenance therapy. Twice daily triple inhaled (ICS/LABA/LAMA) medications should be withheld at least 12 hours prior to scheduled spirometry at site. Once daily triple inhaled (ICS/LABA/LAMA) medications should be withheld at least 24 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.
Additional ICS on top of COPD ICS maintenance medication	**Restricted**	Can only be given concomitantly with systemic steroids during acute COPD exacerbation treatment while at site or other health care provider. Additional use of ICS outside of this is not allowed.
Systemic corticosteroids (tablets or injections)	**Restricted**	Prohibited as maintenance treatment within 3 months prior to Visit 1 and throughout the study. Allowed to treat a COPD exacerbation or an AE where there is no alternative treatment available, for no more than 14 days. If treatment duration is expected to exceed 14 days, the AstraZeneca study physician must be contacted.
Maintenance SABA (short-acting β2-	**Prohibited** if	Please see below. Use on their own, or for

Medication	Allowed/ Restricted/ Prohibited	Details
agonists) administered by either MDI or nebulizer	administered as part of maintenance double/triple therapy.	step-up or step-down are not allowed.
SABA (short-acting β2-agonists administered by an MDI or nebulizer)	**Allowed** as rescue medication and for treatment of acute COPD exacerbation. **Prohibited** if administered as maintenance medication or in a scheduled dose.	Prophylactic use of SABA in the absence of symptoms is discouraged. However, if deemed necessary by the subject and Investigator (e.g., prior to planned exercise), it can be used, but such use of prophylactic inhalations should be documented in the medical notes and recorded in the eCRF. Use of SABA is to be avoided 6 hours before a scheduled ECG, FeNO and spirometry assessment. Occasions (# of times used) where SABA was administered via an MDI will be recorded separately from the nebulized inhalations in the eDiary.
Maintenance SAMA (short acting muscarinic antagonists = short acting anticholinergics administered by MDI or nebulizer)	**Prohibited** if administered as part of maintenance double/triple therapy.	Please see below. Use on their own, or for step-up or step-down is not allowed.
SAMA (short acting muscarinic antagonists = short acting anticholinergics administered by MDI or nebulizer)	**Allowed** as rescue medication and for treatment of acute COPD exacerbation. **Prohibited** if	Prophylactic use of SAMA in the absence of symptoms is discouraged. However, if deemed necessary by the subject and Investigator (e.g., prior to planned exercise), it can be used, but such use of prophylactic inhalations should be documented in the medical notes and recorded in the eCRF.

Medication	Allowed/ Restricted/ Prohibited	Details
	administered as maintenance medication or in a scheduled dose.	Use of SAMA is to be avoided 6 hours before a scheduled ECG, FeNO and spirometry assessment. Occasions (# of times used) where SAMA was administered via MDI will be recorded separately from the nebulized inhalations in the eDiary.
SABA and SAMA combination products	**Allowed** as rescue medication and for treatment of acute COPD exacerbation. **Prohibited** if administered as maintenance medication or in a scheduled dose.	Prophylactic use of SABA and SAMA combination product in the absence of symptoms is discouraged. However, if deemed necessary by the subject and Investigator (e.g., prior to planned exercise), it can be used, but such use of prophylactic inhalations should be documented in the medical notes and recorded in the eCRF. Use of SABA and SAMA combination product is to be avoided 6 hours before a scheduled ECG, FeNO and spirometry assessment. Occasions (# of times used) where SABA and SAMA combination product was administered via MDI will be recorded separately from the nebulized inhalations in the eDiary.
Antitussives prn	**Allowed**	
Mucolytics	**Allowed**	
Antihistamines prn	**Allowed**	
Dermal topical steroids, intra-articular, nasal steroids, topical ophthalmic and otic	**Allowed**	

Medication	Allowed/ Restricted/ Prohibited	Details
corticosteroids		
Xanthines	**Restricted**	Allowed only if on maintenance treatment for 12 months and on a stable dose for 3 months prior to enrolment (Visit 1). Allowed in a dose equivalent to theophylline ≤400mg q day. For doses greater than 400 mg, the dose must be stable and theophylline blood levels should be confirmed to be equal to or below 12 mg/dl, within 8 weeks prior to Visit 1 or during the screening period. Theophylline blood levels greater than 12mg/dl should be managed according to local standards of care and the Investigator's judgment and discussed with AZ study physician. It is recommended that additional increments in dose are evaluated with blood levels. Twice daily xanthines should be withheld for at least 12 hours prior to scheduled spirometry at site. Once daily xanthines for at least 24 hours prior to scheduled spirometry at site.
Antibiotics	**Restricted**	Allowed to treat COPD exacerbations and/or AEs. Antibiotics to treat a COPD exacerbation should not be used for more than 14 days. If treatment duration is expected to exceed 14 days, the AstraZeneca study physician must be contacted. Chronic use (>3wks) and use for the prevention of COPD exacerbations is

Medication	Allowed/ Restricted/ Prohibited	Details
		disallowed, unless the patient is on stable dose and regimen for ≥9 months prior to randomization and has had ≥2 COPD exacerbations while on stable therapy (see exclusion criterion 24, Section 5.2). In all other cases of chronic use, ≥6 weeks wash-out period should be in place after the last dose of antibiotic and prior to randomization.
Allergen immunotherapy	**Restricted**	Allowed, if on stable therapy for at least 2 months prior to date of Visit 1 with no anticipated change during the screening and the treatment period. These should not be administered on the same day as IP administration.
Inactive/killed vaccinations (e.g., inactive influenza)	**Restricted**	Allowed, except - within 5 days before or after any IP dosing visit - within 3 weeks before sputum collection (Visit 3) for subset of subjects only. - 3 weeks prior to EOT visit for sub-study subjects only
COVID-19 vaccinations	**Restricted**	COVID-19 vaccination is allowed, provided it is not administered within 28 days before and 14 days after IP administration. Administration timing of COVID-19 vaccination should be discussed with the AstraZeneca Study Physician. If participant receives COVID-19 vaccine less than 14 days before the next scheduled dose of study intervention, the study intervention administration should be rescheduled or skipped to ensure the next study intervention dose is at least 28 days after the vaccine

Medication	Allowed/ Restricted/ Prohibited	Details
		administration. COVID-19 vaccination schedule should follow country-specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the study intervention dosing/COVID-19 vaccination intervals are maintained. 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 study intervention dosing (mentioned above) is maintained. As these intervals might change, please discuss with AstraZeneca Study Physician for the most current recommended time interval prior to any vaccine dose Refer to section 8.2.10
Roflumilast (Daxas®, Daliresp®)	**Restricted**	Allowed only if on maintenance treatment for 12 months, on a stable dose for 3 months prior to enrolment (Visit 1), and only if locally approved for COPD. If roflumilast is discontinued at Visit 1, approximately 7 days must elapse before performing spirometry testing at Visit 2.
Leukotrienes (LTRA)	**Restricted**	Restricted for at least 24 hours prior to scheduled spirometry at site.
Immunoglobulin and Blood products	**Prohibited**	Prohibited within 30 days prior to enrolment (Visit 1) and throughout the treatment period.

Medication	Allowed/ Restricted/ Prohibited	Details
Medications containing ephedrine	**Prohibited**	From Visit 3 and throughout the treatment period.
Live attenuated vaccines	**Prohibited**	Prohibited within 30 days prior to Visit 3, during the treatment period and for 16 weeks (5 half-lives) after the last dose of IP.
Omalizumab, denosumab or any other monoclonal or polyclonal antibody therapy (e.g., gamma globulin)	**Prohibited**	Prohibited if taken for any reason within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 and during the study (even if the subject has discontinued IP).
Systemic immunomodulators and immunosuppressive medication (including but not limited to methotrexate, cyclosporine, any experimental anti-inflammatory therapy	**Prohibited**	Prohibited within 3 months prior to Visit 1 and throughout the study or 4 weeks after the last dose of IP. Refer to Systemic corticosteroids (tablets or injections) for further restrictions.
Long term oxygen therapy (LTOT)	**Restricted**	Prohibited with signs and/or symptoms of cor pulmonale and/or right ventricular failure or receiving LTOT >4.0 litres/minute (L/min), or saturation <89% despite LTOT. During the treatment phase, any increase in maintenance oxygen therapy up to 4 L/min is allowed, based on investigator's judgement.
Investigational non-biologic products	**Prohibited**	Prohibited within 30 days or 5 half-lives whichever is longer prior to Visit 1 and during the study.

6.5.1 Background (Maintenance) Medication

All subjects are required to be treated with maintenance locally approved triple inhaled therapy (ICS/LABA/LAMA) for COPD for at least 12 months prior to enrolment (Visit 1) with a stable dose of ICS for the 3 months prior to Visit 1.

The aim of this study is to establish the treatment effect of tezepelumab as add-on therapy. Therefore, the background medications should be maintained at the same dose and schedule from Visit 1 until the end of the study, i.e., when the subject has completed his/her last scheduled contact.

Subjects currently receiving background therapy that is not approved for COPD are not eligible for the study. However, for individual cases when subjects are treated with background therapy that is not approved for COPD, the subject may be considered for enrolment and maintain their maintenance medication during the study if the following criteria are met:

- Current treatment regimen is considered the best option for the subject by the treating physician/Investigator without acceptable alternative;
- Medication/dose/device is approved for COPD in other countries or contains components and doses equivalent to those in approved medication/combination therapy.

These cases should always be consulted with the AZ Study Physician prior to the decision to enrol the patient into the study.

Changes to the subject's maintenance therapy are discouraged during the treatment period, unless judged medically necessary by the Investigator. Any changes should be discussed with the AstraZeneca Study Physician and the justification for treatment changes should be documented in the source notes along with the rationale for the change. Changes should be recorded in the eCRF.

During the study, inhaled background medications that are given once daily should be administered in the morning to conform with spirometry measurements requirements.

Recommended background medication compliance during the treatment period is ≥70%. It is recommended that compliance levels below 70% prompt the site/investigator to evaluate the reasons for low compliance and to provide re-education to the patient in regard to the importance of compliance. It is strongly recommended that when compliance level falls below 50%, the site contacts the AZ study physician in order to discuss the potential safety implications for the patient and future decisions.

Background medication adherence will be assessed daily via the eDiary. The patient will be asked if they took their regularly scheduled COPD medicine (yes/no) and instructed not to consider instances of rescue inhaler usage when answering this question.

6.5.2 Other Concomitant Treatment

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

6.5.3 Rescue Medication

SABA (short-acting β2-agonists) and/or SAMA (short acting muscarinic antagonists = short acting anticholinergics) or SABA/SAMA combinations may be used as rescue medication during the study in the event of a worsening of COPD symptoms (see Table 6).

6.5.4 Allowed Medications to Treat a COPD Exacerbation

Medications to treat an exacerbation should not be used for more than 14 days.

The restrictions that apply during the study are summarized in Table 6.

If the Investigator makes the clinical decision that a subject needs treatment with any disallowed medication, e.g., "step up" or treatment for an exacerbation for more than 14 days, the Investigator must contact the AstraZeneca Study Physician to discuss justification for disallowed medication use and/or prolonged oral corticosteroid treatment. The Investigator must document outcome of discussion in the source documentation.

6.5.5 COPD Medication Restrictions on the Days of Scheduled Spirometry and FeNO Visits

Spirometry assessments will be performed at the site at scheduled visits (see Table 1 and Table 2). There are restrictions regarding the subject's COPD medications prior to the spirometry assessments. Please see Section 8.1.2.1.

NOTE: Screening (Visit 1 and Visit 2) and Randomization spirometry and FeNO are not allowed without proper medication wash out.

Screening Visit 1 and Visit 2

Screening lung function assessments can only be done when there are no restrictions to medications (also refer to Section 8.1.3) and Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is negative. If the SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result will not be available on the day of Visit 1, the screening lung function

assessments must be postponed until next visit, the postponed Visit 1, after the SARS-CoV-2 naso/oropharyngeal) swab test (or rapid test) result is confirmed negative.

At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed. Visit 2 should be scheduled, if the Visit 2 post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test result. The subject must meet the COPD medications restrictions in order to perform the lung assessments.

Subjects will be asked to withhold their triple inhaled (ICS/LABA/LAMA) medications on the morning of the screening pre-BD and post-BD spirometry and FeNO (should be at least 12 hours prior to the assessment for twice daily medication and for 24 hours prior to the assessment for once daily medications) for the eligibility assessment (see Section 5.1, inclusion criterion 7). In addition, SABA and SAMA should not be used within 6 hours of this spirometry and FeNO assessment. The subject's usual COPD medications may be administered following completion of the screening lung function procedures.

Treatment Visits 3-15

Subjects will be asked to withhold their usual triple inhaled (ICS/LABA/LAMA) medications on the mornings of the scheduled spirometry and FeNO visits and preferably for at least 12 hours prior to the spirometry and FeNO assessment (for medications that are administered twice daily)/24 hours prior to the assessment (for once daily medications). This is especially important prior to scheduled spirometry and FeNO assessments (see Table 1 and Table 2) in order to maintain the integrity of planned efficacy analyses around lung function improvement. In addition, SABA and SAMA should not be used within 6 hours prior to the spirometry assessments. The subject's usual COPD medications may be administered following completion of the post-BD spirograms or sputum post-BD spirograms (for patients participating in sputum sub-study). The IP will be administered at a scheduled visit after the pulmonary lung function assessments.

If the subject has taken their usual triple inhaled (ICS/LABA/LAMA) medications on the morning of the scheduled spirometry and FeNO visit, the Investigator/authorized delegate should remind the subject of the importance of withholding their usual morning maintenance therapy, and reschedule the visit for another day, within the allowed window. If rescheduling is absolutely not feasible for the subject, spirometry and FeNO may be performed with a notation indicating that spirometry and FeNO was performed without proper washout of the usual triple inhaled (ICS/LABA/LAMA) medications. Exception is randomization visit, which must be performed when medications restrictions are met.

If the subject has taken the rescue SABA and/or SAMA within 6 hours of the planned site visit spirometry they should ideally remain at the site until such time that the 6 hours withholding time has been reached if it does not exceed the 1.5-hour spirometry window or return on another day, within the visit window. If neither of options is feasible for the subject, spirometry may be performed with a notation indicating that spirometry was conducted within 6 hours of SABA and/or SAMA use.

6.5.6 COPD Medication Restrictions at Unscheduled and Exacerbation Visits

COPD medication restrictions at an unscheduled or an exacerbation visit may not be feasible and may be applied at the discretion of the Investigator. Timing of the triple inhaled (ICS/LABA/LAMA) medications and rescue SABA and/or SAMA use relative to the unscheduled spirometry should be recorded.

6.5.7 COPD Medication Restrictions at Centre Visits with Scheduled ECG Assessment

The subjects should be instructed not to take their usual triple inhaled (ICS/LABA/LAMA) medications prior to the scheduled ECG assessment. The use of a SABA and/or SAMA should be avoided within 6 hours before the ECG assessments. See Section 8.2.6.

NOTE: Screening and Randomization ECG are not allowed without proper medication wash out.

6.6 Endobronchial Therapy

Subjects should not be treated with bronchial thermoplasty or receive endobronchial valves during the study or within 12 months prior to study enrolment.

6.7 Dose Modification

Dose modification of background COPD medications is not allowed in the study. If the Investigator makes the clinical decision that a subject needs dose modification, the Investigator must contact the AstraZeneca Study Physician to discuss justification for modification and document outcome of discussion in the source documentation.

6.8 Treatment After the End of the Study

Subjects who complete Week 64 should be given locally available SoC at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Treatment

Note that discontinuation from IP does NOT mean complete withdrawal from the study.

Subject may be discontinued from IP in the following situations:

- Subject decision. The subject is at any time free to discontinue IP, without prejudice to further treatment
- An adverse event considered to jeopardise the safety of a subject participating in the study
- Pregnancy
- Severe non-compliance with the Clinical Study Protocol
- Lost to follow up
- 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
  - Intensive care unit admission with intubation or extensive mechanical ventilation for a COPD related event
- Any malignancy, except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy has been excised and determined to have clear 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% based on local laboratory results)

- Other reasons

Before a decision to discontinue a subject from IP is instituted, the AstraZeneca Study Physician should be consulted regardless of the reason for discontinuation.

See the SoA 1.1 for data to be collected at the time of IP discontinuation and follow-up and for any further evaluations that need to be completed.

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific withdrawal' on the Discontinuation of Investigation Product form in the eCRF.

7.1.1 Procedures for Discontinuation of Study Treatment

Subjects are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Discontinuing study treatment is not the same as study withdrawal. In the case of early study withdrawal, the EOT visit should be completed immediately. Subjects who do not wish to have any follow-up contacts as detailed below, will be withdrawn from the study. Procedures to follow for study withdrawal are detailed below in Section 7.3. All withdrawn subjects must return the eDiary device at the EOT visit (and at IPD visit for subjects choosing option 3 below). If the subject decides to withdraw consent, then the reason for this must be recorded separately in the eCRF.

A subject that decides to discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Subjects permanently discontinuing IP administration should be given locally available SoC therapy, at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until Week 64 even if the subject has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of COPD have not been conducted. For additional information regarding pharmacokinetic and pharmacodynamic effects of tezepelumab, please see the Investigator brochure.

All subjects who prematurely discontinue IP should return to the site and complete the procedures described for the premature IP Discontinuation visit (IPD) at 4 weeks (+/-5 days) post last IP administration. Subjects who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments.

At the IPD visit the subject will be given three options as to how they will be followed as follows:

1. The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding IP administration) until the EOT visit at Week 52 (+/-5 days).

2. The subject will be offered follow-up on a monthly basis via telephone calls while continuing eDiary completion (no further procedures will be performed) until the subject completes the EOT visit at Week 52 (+/-5 days). 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 1.1) at home as well.

3. If the subject 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), the Investigator will only contact the subject at 52 weeks post-randomization. No other study assessments will be performed prior to this contact.

If the subject chooses option 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, health care utilization, and COPD exacerbation information.

Subjects who initially choose options 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., subject initially choosing option 1 can continue with options 2 or 3, subjects initially choosing option 2 can continue with option 3).

7.2 Lost to Follow-Up

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

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject or next of kin by either repeated telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.

When at least two of the following methods of contact are failed within 3 months of subjects last IP dose:

- At least 3 attempts of either phone calls, faxes or emails;
- Having sent 1 registered letter/certified mail;
- One unsuccessful effort to check the status of the subject using publicly available sources, if allowed by local regulations

The subject should be considered lost to follow up with unknown vital status and censored at latest follow-up contact.

7.3 Withdrawal from the Study

A subject may withdraw from the study (e.g., withdraw consent), at any time (IP and assessments) at his/her own request, without prejudice to further treatment. A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contacts, contacts with a relative or treating physician, or information from medical records) as per Section 7.1.1.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow-up subjects as medically indicated. A withdrawal visit is essential to collect as much data as possible for the subject as per EOT visit described in SoA, Table 2. The subject will return all study supplied equipment including eDiary.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

If the subject only withdraws consent for the retention of biological samples (blood, nasal, sputum, urine etc.) for future exploratory use (e.g., scientific health-related research), the subject will not be withdrawn from the study.

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

7.3.1 Withdrawal Due to Recruitment Completion

When the required number of subjects are randomized in the study, ongoing subjects in screening 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 patients is required.

7.3.2 Discontinuation or Suspension of entire study and Site Closure

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

The sponsor designee also reserves the right to close the study site 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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing and order are summarized in the SoA (Table 1 and Table 2). The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

Due to COVID-19 pandemic, it may not be possible to complete all study assessments according to SoA. Please refer to SoA (1.1) and Appendix I for further details.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed electronic CRFs will be archived at the study site. Additional data to assess the impact of COVID-19 pandemic will be collected.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

The suggested order of assessments to be completed before IP administration should be as follows: ePRO, Vital Signs, ECG, FeNO, Spirometry and Blood draws.

During COVID-19 pandemic, the suggested order of screening assessments is: vital signs (starting with body temperature measurement), ePRO, blood draws and SARS-CoV-2 naso/oropharyngeal swab (or rapid) testing. Screening lung function assessments and ECG can only be done when there are no restrictions to medications (refer to Section 6.5.5 and 8.1.3) and Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result is negative.

The amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will be approximately 360 mL (including any extra assessments that may be required) and will not exceed 450 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 COPD Exacerbation Definition

For the purpose of the protocol, a COPD exacerbation will be defined as a change in the subject's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), and may warrant a change in regular medication and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
- Use of antibiotics for at least 3 days
- An inpatient hospitalization due to COPD (defined as an inpatient admission ≥24 hours in the hospital, in an observation area, the emergency department or other equivalent healthcare facility depending on the country and healthcare system)
- Results in death

8.1.1.1 Severity of COPD Exacerbations

All protocol defined COPD exacerbations need to fulfil the symptom criteria as defined in Section 8.1.1.

A COPD exacerbation will be considered **severe** if it results in at least 1 of the following:

- Hospitalization defined as inpatient admission for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility (depending on the country and healthcare system) for the COPD exacerbation
- Death related to COPD or COPD exacerbation

A COPD exacerbation that does not meet the requirements to be classified as severe will be considered **moderate** if it results in at least 1 of the following:

- Use of systemic corticosteroids and/or antibiotics for at least 3 days
- A single depot injectable dose of corticosteroids, which will be considered equivalent to at least 3-day course of systemic corticosteroids

8.1.1.2 Duration of COPD Exacerbations

For **moderate or severe** exacerbations, the duration is defined by the **prescribed treatment** or **duration of hospitalization**

- The start date will be defined as the start date of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital admission, which occurs earlier.
- The stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital discharge, which occurs later.
- A single depot injectable dose of corticosteroids will be considered equivalent to at least 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days.
- If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used.
- For a severe COPD exacerbation with no documented corticosteroid or antibiotics treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates.
- A new COPD exacerbation event must be preceded by at least 7 days between the last COPD exacerbation (refer to Section 8.1.1.1)

8.1.1.3 Approach for Capturing COPD Exacerbations

8.1.1.3.1 COPD Exacerbation eCRF

The investigator should record the COPD exacerbation that meets the COPD exacerbation definition (refer to Section 8.1.1) in the COPD exacerbation eCRF (COPDEX). Associated symptoms of COPD are considered as symptoms of disease under study and should not be recorded as AEs unless meet conditions listed in Section 8.3.7. The serious COPD exacerbation should be recorded in AE/SAE eCRF and in COPDEX. Other COPD related SAEs should be recorded on the AE/SAE eCRF.

8.1.1.3.2 Symptom Reporting

The subject will use the eDiary for daily symptom reporting, entering symptoms twice daily as detailed in Section 8.1.6.1.

If symptoms meet a specific threshold (i.e., 1 major COPD symptom and at least 1 other major or minor symptom for 2 consecutive days), the eDiary generates an alert to the subject and the investigational site. This alert should generate contact between the subject and the investigational site. The Investigator then makes the decision whether or not to initiate (or escalate, as appropriate) treatment for a COPD exacerbation. The Investigator site is responsible for documenting the action taken within 5 working days from the time the eDiary alert was triggered for every alert regardless who initiated contact (site or patient). Detailed instruction will be provided in separate guidance.

- **Major COPD symptoms**: dyspnea, sputum volume, and sputum color
- **Minor COPD symptoms**: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause

If COPD exacerbation is associated with ePRO worsening alert, symptoms should not be reported in the COPD exacerbation eCRF. If COPD exacerbation is not associated with ePRO worsening alert, please refer to section 8.1.1.4 for further guidance.

8.1.1.4 Investigator Justified COPD Exacerbations

If an event is not associated with ePRO symptom worsening alert as described above (e.g., technical issue, subject self-reports symptom worsening/exacerbation event, the exacerbation is identified during a visit or phone contact, the exacerbation is evaluated and treated at non-study centre, or an acute/severe symptom deterioration which is not captured in the ePRO system occurs), the Investigator should interview the subject and evaluate potential worsening and duration of the following symptoms:

- Shortness of breath
- Mucus Volume
- Mucus purulence

- Cough
- Wheezing
- Sore throat
- Cold symptoms such as a runny nose or nasal congestion
- Fever
- Chest Tightness
- Other findings

The Investigator should record all pertinent findings (symptom worsening) associated with the exacerbation event and their duration in source documents and in the COPD exacerbation eCRF.

If an exacerbation is not associated with worsening of COPD symptoms or it was not possible to capture the symptoms (e.g. patient intubated upon arrival to the emergency department), the Investigator must document the justification for diagnosing and treating the event as an exacerbation and record it in the eCRF.

8.1.1.5 COPD Exacerbation visit

COPD Exacerbation visit (EXA) may be initiated when patient experiences a COPD exacerbation. There is no visit window for the EXA visit. The subject should complete the assessments according to Table 2 if he/she experiences an exacerbation during the treatment and follow-up period. If the EXA visit was completed within +/- 5 days of a scheduled visit, the same laboratory assessments do not need to be repeated at the next scheduled visit, unless at the PI's discretion.

If a subject experience a COPD exacerbation at the time of a regular scheduled visit, the subject should complete the assessments from the scheduled visit. In case of additional assessments at EXA visit in comparison with the regular visit, subject will also need to complete those additional assessments from the EXA visit.

Only for sputum sub-study subjects

Performing COPD Exacerbation visit (EXA) for sputum sub-study patients is essential to evaluate exploratory sputum and nasal sub-study endpoints during treatment phase. Refer to Section 3.

Patients participating in sputum sub-study are required to perform pre-BD and sputum post-BD spirometry as part of sputum induction, at EXA visits during treatment. Induced sputum is preferred however spontaneous sputum is acceptable if patient cannot produce induced sputum or if the collection of induced sputum is not permitted per local Health and Safety

regulations or guidance during the COVID-19 pandemic. Please refer to applicable sub-study manual for more information.

Patient should withhold the COPD medications as instructed in Section 6.5.4. If withholding COPD medication is not feasible, the spirometry should be performed with a notation indicating under which conditions spirometry was conducted.

8.1.2 Spirometry

8.1.2.1 General Requirements

Lung function (FEV1 and FVC) will be measured by spirometry using equipment provided by a central vendor. The same equipment will be used for sputum induction. 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 site personnel who will be performing the testing are properly certified. Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual and in the monitoring plan. Patients who exhibit unexpectedly high variability of FEV1 will be evaluated by the investigator for etiology of variability, necessary follow-up actions, and assessment of continued patient eligibility. The investigator will discuss unexpectedly high variability with the AZ study physician.

- Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the site.
- Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the site.
- Subjects should not smoke/vape on the same day(s) prior to the lung function test is being performed.
- Subjects should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below:
  - SABA and SAMA should be withheld at least 6 hours prior to scheduled spirometry at site.
  - Twice daily LABA or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at site.
  - Once daily LABA or LAMA-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at site.

- LTRA should be restricted for at least 24 hours prior to scheduled spirometry at site.
- Twice daily theophylline should be withheld for at least 12 hours prior to scheduled spirometry at site.
- Once daily theophylline for at least 24 hours prior to scheduled spirometry at site.
- Twice daily triple inhaled (ICS/LABA/LAMA) medications should be withheld at least 12 hours prior to scheduled spirometry at site.
- Once daily triple inhaled (ICS/LABA/LAMA) medications should be withheld 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 (See section 6.5.5).

As part of the procedure for induced sputum pre-BD and post BD spirometry will be performed (see Section 8.8.5 and 8.1.2.3).

Applicable during COVID-19 pandemic

During screening, lung function assessments must be performed only when Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test or alternative test approved locally) result is available and negative (refer to footnote a and footnote l under Table 1, section 1.1 and to section 6.5.5.).

SARS-CoV-2 testing should be performed prior to lung function assessments at subsequent visits, if required per local regulations and guidance. If SARS-CoV-2 testing is conducted, a negative result must be obtained before conducting visit assessments.

Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the SoA. 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.

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.

Note: FeNO test should be performed prior to spirometry. Please refer to Section 8.1.3 for more details.

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 Review (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 et al 2012).

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

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

Order of administration for the COPD maintenance medication and IP relative to the scheduled pre- and post-bronchodilator spirograms

The subject's usual COPD morning maintenance therapy must not be given until spirograms are complete for the reasons discussed above. IP dosing should also be withheld until pre-bronchodilator/post bronchodilator/sputum post-BD spirometry is completed.

Record keeping

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

8.1.2.2 Post-BD Spirometry

Post-BD spirometry will be performed at Visit 2 or at postponed Visit 1 (when Visit 1 and Visit 2 are combined) (to evaluate inclusion criterion 5, see Section 5.1), Visit 3, Visit 9, Visits 16 (EOT) and IPD.

Endpoint maximal bronchodilation will be induced using albuterol (90µg metered dose) or salbutamol (100µg metered dose) with or without a spacer device up to a maximum of 4 inhalations administrated between 15 and 45 minutes of the final pre-BD spirometry measurement. SABA administration should start at least 15 minutes after final pre-BD spirometry and should end no later than 45 minutes after final pre-BD spirometry. Post-BD spirometry will be performed 15-30 minutes after last SABA inhalation. SABA administration can start earlier (less than 15 minutes of the final pre-BD spirometry) for safety reasons.

8.1.2.3 Sputum post-BD spirometry

Sputum post-BD spirometry should be performed per schedule in Table 2 (Visit 3, Visit 16, IPD and EXA) as part of induced sputum procedures if subject is participating in the sputum sub-study, after post-BD spirometry (where applicable, refer to Section 8.1.2.2). It is conducted solely to ensure patient safety in inducing sputum and results will neither be captured for the eCRF, nor for study endpoints. More details will be provided in applicable sputum sub-study manual.

8.1.3 FeNO

Airway inflammation will be evaluated using a standardized single-breath FeNO test in accordance with the SoA. A single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017). Detailed procedure for performing FeNO will be described in a separate instruction manual.

The FeNO test will be performed prior to spirometry.

Restrictions on the day of scheduled FeNO assessment:

- The FeNO measurements should not be performed within 2 weeks of a respiratory infection.
- Subjects should not eat or drink 1 hour prior to having the FeNO test.
- Subjects should not use their rescue SABA and/or SAMA medication within 6 hours of the measurement.
- Inhaled BDs should be withheld for the effect duration specific to the BD as described in Section 6.5.5.

The assessment should be postponed till after the required time has passed since last dose of BD or meal/drink. However, if not possible the visit must be rescheduled within the allowed visit window.

The NIOX VERO® Airway Inflammation Monitor will be used to measured FeNO. Instructions for use of this monitor will be provided in a separate user's manual.

NIOX VERO® sensors will be replaced as recommended by the manufacturer. The vendor supplying the equipment will be responsible for ensuring that the equipment and procedures for the measurement of FeNO are validated prior to the start of the study.

All post-randomization FeNO assessments should be performed within ± 1.5 hours of the time that the randomization FeNO was performed.

Two acceptable FeNO measurements will be performed to establish repeatability; up to 8 measurements can be performed. After FeNO repeatability is met, it will not be possible to perform any further FeNO measurements at that visit.

The sponsor will be unblinded to the FeNO values prior to randomization (Visit 2 and any repeat testing that is performed during screening, and prior to IP administration) and blinded to the subsequent FeNO values post randomization. Sites will be blinded to the FeNO values for the whole study duration.

8.1.4 COPDCompEx

COPDCompEx is a composite endpoint for exacerbations (moderate or severe) in COPD. COPDCompEx combines exacerbations with events defined from patient daily diaries. The definitions for both types of exacerbation are as follows:

- **Exacerbations:** episodes leading to one or more of the following: hospitalization, emergency room visit, treatment with systemic corticosteroids, or treatment with antibiotics.
- **Diary events**: defined by threshold and slope criteria using the following diary variables: individual domains of the breathlessness, cough, sputum scale, sleep, chest tightness and rescue medication use.

The analysis of this endpoint will primarily be time to first COPDCompEx event, but the events may also be analysed with models addressing event rates or time to recurrent event. More details on the derivation and analysis of this variable will be given in the Statistical Analysis Plan (SAP).

8.1.5 Clinically Important Deterioration (CID)

CID is a composite endpoint measuring worsening of the key clinical features of COPD, namely lung function, patient-reported outcomes and exacerbations. CID is defined as 1) a decrease of ≥100 mL from baseline in trough FEV1, 2) a deterioration in health-related quality of life defined as ≥4-unit increase from baseline in SGRQ total score, 3) the occurrence of an on-treatment moderate-to-severe COPD exacerbation (defined as an acute worsening of COPD symptoms requiring the use of additional treatment including oral corticosteroids, antibiotics, emergency department treatment, or hospitalization).

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 this device and detailed procedures for using the device will be described in a separate instruction manual. Subjects

will be trained on at home use of the eDiary at Visit 2 or Visit 1 (if Visit 1 and Visit 2 are combined). The site staff will set assessment reminder alarms on the device. Training will emphasize the importance of completing the PRO assessments as scheduled to capture the subject's experience and meet the objectives of the study.

Subjects will complete assessments twice daily and at other timepoints specified in the SoA.

The Investigator/authorized delegate will check subject'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 on the ePRO Study Works portal will be completed by the Investigator between visits to ensure sufficient data is available to meet inclusion criteria 16 and 17 at randomization (Visit 3).

8.1.6.1 Major/Minor Symptom Worsening Assessment and Alert System

Symptoms will be assessed each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the site of a potential symptom worsening event that warrants contact between the subject and Investigator/authorized delegate for further evaluation.

Each morning the subject will complete 3 questions pertaining to the major symptoms of a worsening event (dyspnea, sputum volume, and sputum color). Subject reported worsening of 1 or more of these symptoms will trigger assessment of the minor symptoms of a worsening event (sore throat, cold, fever without other cause, cough, and wheeze). All questions will have a 24-hour recall period. Questions pertaining to the severity of symptoms vs. their usual state will have 3 response options (e.g., How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, more breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g., Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

An alert will be triggered if two or more major symptoms (dyspnea, sputum volume, and sputum color) worsen for two consecutive days or if one major symptom and one minor symptom (e.g., sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least two consecutive days. When either of these criteria is met the subject will be alerted via the ePRO device to contact the site as soon as possible for further evaluation. Likewise, the site will be alerted to contact the subject within approximately 24-72 hours if he or she has not yet contacted the site for further evaluation.

8.1.6.2 Rescue Medication

Rescue medication usage including reliever inhaler and nebulizer use will be captured twice daily. Inhaler usage will be reported as the number of puffs, (i.e., the sum of different relievers, if applicable) in a given period whereas nebulizer use will be reported as the number

of times. Rescue medication usage at night will be assessed in the morning and rescue medication used during the day will be assessed in the evening.

8.1.6.3 Nocturnal Awakenings

Subjects will be asked to report the occurrence of nocturnal awakenings due to COPD symptoms each morning using the ePRO device. A single question with yes/no response options will be used.

8.1.6.4 Maintenance Medication

Maintenance medication adherence will be assessed each evening. The subject will be asked if they took their regularly scheduled inhaler and instructed not to consider instances of rescue inhaler usage when answering this question.

8.1.6.5 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients 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 patients, a decrease 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 using eDiary in accordance with the SoA. If the subject is not able to visit the site, SGRQ may be completed by the subject at home/alternative location . Refer to **Appendix I for details.**

8.1.6.6 COPD Assessment Test (CAT)

The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. The CAT will be measured at Visits 1, 3, 6, 9, 12, IPD and 16/EOT. If

the subject is not able to visit the site, CAT may be completed by the subject at home/alternative location. Refer to Appendix I for details.

8.1.6.7 Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) and Evaluating Respiratory Symptoms in COPD (E-RS™: COPD)

The EXACT-PRO is a 14-item PRO instrument developed to assess the frequency, severity, and duration of COPD exacerbations (Jones et al 2011, Leidy et al 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences "today". The daily EXACT-PRO total score has a range of 0-100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT-PRO defined exacerbation event. In identifying event onset and recovery, the EXACT-PRO can provide information on event frequency and duration as well as event severity.

The E-RS™: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD (Sexton et al 2010, Sexton et al 2011). The E-RS™: COPD is a subset of items from the EXACT-PRO. The E-RS™: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS™: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

8.2 Safety Assessments

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

8.2.1 Clinical Safety Laboratory Assessments

See Table 7 for the list of clinical safety laboratory tests to be performed, and the SoA for the timing and frequency. All protocol-required laboratory assessments as defined in the SoA, must be conducted in accordance with the laboratory manual.

During the COVID-19 pandemic, it may not be possible to collect clinical safety laboratory tests at the site due to local restrictions. If the subject has re-consented to home/alternative location IP administration visits, it is possible that the HCP can collect clinical safety laboratory tests in the subject's home/alternative location. Please refer to Appendix I.

The Investigator should assess the available results regarding 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 8.3.7.

The safety samples (clinical chemistry, hematology and urinalysis) will be performed at a central laboratory. If central laboratory kits are not available, the safety samples can be collected and analysed at the local laboratory at the discretion of the PI. However, all laboratory assessments for Visit 1, Visit 3 and EoT or IPD Visit (as per SoA) must be analysed at the central laboratory.

Maintaining the blind to the patient's blood immunoglobulin, eosinophil, basophil and monocyte counts

The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (Visit 1 and 2), any repeat testing that is performed during the screening, and prior to 1st IP administration.

If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. 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 immunoglobulin, 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 such cases.

Site staff who are directly involved in the patient's management should remain blinded to any blood immunoglobulin, eosinophil, basophil and monocyte counts results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (e.g. administrator or another ancillary person) not directly involved in patient management, to receive and blind any immunoglobulin, eosinophil, basophil and monocyte counts results prior to the report being handed over to the site staff involved in the patient's management and prior to filing the laboratory report as a source document. Similarly, immunoglobulin, eosinophil, basophil and monocyte counts results must be redacted from all communications with the sponsor.

Table 7 - Laboratory Safety Variables

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

*Urinalysis (Dipstick) central laboratory report will contain results from variables as listed in the laboratory manual, however only for variables U-Hb/Erythrocytes/Blood, U-Protein/Albumin and U-Glucose requires confirmation in laboratory eCRF module if the result is clinically significant. If there are any clinically significant results from other variables, it will be the investigator decision to document them in the eCRF as an AE.

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

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

8.2.1.1 Pregnancy Test

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

– Serum ß-human chorionic gonadotropin (ß-HCG) – the test done at enrolment (Visit 1) only, for WOCBP (analyzed at central laboratory).

– FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrhoeic for >12 months. Until FSH is documented to be within menopausal range, treat the subject as WoCBP.

– Urine HCG – the test will be performed at the study site for WOCBP at each treatment visit before IP administration using a dipstick. Positive urine test result must be confirmed with serum β-HCG.

8.2.2 Smoking Status

Smoking status will be assessed at every visit starting from enrolment (Visit 1) until the end of the last Follow Up Visit (Week 64) by collecting the subject's response to a single yes/no question from study personnel: 'What is your smoking status as of today, do you currently smoke? Smoking status changes during Visit 3 to the end of the last Follow Up Visit (Week 64) will be captured on the eCRF but the subject will be permitted to continue in the study.

8.2.3 Weight and Height

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

8.2.4 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 8.3.7 for details.

8.2.5 Vital Signs

Vital signs (body temperature, pulse, blood pressure and respiration rate) will be obtained in accordance with the schedule provided in Table 1 and Table 2.

Body temperature will be measured before IP administration in accordance with local standards.

Body temperature should be done as the first study assessment (at Visit 1 when ICF is obtained).

- Subject with fever (≥ 38°C; ≥ 100.4°F) suspected due to COVID-19 infection during screening or at randomization should be screen failed (Exclusion criterion 38).
- IP should not be administered if the subject is febrile (≥ 38°C; ≥ 100.4°F) or is suspected of having COVID-19. Refer to section 6.1.2.

The pulse rate and blood pressure should be measured after the subject has been resting for at least 5 minutes. The measurement will be taken in a sitting position.

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

8.2.6 ECG

ECG will be performed in accordance with the schedule provided in Table 1 and Table 2. The equipment will be provided by a central vendor.

A 12-lead digital electrocardiogram (dECG) will be taken in the supine position, after the subject has been resting for at least 5 minutes. The assessment should be performed before interventions with the subject (e.g., spirometry and administration of the COPD related medications and IP).

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 subject's participation in the study.

ECG evaluation will be recorded in the eCRF.

8.2.7 Supplemental Oxygen (O_2)

Oxygen use will be assessed according to the schedule in Table 1 and Table 2. Use of LTOT should be recorded as a concomitant medication in the eCRF.

8.2.8 Oxygen Saturation (SpO_2)

Pulse oximetry will be used to measure the subject's oxygen saturation according to the schedule in Table 1 and Table 2.

8.2.9 Chest X-ray

A chest X-ray done during the screening period before first IP administration is required to ensure there are no abnormal radiological findings as per exclusion criterion 14 and exclusion criterion 40.

Under special circumstances, recently done historical chest X-ray (anterior-posterior)/CT/MRI for other reasons (not study related) might be acceptable. The outcome of the X-ray/CT/MRI must be documented in the patients' medical records. Study Physician approval of historical X-ray must be obtained prior to randomization.

8.2.10 Vaccination Restrictions

Pneumococcal and Annual Influenza Vaccination

Subjects should have a pneumococcal vaccination if they have not had one before, unless contraindicated. In the event that they have previously received a vaccination, the Investigator must ensure that the subject does not require a booster (generally after 5-6 years according to current guidelines, e.g., CDC 2010). If a booster is required, it should be given at Visit 1, or at any time prior to randomization. Subjects should receive an annual influenza vaccination in the autumn or winter period unless the subject has received it prior to study start (refer to current CDC guidelines e.g., CDC 2021-2022). If the subject has previously received the influenza vaccination within the last 12 months prior to study start, the vaccination should be given at the next autumn or winter period. If a subject has an egg intolerance, the vaccination may be omitted. If the PI decides to not vaccinate with either vaccine, the rationale should be clearly specified.

See exclusion criteria 25 for subjects participating in the sub-study.

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 vaccine administration. For vaccines that are currently approved under emergency use authorization (EUA), please refer to relevant health authority websites for

further guidance. Any live attenuated vaccine is prohibited during study conduct (see Table 6).

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 provided in Table 8 should be followed depending on the study phase.

Table 8 - COVID-19 Vaccination Guidance

Study Period	Vaccine usage
Patient in screening/run-in period	If Covid-19 vaccination is in the best interest of the patient and the patient 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 study physician for the most current recommended time interval prior to any vaccine dose. See exclusion criteria 41.
Patient in treatment period	If Covid-19 vaccination is in the best interest of the patient and the patient 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 patient receives COVID 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 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 subject receives a COVID vaccine dose. However, even if IP is not administered at a study visit because of

Table 8 - COVID-19 Vaccination Guidance

Study Period	Vaccine usage
	COVID-19 vaccination restrictions, other site visit assessments should be still be performed according to the SoA. At every study visit during the treatment period, the investigator must ask if the patient 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 patient will miss two consecutive IP administrations, the AstraZeneca study physician should be contacted to discuss further patient 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.
Patient in follow-up period	If COVID vaccination is in the best interest of the patient, COVID-19 vaccination could be administered. Patient should follow schedule of assessments; no special adjustments are needed. It is advised that subject wait for 14 days after the last IP dose.

The suggested IP dosing/COVID-19 intervals is summarized in Figure 3.

Figure 3 - COVID-19 Vaccination between IP Dosing

Reporting of COVID-19 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 patient 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 of the CSP.

8.2.11 Other Safety Assessments

8.2.11.1 Serology

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

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

8.2.11.2 SARS-CoV-2 testing

The following test is applicable only for new subjects enrolled into the study:

- SARS-CoV-2 naso/oropharyngeal swab test, rapid test or alternative test (approved by local health authorities) – done at enrolment (Visit 1) only.

The following test is applicable for new subjects enrolled into the study and for remaining ongoing active subjects:

- SARS-CoV-2 serology test – for newly enrolled subjects done at first IP administration visit. For remaining ongoing active subjects, the test should be done as soon as possible, but preferably at next on-site visit.

SARS-CoV-2 nasopharyngeal swab test and SARS-CoV-2 serology will be analysed at central laboratory. Instructions for sample collection, processing, storage, and shipment will be included in a separate laboratory manual provided to the sites. SARS-CoV-2 serology data will be used to assess individual cases but will not be used for subgroup analyses (e.g. serology positive/negative).

In case of long turnaround time of the nasopharyngeal swab test results from central laboratory, the site has the following alternatives:

- Perform naso/oropharyngeal swab test through local lab
- Perform a rapid antigen test or alternative tests at the site, provided it is approved by local health authorities

SARS-CoV-2 testing should be performed prior to lung function assessments and sputum sub-study assessments at subsequent visits, if required per local regulations and guidance.

8.3 Collection of Adverse Events

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

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

The definitions of device constituent-related safety events can be found in Appendix J. Device constituent deficiencies are covered in section 8.3.10.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative). The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.3.3.

8.3.1 Method of Detecting AEs and SAEs

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

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events and Serious Adverse Events will be collected from the time of informed consent and throughout the duration of the study. This includes subjects who discontinue treatment and is followed up according to the options described in Section 7.1.1.

SAEs will be recorded from the time of signing of ICF throughout the duration of the study.

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

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

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

8.3.3 Follow-up of AEs and SAEs

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

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

8.3.4 Adverse Event Data Collection

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the IP(s) (yes or no)
- Action taken with regard to IP(s)
- Select the appropriate as required: AE caused subject's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason of AE being considered serious
- 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(s)

8.3.5 Causality Collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

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

8.3.6 Adverse Events Based on Signs and Symptoms

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

8.3.7 Adverse Events Based on Examinations and Tests

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

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., 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.

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. COPD 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 patient discontinues IP due to the sign or symptom.
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing COPD history (defined as within 1 year of Visit 1) as judged by the Investigator.

Worsening of COPD should be recorded as an AE or SAE only if it fulfils any of the above criteria.

8.3.7.1 Adverse Events of Pneumonia Requiring a Confirmed Diagnosis

Events of suspected pneumonia should be confirmed by the presence of a new infiltrate on x-ray within approximately 48 hours, as well as at least 2 of the following signs and symptoms: increased cough, increased sputum purulence or production, consistent auscultatory findings, dyspnea or tachypnea, fever, leukocytosis, or hypoxemia.

Events of confirmed diagnoses of pneumonia must be recorded as the AE "Pneumonia (confirmed)". The severe infection pages in eCRFs must 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 (refer to section 8.3.8).

8.3.8 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 infection' 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.

8.3.9 Hy's Law

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

8.3.10 Medical Device Deficiencies

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

The definition of a Medical Device deficiency or deficiency in the device constituent of a combination product is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

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

The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be used to collect the deficiency.

8.3.10.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.

- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Appendix J.

8.3.10.2 Follow-up of Medical Device Deficiencies

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

8.3.10.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Only deficiencies associated with the device constituent part of the tezepelumab combination product should be reported to the sponsor.
- Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be sent to AstraZeneca by email.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.4.1.
- The sponsor will be the contact for the receipt of medical device deficiency reports.

8.3.10.4 Regulatory Reporting Requirements for Device Deficiencies

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

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

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

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative(s).

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

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

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

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study subject has received any study drug. If a pregnancy is reported, the Investigator should inform the sponsor within 24 hours of learning of the pregnancy. Any cases of pregnancy during the study period or follow up will be recorded in the specific eCRF module.

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

8.4.2.1 Maternal Exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal Exposure

Pregnancy of the subject's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital 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.

8.4.3 Overdose

A dose in excess of tezepelumab 700 mg SC administered within a 2-week period is considered an overdose.

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

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication Error, Drug Abuse and Drug Misuse

8.4.4.1 Timelines

If an event of medication error, drug abuse or drug misuse occurs in the course of 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 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.4.1) and **within 30 days** for all other medication errors.

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

8.4.4.3 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 8

8.4.4.4 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 8

8.4.5 Management of IP-related Toxicities

Appropriate drugs, such as epinephrine, 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 G.

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.

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 3 and 4, subjects 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, subjects 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 subject as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase. The sample will be tested at the local lab or central lab where applicable.

8.4.6 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is an independent expert advisory group commissioned and charged with the responsibility of assessing all SAEs (including deaths and all hospitalizations), non-serious AEs and cardiovascular events. The IDMC will

evaluate cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. The IDMC will function independently of all other individuals associated with the conduct of the studies, including the study sponsor, AstraZeneca. The committee will operate in accordance with an IDMC Charter.

The IDMC will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the IDMC.

8.4.7 Independent Adjudication Committee

An IAC will assess blinded data to confirm the diagnosis and causality of MACE (defined in the IAC charter), serious cardiac events, and deaths, as well as diagnosis of malignancies that occur from randomisation until the end of the follow-up period.

The IAC will 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 COPD.

Details on the adjudication process, including scope of adjudication and the committee membership, will be included in the Adjudication Committee Charter/Manual of Operations.

8.5 Pharmacokinetics

8.5.1 Collection of Samples to Measure Drug Concentration

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

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

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

Samples from patients who receive placebo will not be measured initially but will be retained for subsequent analysis if deemed appropriate

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

8.5.2 Collection of Samples to Measure for the Presence of ADAs

The presence of ADA will be assessed in serum samples according to the SoA (Table 2).

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

8.5.3 Storage and Destruction of Pharmacokinetic/Immunogenicity Samples

The PK and immunogenicity samples will be retained for future use at AstraZeneca or designee for a maximum of 15 years following Last Subject's Last Visit.

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

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated using biomarkers (see Section 8.8).

8.7 Genetics

8.7.1 Optional Exploratory Genetic Sample

Whole blood will be collected from adult subjects that have been randomized into the study for extraction of DNA and genetic analyses including but not limited to genetic polymorphisms, epigenetic modifications and the microbiome associated with COPD, TSLP or response to tezepelumab.

Approximately 6 mL blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study as per Table 2 in the SoA.

The collection of blood for a DNA sample for genetic research is optional. Should a subject not wish to provide a sample for this research, he/she will still be allowed to participate in the main study.

The blood sample for genetic research should be obtained from the subjects at Visit 3, as outlined in the SoA.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual. The results of any analyses of these samples will not be reported in the CSR itself but as an addendum, or separately in a scientific report or publication.

Please refer to Appendix D for further details.

8.7.2 Storage and Destruction of Genetic Samples

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

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

8.8 Biomarkers

Serum and plasma samples will be collected according to the schedule in Table 2 in the SoA to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to COPD, inflammation and the TSLP pathway. Baseline and early post-dose levels of serum and plasma biomarkers may also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analyzed are cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway. The results of exploratory biomarker analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

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

8.8.1 Storage, Re-use and Destruction of Biomarker Samples

All biomarker samples described in Section 8.8 (for example blood, sputum, nasal, and urine samples) will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research. Any residual biological samples may be retained for up to 15 years and used for the purpose of investigating COPD, the pharmacology of tezepelumab, predictors of response, or assay development. If a subject does not allow samples to be used for future biomarker research

(e.g., scientific health-related research), they may continue with their samples being used for the main study. The results of any future analyses will not be reported in the CSR itself but as an addendum, or separately in a scientific report or publication

8.8.2 Total Serum Immunoglobulin

The levels of total serum IgE, IgA, IgG and IgM will be tested by a central laboratory in accordance with the SoA. The results of the total serum immunoglobulin data will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. Instructions for sample collection, processing, storage and shipment will be provided in a separate laboratory manual. The sponsor and site will be blinded to the values except screening visits (Visit 1 and 2), any repeat testing that is performed during the screen visits, and prior to IP administration.

8.8.3 Transcriptomics

Whole blood samples will be collected in PAXgene® tubes for ribonucleic acid (RNA) sample preparation in accordance with Table 2 in the SoA. RNA may be used in the analyses of host gene expression and microbiome research using quantitative methods that may include but not be limited to RNA microarrays, RNA-Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses. The results of this transcriptomic research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. Instruction for sample collection, processing, storage and shipment will be provided in a separate laboratory manual.

8.8.4 Nasal Epithelial Cell and Sputum Cell Transcriptomics

Nasal epithelial cell transcriptomic samples and/or sputum cell transcriptomic samples will be obtained, in accordance with the schedule provided in Table 2 in the SoA, in a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before sputum collection. If the subject is not able to produce sputum (spontaneous or induced) at Visit 3, then the subject should be withdrawn from the sub-study only and nasal samples should be discarded. Please note that the subject can continue in the main study.

Nasal epithelial and/or sputum cell RNA may be used in the analyses of host gene expression research using quantitative methods that may include but not be limited to RNA microarrays, RNA-Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses.

The results of this transcriptomic research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. Detailed procedures for

obtaining, processing, storing, transporting and analysing the samples will be described in applicable manual.

8.8.5 Sputum Induction

The aim of sputum induction is to obtain satisfactory samples of sputum originating from the lower airways. Sputum induction will be performed in accordance with the schedule provided in Table 2 in a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before collection of spontaneous or induced sputum. Attempts will be made to perform sputum induction as close to the baseline assessment time at each of the scheduled visits. If the subject is not able to produce sputum (spontaneous or induced) at Visit 3, then the subject should be withdrawn from the sub-study and nasal samples should be discarded. Please note that the subject can continue in the main study. For other sub-study visits, sputum sub-study samples will be collected if sub-study laboratory kits and supplies are available within visit window. In the event of missing supplies, sites should make reasonable effort to collect and process samples where feasible, and with the approval of Study Physician. During the COVID-19 pandemic, sputum samples will only be collected if allowed per local Health and Safety regulations or guidance and if sub-study laboratory test kits are available.

Sputum induction is conducted by inhalation of nebulised sterile saline solution followed by coughing and expectoration of airway secretions. Since saline inhalations may cause bronchoconstriction lung function will be monitored during the process. Detailed procedure for performing induced sputum will be described in applicable instruction manual.

If spontaneous sputum is produced immediately prior to beginning the induced sputum procedure, it may be used as a secondary option for outcome measures if an adequate volume of induced sputum is not acquired or induced sputum is not permitted per local regulations or guidance during COVID-19 pandemic.

Sputum biomarkers may be measured to evaluate the pharmacology of tezepelumab, microbiome and to evaluate changes in biomarkers related to COPD, inflammation and the TSLP pathway. Baseline levels of sputum biomarkers will also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analyzed may include but are not limited to cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway. Drug concentrations may also be measured in the sputum samples, if feasible. If appropriate, urea concentrations may be measured to correct for the dilution factor of the sputum samples. The results of these exploratory analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

The sputum will be induced and processed locally at the clinical sites according to the methods and processes detailed in the applicable sputum induction and processing manual. Depending on individual site capability, sputum processing will follow one of two sputum processing protocols (full processing or partial processing). Sputum sample processing will result in the production of cytospin slides (for full sputum processing only), microbiome sample, cell pellets for RNA transcriptome, and aliquots of sputum supernatant. The clinical sites performing full sputum processing procedures will also generate and record total cell count and cell viability data on their sputum processing worksheets. The microbiome sample, cytospin slides, cell pellet for RNA transcriptome and the sputum supernatants will be analyzed by a different central laboratory.

Additional local or national regulations or guidance must be followed for sputum processing during COVID-19 pandemic.

The sputum microbiome, cytospin slides, cell pellets and the sputum supernatants will be retained at AstraZeneca or designee for a maximum of 15 years following the Last Patient's Last Visit. The results of this biomarker research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

8.8.6 Nasal Lining Fluid

The nasal lining fluid procedure is a quick and simple technique for sampling nasal secretions. Nasal lining fluid samples will be obtained in accordance with the schedule provided in Table 2 in a subset of subjects only participating in the sub-study, and if nasal lining fluid sampling supplies are available. If sputum and nasal collections occur at the same visit, nasal sampling should occur before spontaneous/sputum induction. Nasal lining fluid biomarkers will be measured to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to COPD, inflammation and the TSLP pathway. Baseline and early post-dose levels of nasal lining fluid biomarkers may also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analyzed include but are not limited to cytokines, chemokines and inflammatory mediators associated with COPD and the TSLP pathway. Drug concentrations may also be measured in the nasal lining fluid samples, if feasible. If appropriate, urea concentrations may be measured to correct for the dilution factor of the nasal lining fluid samples. The results of these exploratory analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. Detailed procedures for obtaining, processing, storing, transporting and analysing the samples will be described in applicable manual. During the COVID-19 pandemic, nasal samples will only be collected if allowed per local Health and Safety regulations or guidance if sub-study laboratory test kits are available.

The nasal lining fluid samples will be retained at AstraZeneca or designee for a maximum of

15 years following the Last Patient's Last Visit. The results of this biomarker research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication.

8.8.7 Urine Biomarkers

Urine will be collected in accordance to the schedule provided in Table 2. Urine analysis may include but is not limited to biomarkers of inflammation associated with COPD and TSLP pathway. The results of these exploratory analyses will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. The urine samples will be retained by AstraZeneca or a designee for a maximum of 15 years following Last Patient Last Visit.

8.9 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 subjects 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 CSR.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

The null hypothesis is that the exacerbation rate on tezepelumab is greater than or equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on tezepelumab is less than the exacerbation rate on placebo, i.e.,

$$H_0: \text{Rate ratio (tezepelumab vs Placebo)} \geq 1$$
$$H_a: \text{Rate ratio (tezepelumab vs Placebo)} < 1.$$

9.2 Sample Size Determination

Original Sample Size

For the primary endpoint of reduction in COPD exacerbation rate, 141 subjects per treatment arm (282 total) will be randomized to achieve 80% power of detecting a 30% reduction in tezepelumab versus placebo over a fixed time period of 52 weeks. This calculation has assumed a one-sided 5% alpha level test, an annual placebo rate of 1.6 events/subject/52

weeks, a negative binomial shape parameter of 0.6, and 10% uniform drop out.

In the absence of the interim analysis for futility, this design would provide 81.2% power, and only 136 subjects per treatment arm would be required for 80% power.

This power statement accounts for the power loss associated with the futility interim analysis that was originally planned to occur when 182 subjects had been randomized. In simulated results, 1.2% of simulated trials were stopped early for futility but would have been successful at the final analysis of the primary endpoint had they been allowed to continue. Therefore, the overall power for this trial accounting for the interim analysis is 80%. Note that as a result of the pause in recruitment due to COVID-19, the futility analysis is now planned to occur when approximately 30% of follow-up data are available but the expected power loss will be comparable under these conditions.

The primary endpoint will also be tested using a one-sided 2.5% alpha level test, but the sample size has not been determined based on providing power for this test.

Updated Sample Size

The sample size has been reassessed due to the potential for reduced exacerbation rates due to limited person-to-person contact and exposure to respiratory infections during the COVID-19 pandemic. Assuming the same treatment effect (0.7) and dispersion parameter (0.6) as originally assumed, a sample size of 169 subjects per treatment arm (338 overall) will maintain the study power if the placebo exacerbation rate is as low as 1.2 exacerbations/subject-year.

9.2.1 Estimands

The **Primary estimand** is described as follows**:**

- Population - subjects with moderate to very severe COPD who are randomised and receive at least one dose of IP
- Variable - annual rate of moderate or severe COPD exacerbations up to Week 52
- Population-level summary measure – exacerbation rate ratio of tezepelumab versus placebo
- Handling of intercurrent events:
    - Treatment discontinuation: All available data are used regardless of whether treatment discontinuation occurs.

- Use of an alternative biologic: All available data are used regardless of whether subject switches to an alternative biologic therapy.

The **Supplemental estimand** is described as follows**:**

- Population - subjects with moderate to very severe COPD who are randomised and receive at least one dose of IP
- Variable - annual rate of moderate or severe COPD exacerbations up to Week 52
- Population-level summary measure – exacerbation rate ratio of tezepelumab versus placebo
- Handling of intercurrent events:
    - Treatment discontinuation: All available data are used up until randomised treatment is discontinued.
    - Use of an alternative biologic: All available data are used up until subject switches to an alternative biologic therapy.

A different approach may be considered depending on the number and pattern of drop-outs. Further detail will be provided in the SAP.

Secondary estimands and estimands to explore the impact of the COVID-19 pandemic may be detailed in the SAP.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Analysis Set Description
All subjects analysis set	This analysis set comprises all enrolled subjects who signed the informed consent form, including screening failures, and will be used for the reporting of disposition.
Randomized subjects analysis set	This analysis set comprises all subjects randomized to study treatment, irrespective of whether IP was subsequently taken, and will also be used for the reporting of disposition.
Full analysis set (FAS)	This analysis set comprises all subjects randomized to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.

	Efficacy analyses will be performed using all subjects in the FAS. Subjects will be analyzed according to their randomized treatment (including in the case of any discrepancies between randomized and actual treatment at one or more visits).
PK analysis set	All subjects who received at least one dose of tezepelumab and have at least one detectable serum concentration post first dose that is not affected by factors such as protocol deviations (e.g., disallowed medication or incorrect study medication received).
Safety analysis set	This analysis set comprises all subjects who received at least one dose of IP. Safety analyses will be performed using all subjects in the safety analysis set. Subjects will be analyzed according to their actual treatment in the case of any discrepancies between randomized and actual treatment. Specifically, a subject randomized to placebo who has on one or more occasion actually received active (tezepelumab) treatment will be assigned to the tezepelumab group. A subject who has on no occasion actually received any active (tezepelumab) treatment will be assigned to the placebo group.

9.4 Outcome Measures for Analyses

9.4.1 Definition of Baseline and Subject Baseline Analyses

In general, the last measurement on or prior to the date of randomization will serve as the baseline measurement. If there is no value on or prior to the date of randomization, then the baseline value will not be imputed and will be set to missing. The baseline for outcome variables based on efficacy biomarkers is defined as the value recorded at randomization; if a measurement is not scheduled to be measured at randomization visit or if the randomization visit measurement is missing, the last non-missing value before randomization will be used as baseline instead.

For spirometry, laboratory data and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose.

Absolute change from baseline is computed as

(post-randomization value –baseline value).

Percent change from baseline is computed as

100 x ((post-randomization value – baseline value) / baseline value) %.

If either the post-randomization value or the baseline value is missing, then the absolute or percent change from baseline value will also be set to missing.

9.4.2 Calculation or Derivation of Efficacy Variables

9.4.2.1 Exacerbation Rate

The annual COPD exacerbation rate will be used as the primary efficacy variable.

A COPD exacerbation is defined in Section 8.1.1.

In order to calculate the number of exacerbations experienced by a subject during the treatment period, the following rule will be applied:

The start of an exacerbation is defined as the start date of systemic corticosteroids or antibiotic treatment or hospital admission, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital discharge, whichever occurs later.

Additional systemic corticosteroid treatments, emergency room visits requiring use of systemic corticosteroids, or inpatient hospitalization due to COPD occurring during an exacerbation should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

The follow-up time for exacerbations for a subject is approximately 52 weeks; defined as the time from randomization to the date of Visit 16, regardless of whether subjects remain on randomized treatment. For a subject lost to follow-up or prematurely withdrawing from the study prior to Visit 16, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

The number of days that the subject experiences an exacerbation during the follow-up time, including the subsequent 7 days (when a further exacerbation would not be considered a separate event (and if within the follow-up time) will be subtracted from the follow-up time to give the time at risk of exacerbation.

In the statistical analysis, the number of COPD exacerbations experienced by a subject during their follow-up time will be used as response variable, and the logarithm of the subject's corresponding time at risk will be used as an offset in the analysis to adjust for subjects having different observation times during which the events occur.

For the production of summary statistics, the annual exacerbation rate per subject is calculated, and standardized per 52-week period according to the formula described below.

*Annual exacerbation rate=Number of exacerbations*365.25 / (Time at Risk of Exacerbation).*

For subjects who prematurely discontinue treatment, efforts will be made to continue collecting the exacerbation data until the scheduled Visit 16/EOT at Week 52 after randomization. In the statistical analysis of exacerbation rate for the primary estimand, the data collected up to Visit 16/EOT will be included for the patients who prematurely discontinue treatment according to the intent-to-treat principle. For the patients who died during the treatment period the exacerbation data collected up to the date of death will be included in the statistical analysis.

If the cause of any death is related to COPD or a COPD exacerbation, the event will also be included in the rate calculation as a severe exacerbation.

To examine the sensitivity of results of the primary analysis to the underlying assumptions, sensitivity analyses may be performed using different assumptions for missing data following study withdrawal. Further details will be given in the SAP.

The annual rate of moderate or severe COPD exacerbations, excluding those moderate exacerbations treated only with antibiotics, will be used as a supportive endpoint for the primary endpoint. This supportive endpoint includes all severe COPD exacerbations and moderate COPD exacerbations treated by OCS with or without antibiotics.

9.4.2.2 Proportion of Subjects with ≥ 1 COPD Exacerbation

The proportion of subjects with ≥ 1 COPD exacerbation will be a secondary efficacy variable.

9.4.2.3 Time to First Exacerbation

Time from randomization to the first COPD exacerbation will be a secondary efficacy variable, and is calculated as follows:

Start Date of first COPD exacerbation – Date of randomization + 1.

The time to first COPD exacerbation for subjects who do not experience a COPD exacerbation will be censored at the time point after which an exacerbation could not be assessed. For subjects lost to follow-up or prematurely withdrawing from the study, the time to first COPD exacerbation will be censored at the end of the maximum follow-up time, as described in Section 9.4.2.1.

9.4.2.4 Annual Rate of Severe COPD Exacerbations

The annual rate of severe COPD exacerbations will be a secondary efficacy variable. If the cause of any death is related to COPD or a COPD exacerbation, the event will also be included.

In the statistical analysis, the number of severe COPD exacerbations will be used as response variable, and the logarithm of the subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different observation times during which the events occur.

Follow-up time is derived as described in Section 9.4.2.1.

Time to first severe COPD exacerbation and proportion of subjects with at least one severe COPD exacerbation will be used as supportive variables to this secondary efficacy variable.

9.4.2.5 Forced Expiratory Volume in 1 Second

The change in FEV_1 from baseline to each of the post-randomization visits up to and including the Week 52 visit (Visit 16) will be assessed with change from baseline at week 52 used as the secondary efficacy variable. The last pre-bronchodilator measurement recorded prior to the first dose of IP will be used as baseline FEV_1.

9.4.3 Calculation or Derivation of Safety Variables

9.4.3.1 Safety Variables

The following safety data will be collected: vital signs, physical examination, 12-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline (last measurement prior to first IP administration) to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarized by means of descriptive statistics and qualitative summaries.

9.4.3.2 Adverse Events

Adverse events experienced by the subjects will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data will be categorized according to their onset date into the following study periods:

- AEs occurring during screening (onset date ≥ Visit 1 and before the first dose of study treatment)
- AEs occurring during treatment (onset date ≥ the first day of study treatment and ≤ the last day of study treatment + 4 weeks)
- AEs occurring during follow-up
  - (onset date > the last day of study treatment + 4 weeks and ≤ the last day of study treatment + 16 weeks)

The timing of AEs will be assigned to the period in which they first occurred. If an AE has a missing onset date, then unless the stop date of the AE indicates otherwise, this will be considered an on-treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE.

9.4.3.3 Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or discontinuations due to AEs.

Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that led to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

9.4.3.4 Laboratory Variables

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times detailed in the CSP and will be assessed in a central laboratory. The parameters outlined in Table 7 in Section 8.2.1, will be collected. Laboratory data will be reported in SI units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent on treatment assessment will be calculated as described in Section 8.2.1. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The AstraZeneca extended

reference ranges will be used for laboratory variables (where they exist). All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorized as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each time-point.

For the purposes of hematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and on-treatment will be defined as the latest non-missing assessment whilst the subject is ongoing on treatment.

For the liver function tests: AST, ALT, ALP, GGT and total bilirubin, the multiple of the AstraZeneca ULN (not extended) range will be calculated for each data point.

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e., if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Subjects who meet any of the following criteria at any point during the study will be flagged:

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

9.4.3.5 ECGs

12 lead digital ECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as any time between Visit 1 and Visit 2 inclusive.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

9.4.3.6 Physical Examination

Complete and brief physical examinations will be performed at time points specified in Table 2.

What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 8.2.4. For the brief physical examination, only information on whether the assessment was performed or not will be recorded.

Each component of the complete physical examination at baseline visit will be recorded as normal or abnormal. Each component of the physical examinations at follow-up will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s), or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

9.4.3.7 Vital signs

Vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate and body temperature) will be obtained in accordance with the schedule provided in Table 1 and Table 2.

Changes in vital sign variables between baseline and each subsequent scheduled assessment will be calculated as described in Section 9.4.1. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index (BMI) will be calculated from the height (in meters) and weight (in kilograms) as BMI = kg/m^2.

9.4.4 Calculation or Derivation of PRO variables

9.4.4.1 SGRQ

Potential health status treatment benefits of tezepelumab will be evaluated by comparing the change from the baseline at Week 52 in SGRQ total scores. For the responder analysis of SGRQ a responder will be defined as an individual with a ≥ 4-point decrease (improvement) in SGRQ total score at Week 52.

9.4.5 Calculation or Derivation of Pharmacokinetic Variables

Serum samples will be collected at specified time points according to the schedule of assessment for determination of tezepelumab concentrations. Serum trough tezepelumab concentrations in the tezepelumab group will be summarized by time point.

9.4.6 Calculation or Derivation of Immunogenicity Variables

Serum samples will be collected at specified time points according to the schedule of assessment to detect the presence of ADAs against tezepelumab. The number and percentage of patients who develop detectable ADAs, as well as ADA titers for the samples confirmed positive for the presences of ADAs will be summarized by time point for both tezepelumab and placebo treatment groups. The prevalence and incidence of ADA over the course of the study will be calculated and tabulated for both treatment groups.

9.5 Statistical Analyses

There will be two DBLs in this study. The primary DBL will be conducted after the last subject completes Week 52, and the final DBL will be conducted once the last subject has completed the last safety follow-up visit (Week 64). Main analyses of the primary, key secondary efficacy objectives and some supportive summaries will be performed based on both the primary and final DBL data. The results produced at the time of primary DBL will be used to facilitate further design development for Phase 3 only. Although no changes are anticipated in conclusions given the primary DBL occurs after all subjects complete the planned treatment period, any discrepancies in the conclusions between the two DBLs will be discussed in the CSR. The CSR will be produced following the final DBL.

All personnel involved with the analysis and conduct of the study will remain blinded until primary database lock and important protocol deviations identified.

After primary database lock, treatment allocation for subjects during this study will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subject.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalized before primary database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

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

9.5.1 Multiple Testing Procedure

In this Phase 2a study, in order to describe the nature of the benefits with tezepelumab and to define study success, the primary endpoint will be tested using a one-sided 5% significance level. In addition, and although not powered, the primary endpoint will also be tested using a one-sided 2.5% alpha in order to strongly control type I error. No additional adjustment for multiplicity will be implemented.

9.5.2 Efficacy Analyses

9.5.2.1 Primary Analysis Methods

The primary efficacy variable is the annual COPD exacerbation rate and the primary analysis is to compare the annual COPD exacerbation rate of tezepelumab with placebo. Patients will be analyzed using the full analysis set according to randomized treatment.

The null hypothesis is that the exacerbation rate on tezepelumab is greater than or equal to the exacerbation rate on placebo. The alternative hypothesis is that the exacerbation rate on tezepelumab is less than the exacerbation rate on placebo, i.e.,

H_0: Rate ratio (tezepelumab vs Placebo) ≥ 1
H_a: Rate ratio (tezepelumab vs Placebo) < 1

Annual exacerbation rate in the tezepelumab group will be compared to annual exacerbation rate in the placebo group using a negative binomial model for the primary analysis. The response variable in the model will be the number of COPD exacerbations experienced by a patient during the follow-up for exacerbations. The model will include covariates of treatment group and the stratification factors (region, and the number of exacerbations in the year prior to study entry). The logarithm of the patient's corresponding time at risk of exacerbation will be used as an offset variable in the model to adjust for patients having different observation times during which the events occur.

The COPD exacerbation rate and the corresponding 90% confidence interval (CI) within each treatment group will be presented. The estimated treatment difference from placebo (i.e., the absolute difference between tezepelumab and placebo, and the rate ratio of tezepelumab versus placebo), corresponding 90% CI, and 1-sided p-value for the rate ratio will be presented. The 95% CI, and 2-sided p-value for the rate ratio will also be presented. Marginal standardization methods will be used on the model estimates for all negative binomial analyses, unless otherwise specified.

9.5.2.2 Secondary Analysis Methods

Secondary efficacy endpoints in this study are:

- Time to first COPD exacerbation
- Proportion of subjects with at least 1 COPD exacerbation
- Rate of severe exacerbations
- Time to first severe exacerbation
- Proportion of subjects with at least one severe COPD exacerbation
- Change from baseline in pre-BD FEV_1 at week 52
- Proportion of subjects achieving an MCID of 4 units or more in SGRQ total score over 52 weeks
- Change from baseline in SGRQ at Week 52
- Change from baseline in CAT at Week 52

Time to first COPD exacerbation over the 52-week treatment period will be analyzed to explore the extent to which treatment with tezepelumab delays the time to first exacerbation compared to placebo. A Cox proportional hazard model will be fitted to the data with

covariates of treatment, region and number of exacerbations prior to study entry in the year before the study

Proportion of subjects with at least one COPD exacerbation in tezepelumab group will be compared to with the proportion in the placebo group using a logistic regression model with region and number of exacerbations in the year prior to the study entry as covariates.

Annual rate of severe COPD exacerbations will be analyzed using a Negative Binomial Model as outlined for the primary efficacy variable.

Time to first severe COPD exacerbation will be analyzed using a similar model for time to first COPD exacerbation.

Change from baseline in pre-dose/pre-BD FEV_1 at Week 52 will be compared between tezepelumab and placebo using a repeated measures analysis on subjects with a baseline pre-dose/pre-BD FEV_1 and at least one post-randomization pre-dose/pre-BD FEV_1 in the FAS. The dependent variable will be the change from baseline in pre-bronchodilator FEV_1 at post-baseline protocol-specified visits (up to the EOT visit). Treatment group will be fitted as the explanatory variable, and region, visit, baseline pre-bronchodilator FEV_1 and the interaction between visit and treatment will be fitted as covariates. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance covariance matrix will be used instead. The model is:

*Change in FEV_1=Treatment group+ baseline FEV_1+ region + prior exacerbation strata + visit + treatment*visit*

Changes from baseline in SGRQ total score and CAT total score at Week 52 will be analyzed using a similar model for change from baseline in pre-dose/pre-BD FEV_1; the appropriate baseline value will be used in each model.

Proportion of subjects achieving an MCID of 4 units or more in SGRQ total score over 52 weeks in tezepelumab group will be compared with the proportion in the placebo group using a similar logistic regression model as that used for the proportion of subjects with at least one COPD exacerbation. The baseline SGRQ score will be included as a covariate in this model.

9.5.3 Subgroup Analyses

Details of all subgroup analyses and statistical modelling including possible testing of interaction between treatment group and covariates will be described in the SAP.

9.5.4 Safety Analyses

AEs will be summarized by means of counts and exposure adjusted rate summaries by study period (treatment period and follow-up period). AEs will be listed for each subject and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. Laboratory safety variables will be summarized using standard summary statistics and plots as appropriate. Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis. Changes in vital signs and ECGs will be examined at each visit and at endpoint. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

9.5.5 Pharmacokinetic and Immunogenicity 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 PK data collected in this study may be combined with data from other studies for population PK analysis. The results of such an analysis, if performed, will be reported separately.

The prevalence and incidence of anti-drug antibodies (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 archived for possible testing for neutralizing antibodies (nAb). The potential effects of ADA status and ADA titer on pharmacokinetics of tezepelumab will be evaluated. The potential association of immunogenicity with efficacy and safety may be evaluated if appropriate.

9.5.6 Biomarker Analyses

Biomarkers will be summarized using descriptive statistics. Details of the analyses will be described in the exploratory analyses plan, which will be finalized before the database lock. The results will be reported outside the CSR.

9.6 Interim Analyses

A data cut off for an interim analysis to potentially stop the study due to futility of efficacy

was originally planned to occur when 182 subjects had been randomized. As a result of the pause in recruitment due to COVID-19, the futility analysis is now planned to occur when approximately 30% of information has been achieved. An Independent Data Monitoring Committee (IDMC) will be used. Futility will be declared if the lower bound of an 80% Confidence Interval for the exacerbation rate ratio of tezepelumab vs. placebo is greater than 0.80. The futility boundary and method of assessing futility were chosen based on the operating characteristics of ~33% chance of stopping the study under the null hypothesis and ~4% chance of stopping the study assuming an exacerbation rate ratio of 0.70. Full details about the futility analysis decision rules and procedures will be specified in an IDMC charter, which will also specify the roles and responsibility of the IDMC members. Conducting the futility analysis results in power loss, but no alpha adjustment is required as there is no decision rule in place for stopping the study early to claim efficacy and no recovery of alpha from the futility analysis.

A data cut off for an interim analysis to inform sponsor Phase 3 planning will be conducted approximately 1 month after Last Subject Randomized. The study will continue, even if sufficient efficacy is observed to inform an early go for planning purposes. The Independent Data Monitoring Committee (IDMC) will be used and a blinding plan will be written to ensure that the study team, investigational site staff and patients remain blinded to subject level treatment revealing data if an early planning decision is made. As the study will continue regardless, no adjustment to the type I error is required.

9.6.1 Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized for this study. Details regarding IDMC are provided in Section 8.4.6.

10. REFERENCES

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

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

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

Any amendments to the protocol will require IRB/IEC 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 subjects.

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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

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

  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., 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 subject or his/her legally authorized representative and answer all questions regarding the study.

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

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

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

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

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

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

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

During the COVID-19 pandemic, re-consenting of subjects must follow local and regional guidelines with regard to informed consent. It is critical that where written re-consent cannot be obtained, and local and regional guidance allows, the subject's verbal consent via phone or teleconference is obtained before conducting any patient related changes implemented during

COVID-19 pandemic. Confirmation of subject's re-consent needs to be documented in the source documents.

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

A 4 Data Protection

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

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

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

A 5 Committees Structure

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

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

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

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

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

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

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

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to

request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

A 9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

A 10 Publication Policy

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

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

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

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

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

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

B 3 Life Threatening

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

B 4 Hospitalisation

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

existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important Medical Event or Medical Treatment

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

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

Examples of such events are:

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

B 6 Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 7 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

Is this a recognized feature of overdose of the drug?

Is there a known mechanism?

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

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

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

B 8 Medication Error, Drug Abuse and Drug Misuse

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 recognized that could have led to an error

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

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

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

- Errors related to or resulting from IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

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 of Biological Samples

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

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient
- Temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf.)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

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

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

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

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

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

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

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

Study selection record

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

Inclusion criteria

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

Exclusion criteria

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

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

Withdrawal of consent for genetic research

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

Collection of samples for genetic research

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

Coding and storage of DNA samples

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

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

The link between the subject enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for

analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

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

Informed consent

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

Subject data protection

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

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

Data management

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

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

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

Statistical methods and determination of sample size

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

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.

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

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether 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 AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

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

E 3 Identification of Potential Hy's Law Cases

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

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

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

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

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

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

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

E 4 Follow-Up

E 4.1 Potential Hy's Law Criteria Not Met

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

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

E 4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.3.10 Safety Reporting)
- Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
  - For subjects that met PHL criterial prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition

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

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available

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

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

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

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

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

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

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

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

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

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

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

E 6 Laboratory Tests

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

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

Hy's Law lab kit for central laboratories

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

References

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

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

Appendix F Maintenance Therapy Equivalence Table

Inhaled Corticosteroids dose conversion tables should be used to assess Inclusion 7.

ICS component	**Conversion Factor** (i.e. multiply dose by X)	**Minimum acceptable daily dose (mcg)**
Fluticasone propionate	1	>250
Fluticasone propionate HFA	1.14	>220 (per actuation)
Fluticasone furoate	2.5	≥100 (metered) ≥92 (delivered)
Budesonide (metered/delivered dose)	0.63/0.78	>400 (metered) >320 (delivered)
Budesonide (nebulized)	0.5	>0.5 mg (2 ml ampules)
Beclomethasone	0.5	>500
Beclomethasone (Trimbow)	1.25	400 (metered) 348 (delivered dose)
Beclomethasone extra-fine particles and HFA (Fostair, QVAR)	1.04 (metered dose) 1.25 (dose per actuation)	>250 (metered dose) >200 (per actuation)
Ciclesonide	1.56	>160
Mometasone furoate	1.14	>220 (metered) >200 (per actuation)
Flunisolide	0.25	>1000
Triamcinolone	0.25	>1000

Sources: GOLD 2018; GINA 2018

Example conversion

Converting budesonide (delivered dose) to fluticasone propionate (in mcg):

ICS component	**Conversion Factor** (i.e. multiply dose by X)	**Minimum acceptable daily dose (mcg)**
Budesonide (metered/delivered dose)	0.63/0.78	>400 (metered) >320 (delivered)

For a budesonide dose of 160 mcg, use a conversion factor of 0.78

160 mcg of budesonide x 0.78 = 124.8 mcg fluticasone propionate equivalent

The minimum acceptable daily dose (mcg) for Budesonide (delivered dose) must be higher than 320mg daily for subject to be eligible for the study (320mcg daily dose is not acceptable).

Appendix G Anaphylaxis: Signs and Symptoms, Management

G 1 Introduction

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

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

G 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

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

G 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles

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

G 4 Management of Acute Anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(f) Consider epinephrine infusion.

(g) Consider H1 and H2 antihistamines.

(h) Consider nebulized β2 agonist [e.g., albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

(i) Consider systemic corticosteroids.

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

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

(l) Consider atropine for symptomatic bradycardia.

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

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

Adapted from: Kemp et al 2008

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

Appendix H Abbreviations

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

Abbreviation or special term	Explanation
21 CFR	21 Code of Federal Regulations
ABPA	Allergic bronchopulmonary aspergillosis
ACOS	Asthma-COPD Overlap Syndrome
AD	Atopic Dermatitis
ADA	Anti-Drug Antibodies
ADE	Adverse Device Effect
AE	Adverse Event
AECOPD	Acute Exacerbations of COPD
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APFS	Accessorized pre-filled syringes
ATS	American Thoracic Society
AST	Aspartate Aminotransferase
AUC	Area under the curve
AZ	AstraZeneca
BAL	Bronchoalveolar Lavage
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass Index
BP	Blood Pressure
BTR	Best Test Review
BUN	Blood Urea Nitrogen
CAT	COPD Assessment Test
CDC	Centers for Disease Control and Prevention

Abbreviation or special term	Explanation
CSP	Clinical Study Protocol
CID	Clinically Important Deterioration
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CSR	Clinical Study Report
CT Scan	Computed Tomography Scan
CTIS	Clinical Trial Information System
CTT	Clinical Trial Transparency
DAE	Discontinuation of Investigational Product due to Adverse Event
dECG	Digital electrocardiogram
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EGPA	Eosinophilic granulomatosis with polyangiitis
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
ER	Emergency Room
E-RS™: COPD	Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms
ERS	European Respiratory Society

Abbreviation or special term	Explanation
EU	European Union
EUA	Emergency Use Authorization
EXA	COPD exacerbation visit
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool – Patient-reported Outcome
FAS	Full Analysis Set
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
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Hemoglobin
HCG	Human chorionic gonadotropin
HCP	Healthcare practitioner
HFA	Hydrofluoroalkane
Hg	Mercury
HIPAA	Health Insurance Portability and Accountability Act
HIV-1/2	Human immunodeficiency virus-1/2
HL	Hy's Law
HRU	Healthcare resource utilization
IATA	International Air Transport Association
ICH	International Conference on Harmonization

Abbreviation or special term	Explanation
ICI	International Co-ordinating Investigator (If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally).
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IDMC	Independent data monitoring committee
IEC	Independent ethics committees
IFU	Instructions for Use
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-5	Interleukin-5
IL-13	Interleukin-13
IL-25	Interleukin-25
IL-33	Interleukin-33
ILC2	Type 2 Innate Lymphoid Cells
IMP	Investigational Medicinal Product
IND	Investigation New Drug (application)
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	Intrauterine device
IUS	Intrauterine system
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists

Abbreviation or special term	Explanation
LRTI	Low Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit
LTOT	Long term oxygen therapy
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimum Clinically Important Difference
mmHg	Millimeter of mercury
MMRM	Mixed effect Model Repeated Measures
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
nAb	Neutralizing Antibodies
NIMP	Non- Investigational Medicinal Product
NIPPV	Noninvasive positive-pressure ventilation
O_2	Oxygen
OAE	Other Significant Adverse Event
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PGx	Genetic research
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRN	Pro Re Nata (as needed)
PRO	Patient Reported Outcome
PT	Preferred Term

Abbreviation or special term	Explanation
Q4W	Every 4 Weeks
R	Randomization
RBC	Red blood cell
RNA	Ribonucleic Acid
SABA	Short-Acting β2-Agonist
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAMA	Short acting muscarinic antagonists
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SNP	Single-nucleotide polymorphism
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen saturation via pulse oximetry
SDV	Source Data Verification
TB	Tuberculosis
TBL	Total Bilirubin
Th2	T-helper cell type 2
TLR	Toll-like Receptor
TPV	Third-Party Vendor
TSLP	Thymic Stromal Lymphopoietin
TSLPR	Thymic Stromal Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled

Abbreviation or special term	Explanation
USADE	Unanticipated Serious Adverse Device Effect
V	Visit
W	Week
WBC	White blood cell
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

Appendix I Coronavirus (COVID-19) Pandemic Guidance

During the COVID-19 pandemic, all actively enrolled subjects in the screening period will be screen failed and randomization visits will be temporarily placed on hold until the pandemic normalizes, and AZ approves the continuation of the study. Sputum and nasal samples will not be collected from subjects in treatment until the pandemic normalizes and AZ approves the continuation of sampling. Sputum and nasal sampling will be performed, if allowed per local regulations and guidance.

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

I 1 Pre-visit assessment during COVID-19 pandemic

A COVID-19 screening questionnaire must be completed via telephone within 72 hours prior to every study visit, regardless of the visit being on-site, at subject's home, or at an alternative location. During the call, subject should be instructed to contact site prior to visit, if subject experiences any COVID-19 symptoms or was exposed to someone diagnosed with COVID-19. For remote visits (phone call and/or virtual visits), the COVID-19 screening questionnaire should be conducted as a part of study visit assessments. Patient COVID-19 screening should include:

- Symptom history
- Exposure to someone diagnosed with COVID-19 in the past 14 days
- Recent travel including to countries with CDC Level 2 or higher travel warning or equivalent or known COVID-19 hot spots
- Unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat and/or new loss of taste or smell within the past 14 days

This questionnaire is to be conducted at minimum and local regulation and guidance should be followed.

Example of questionnaire:

1. Have you experienced unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the past 14 days?
2. Have you been in contact with anyone who is sick or with symptoms (refer to question 1) in the last 14 days?
3. Have you been exposed to someone diagnosed with COVID-19 in the last 14 days?
4. Have you been practicing social distancing over the last 14 days?
   (refer to region/city/country regulations)
5. Have you traveled in the last 14 days, if so where?

(recent travel including to countries/regions with CDC Level 2 or higher travel warning or equivalent or known Covid-19 hot spots)

6. Have you been in isolation or quarantine for any reason in the past 14 days?
7. Have you been diagnosed with Covid-19 at any time, if so where and when?

Sites may use their own version of questionnaire per local guidance. Responses are not considered as part of clinical trial data and are not recorded in RAVE. The site will determine the appropriate course of action based on the responses to questionnaire. Subject reporting symptoms should be referred for further evaluation as per investigator judgment. Visit should be cancelled or re-scheduled, if needed as judged by Investigator.

I 2 Home Visits to Replace On-Site Visits (where applicable)

Due to local travel restrictions and/or site restrictions, patients 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 administration of IP by a qualified HCP, provided this is acceptable within local regulation/guidance. This is to ensure safety of the study subjects and minimum disruption to IP administration that may occur during the COVID-19 pandemic.

NOTE: Before initiating consent for home IP administration visit, the subject must have received at least the first 2 IP administrations at the site.

Where possible study assessments should be conducted according to the SoA. Central lung function assessment at home is not implemented in COURSE study.

Site must contact the subject by telephone to assess possible COVID-19 symptoms before initiating home visit. Refer to I 1.

At minimum, during home visit the qualified HCP is expected to:

- Collect vital signs (visit should start with temperature measurement)
- Collect adverse events reported since last contact with the subject
- Collect information about new or changes in concomitant medications since last contact with the subject
- Completion of SGRQ and CAT (if applicable)
- ePRO compliance check (if applicable)
- Collect information about any worsening of underlying COPD symptoms/COPD exacerbations since last contact with the subject
- Collect smoking status
- Collect information on healthcare resources utilization
- Perform physical examination (if applicable)
- Measure oxygen saturation (SpO_2) (if applicable)
- Collect use of Supplemental O_2 status (if applicable)
- Urine Pregnancy (dipstick) prior to IP administration (if applicable)

- If possible, collect blood and urine samples according to the SoA
- Administer IP. Please refer to the IP home administration instructions for use during COVID-19 pandemic for more information
- Observe the subject for one hour after IP administration for the signs or symptoms of any acute drug reactions
- Document the visit. The form of contact should be documented in the medical records

Laboratory assessments during home visit

If safety blood samples are being collected, they may be obtained within 1-hour post IP administration, to allow additional time for processing of the safety samples at site according to the laboratory manual.

If PK and/or ADA samples are being collected, they have to be obtained prior to IP administration. If it is not possible, these samples are not required to be collected during the home visit.

I 3 Visit at an Alternative 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 subjects' homes, provided this is acceptable within local regulation and guidance.

Site must contact the subject by telephone to assess for possible COVID-19 symptoms before initiating visit at an alternative location. Refer to I 1.

Central lung function assessments at alternative location is not implemented in COURSE study.

I 4 Phone call and/or virtual visits to replace on-site visits (where applicable)

During the COVID-19 pandemic, on-site visits that are not replaced by home/alternative location visits may be replaced by a phone call and/or a virtual visit.

Having a phone call and/or a virtual visit with the subject will allow collection of information regarding:

- Assessment of COVID-19 symptoms (refer to I 1)
- Collect adverse events reported since last contact with the subject
- Collect information about new or changes in concomitant medications since last contact with the subject

- Completion of SGRQ and CAT (if applicable)
- ePRO compliance check
- Collect information about any worsening of underlying COPD symptoms/COPD exacerbations since last contact with the subject
- Collect smoking status
- Collect information on healthcare resources utilization
- Measure oxygen saturation (SpO_2) (if applicable)
- Collect use of Supplemental O_2 status (if applicable)
- Document the visit. The form of contact should be documented in the medical records

I 5 Re-consenting of subjects during the COVID-19 pandemic

COVID-19 addendum to ICF (SoA, Table 2) must be obtained prior to starting any procedures according to Appendix A 3. The standard informed consent process in the trial should be followed. However, if the subject may not be able to visit the site due to COVID-19 illness or travel restrictions, local regulation and guidance should be followed if the subject is re-consenting to the approved updated ICF. This will minimize the risk to the subject of COVID-19 exposure at clinic visits.

I 6 Benefit-risk assessment of re-starting recruitment during COVID-19 Pandemic

Since the first subject was enrolled in this study, coronavirus disease 2019 (COVID-19) has emerged as a worldwide pandemic disease with significant public health implications. AstraZeneca's decision was to place enrolment temporarily on hold until the pandemic normalizes as not all screening assessments required for the evaluation of subject eligibility could be done. Subjects already randomized were allowed to continue with study but alternative options were given to minimize the risk of subject exposure to COVID-19.

However, AstraZeneca is not aware of any current evidence suggesting that tezepelumab either increases the susceptibility to COVID-19 infection or worsens the outcomes of COVID-19 infection. Moreover, available information strongly supports potential benefit of tezepelumab treatment in various diseases including asthma and COPD with low safety concerns. The benefit-risk assessment favours re-starting enrolment in the COURSE study.

AstraZeneca accepts that a careful benefit-risk analysis should be performed in each region before resuming recruitment in a clinical trial that impacts on clinical resources needed for the COVID-19 pandemic. AstraZeneca will resume recruitment in this study in regions only when local and national guidance and clinical sites have indicated that it is acceptable to conduct clinical studies and the safety of site staff and subjects can be ensured. The Sponsor will conduct

risk-based enrolment assessments on a country and site level on a regular basis during the pandemic phase, and decisions will be documented.

Risks mitigations

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

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

- All subjects will have a COVID-19 screening assessment performed by telephone within 72 hours prior to study visit. The site will determine the appropriate course of action based on the responses to the questions.
- Naso/oropharyngeal swab testing (or rapid test) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is required at screening Visit 1 for new patients entering in the study to minimize the risk of enrolling a subject with active COVID-19 infection into the study.
- Testing for SARS-CoV-2 at subsequent visits with spirometry and sputum induction may and should be performed, if required, by local and national guidelines. If SARS-CoV-2 testing is conducted, a negative result should be obtained before conducting visit assessments if required by local regulations and guidelines
- If, a subject is not able to attend their scheduled study visit at the site, alternative visit options are available.
- All site staff should wear personal protective equipment in accordance with local or national guidelines.

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

- Subjects will be able to attend study visits, including remote visits, whilst avoiding contact with concentrations of COVID-19 patients (e.g. hospital entrances used by such patients); and
- The site will be able to conduct the study effectively and safely, considering relevant national and local factors; and

Subjects agree to alternate site visits or home visits as an alternative to on-site visits (if allowed by local and regional guideline), if pandemic restrictions are in place.

Conclusion

Given the limited additional risks to the study population related to COVID-19, from study participation, beyond those they would experience in everyday life, the mitigations described above are considered sufficient to ensure a favourable benefit-risk balance.

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

- This appendix supports the activities described in section 8.3.10
- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See section 6.1.2 for the list of sponsor medical devices.

J 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

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

J 2 Definition of Medical Device SAE, SADE and USADE

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

a. Led to death

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

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

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

SADE definition

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

Unanticipated SADE (USADE) definition

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

J 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

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

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

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

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

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

Assessment of Causality

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

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- 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'.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

Appendix K 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, 21 Mar 2022 Changes to the protocol are summarized below.
Section 1.2 Synopsis, Updated the estimated date of last subject completed to Q1 2024. Section 2.3 Benefit/Risk Assessment, Added "Use of tezepelumab has been demonstrated to show an important benefit in asthma in a phase 2b and phase 3 study." Section 2.3 Benefit/Risk Assessment, Added "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." Section 2.3 Benefit/Risk Assessment, Added "No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 3 program. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host defense against certain infections, there is no clear preclinical or clinical evidence supporting such a role, and no safety signals related to either severe infections or parasitic infections have been detected in the completed studies to date. Risk minimisation measures for important potential risks will be in place during the conduct of this study, in conjunction with the performance of the AstraZeneca's routine pharmacovigilance activities." Section 4.1 Overall Design, Added "Extension of the screening/run-in for any other reason will be allowed only upon approval of the AstraZeneca Study Physician (refer to section 5.4)" Section 4.1 Overall Design, Added "Subjects who have a blood eosinophil count <300 at enrolment Visit 1 can be re-tested at an unscheduled visit, upon approval of the AstraZeneca Study Physician. It is recommended that any re-test for blood eosinophils is performed not earlier than 4 weeks from the previous testing. In case of recent treatment with systemic corticosteroids, an interval of ≥6 weeks from the last dose is recommended." Section 4.3 Justification for Dose, "Based on the efficacy and safety data, as well as exposure-response analysis, of the Phase 2b asthma study CD-RI-MEDI9929-1146, 210 mg Q4W SC was selected as the optimal dose of tezepelumab for adult and adolescent patients with severe asthma and is tested in the Phase 3 studies in severe asthma" updated to "Based on the efficacy and safety data, as well as exposure-response analysis, of the Phase 2b

asthma study CD-RI-MEDI9929-1146, 210 mg Q4W SC was selected as the optimal dose of tezepelumab for adult and adolescent patients with severe asthma and is confirmed in the Phase 3 studies in severe asthma"

Section 5.1 Inclusion Criteria and Section 8.2.1.1 Pregnancy Test, Added "Until FSH is documented to be within menopausal range, treat the subject as WoCBP".

Section 5.1 Inclusion Criteria, Inclusion 7 – Added "See appendix F for ICS dose conversion table."

Section 5.2 Exclusion Criteria, Exclusion 22 - "Receipt of any marketed (eg, omalizumab) or any investigational monoclonal or polyclonal antibody therapy (eg, gamma globulin) taken for any reason within 6 months or 5 half-lives prior to Visit 1, whichever is longer." updated to "Receipt of any marketed (eg, omalizumab) or any investigational monoclonal or polyclonal antibody therapy (eg, gamma globulin) taken for any reason within 4 months or 5 half-lives prior to Visit 1, whichever is longer."

Section 6.1.2 Medical Devices, Added Section 6.1.2 – Medical Devices: regarding sponsor manufactured medical device use in this study and all medical device deficiencies should be documented and reported by investigator throughout the study.

Section 6.5 Concomitant Therapy, Table 5 – "Prohibited if taken for any reason within 6 months or 5 half-lives (whichever is longer) prior to Visit 1 and during the study (even if the subject has discontinued IP)." updated to "Prohibited if taken for any reason within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 and during the study (even if the subject has discontinued IP)."

Section 8 Study Assessments and Procedures, Updated "The amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will be approximately 285 mL (including any extra assessments that may be required) and will not exceed 450 mL" to "The amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will be approximately 360 mL (including any extra assessments that may be required) and will not exceed 450 mL"

Section 8.2.10 Vaccination Restrictions, Updated CDC guidelines reference from "2018-2019" to "2021-2022"

Section 8.3 Collection of Adverse Events, Added "The definitions of medical device-related safety events, can be found in Appendix J. Medical Device deficiencies are covered in section 8.3.10"

Section 8.3.7 Adverse Events Based on Examinations and Tests, Updated "COPD exacerbation should be recorded as an AE or SAE only if it fulfils any of the above criteria" with "Worsening of COPD should be recorded as an AE or SAE only if it fulfils any of the above criteria."

Section 8.3.10 Medical Device Deficiencies, Added Section 8.3.10 - definitions of medical device deficiency and requirements to fulfil regulatory reporting obligations worldwide and investigator's responsibility for detection and documentation of events meeting the definition of device deficiency occurring during the study.

Section 8.4.4 Medication Error, Removed "Medication errors with AZ IP are collected in all studies where medication error is possible. Refer to the PSSR or other appropriate project document for specific considerations for collection of medication errors. For guidance, refer to AZ SOP 'Reporting of Individual Safety Events in Clinical Studies'"

Section 8.5.1 Collection of Samples to Measure Drug Concentration, Added "Samples from patients who receive placebo will not be measured initially but will be retained for subsequent analysis if deemed appropriate"

Section 9.5 Statistical Analyses, Replaced "All analyses of the primary and secondary objectives will be performed based on the primary DBL data" with "Main analyses of the primary, key secondary efficacy objectives and some supportive summaries will be performed based on both the primary and final DBL data. The results produced at the time of primary DBL will be used to facilitate further design development for Phase 3 only. Although no changes are anticipated in conclusions given the primary DBL occurs after all subjects complete the planned treatment period, any discrepancies in the conclusions between the two DBLs will be discussed in the CSR. The CSR will be produced following the final DBL."

Section 10 References, Updated CDC 2010 guidelines link to "https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html"

Section 10 References, Removed reference for 2018-2019 CDC guidelines and added reference for 2021-2022 CDC guidelines.

Appendix A 1 Regulatory and Ethical Considerations, Added "The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations."

Appendix A 1 Regulatory and Ethical Considerations, Added "European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations" Appendix A 7 Data Quality Assurance, Updated study documents retention period from "15 years" to "25 years" Appendix C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document, Updated IATA classification link to https://www.iata.org/whatwedo/cargo/dgr/Documents/infectious-substance-classification-DGR56-en.pdf. Appendix H Abbreviations, Added "ADE: Adverse Device Effect", "SADE: Serious Adverse Device Effect" and "USADE: Unanticipated Serious Adverse Device Effect". Appendix J Medical Device AEs, ADEs, SAEs, SADEs, US ADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up, Added Appendix J – Medical Device AEs, ADEs, SAEs, ADEs, US ADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up Appendix K Protocol Amendment History, Added Appendix K – Moved protocol amendment history to Appendix K.
Version 5.0, 15 Mar 2021 Changes to the protocol are summarized below.
Section 1.1 SoA, Table 1: removed 'if applicable' from 'Chest x-ray (if applicable)' to clarify chest x-ray is a mandatory assessment. Section 1.1 SoA, Table 1, Footnote f, Footnote l, Section 4.1 Overall Design, Section 5.4 Screen Failures and Re-Screening, Section 6.5.5 COPD Medication Restrictions on the Days of Scheduled Spirometry and FeNO Visits, Section 8 Study Assessments and Procedures, Section 8.1.2.1 General Requirements, 8.2.11.2 SARS-CoV-2 testing, Appendix I 6 Benefit-risk assessment of starting recruitment during COVID-19 Pandemic: added 'naso/oropharyngeal' and 'or rapid test' to permit flexibility with the method of SARS-CoV-2 testing to be performed. Section 1.1 SoA, Table 1, Footnote l and Section 8.2.11.2 SARS-CoV-2 Testing: clarified local versus central testing. Due to long turnaround times for central laboratory SARS-CoV-2 testing results and the requirement in some countries to have SARS-CoV-2 testing results available within 24-72 hours before visit assessments, considerations have been made to allow the option of SARS-CoV-2 testing to be performed locally.

Section 1.1 SoA, Table 1, Footnote a, Section 4.1 Overall Design, Screening Period (Enrolment and Run-in), Section 6.5.5 COPD Medication Restrictions on the Days of Scheduled Spirometry and FeNO Visits, Section 8 Study Assessments and Procedures: revised to clarify assessments that must be done at Visit 1 and which assessments can be postponed based on the type of SARS-CoV-2 testing performed.

Section 1.1 SoA, Table 1, Footnote g, Section 5.2 Exclusion Criteria (Exclusion 40), Section 8.2.9 Chest X-ray: added 'Under special circumstances, a recently done historical chest X-ray (anterior-posterior and lateral)/CT/MRI for other reasons (not study related) might be acceptable. The outcome of the X-ray/CT/MRI must be documented in the patients' medical records. Study Physician approval of historical chest X-ray must be obtained prior to randomization.' This is to minimize the need for a subject who recently had a chest X-ray done for non-study related reasons having to repeat a chest X-ray assessment during screening in the study (to limit radiation exposure).

Section 1.1 SoA, Table 1, Footnote k, Section 4.1 Overall Design, Appendix I 1 Pre-visit assessment during COVID-19 pandemic, I 6 Benefit-risk assessment of re-starting recruitment during COVID-19 Pandemic: extended the timeframe for completion of the COVID-19 screening assessment from 'within 24 hours' to 'within 72 hours' prior to every study visit (except remote visits). The extension to 72 hours is to accommodate weekend schedules where site contact with subjects on the weekend may not be possible.

Section 1.1 SoA, Table 2, NOTE: revised the suggested order of assessments to be completed prior to IP administration to, 'ePRO, Vital signs, ECG, FeNO, spirometry and blood draws.' Added clarification, 'Applicable during COVID-19 pandemic: Vital signs, ePRO, ECG, FeNO, spirometry and blood draws' to be consistent with Table 1, Footnote f order of assessments. Vital signs should be performed first to ensure that the patient does not have a fever before performing other assessments.

Section 1.1 SoA, Table 2, Sputum cell pellet: revised wording to 'cell counts and/or RNA transcriptomic profiling' to allow flexibility due to partial sputum processing

Section 1.1 SoA, Table 2, Footnote f, Section 8.1.2.2 Post-PD Spirometry: removed 'X' for post-BD spirometry assessment at EXA visit as sputum post-BD spirometry assessment required as part of sputum induction procedure is already captured in the SOA under sputum sub-study section. Also for footnote f, 'post-BD' removed and added clarification to pre-BD spirometry that it will be performed at EXA visit as part of induced sputum procedures 'during treatment phase'.

Section 1.1 SoA, Table 2, Footnote k, Section 8.8.5 Sputum Induction, Section 8.8.6 Nasal Lining Fluid: rephrased statement regarding sputum and nasal sample collection during the COVID-19 pandemic to the following, 'During the COVID-19 pandemic, sputum and nasal

samples will only be collected if allowed per local Health and Safety regulations or guidance and if sub-study laboratory test kits are available,' since AstraZeneca approves the continuation of sampling as the study has resumed recruitment.

Section 1.2 Synopsis, Section 4.1 Overall Design: removed 'During the COVID-19 pandemic, sputum and nasal samples will not be collected from subjects in treatment phase to minimize risk to subject and site staff from virus. Please refer to Appendix I,' from Section 1.2, and removed 'During COVID-19 pandemic, sputum samples will not be collected from subjects in treatment phase until the pandemic normalizes and AZ approves the continuation of sampling. Please refer to Appendix I,' from Section 4.1, since AstraZeneca approves the continuation of sampling as the study has resumed recruitment.

Section 1.1 SoA, Table 2, Footnote q: added '(in treatment or in follow-up)' to clarify that the SARS-CoV-2 serology test is also applicable to subjects in follow-up.

Section 1.2 Synopsis, Section 3 Objectives and Endpoints, Section 4.1 Overall Design: updated study randomization from approximately '282' to '338' subjects due to sample size reassessment as a suggestion of the IDMC following interim analysis to account for a possible decrease in COPD exacerbations related to the COVID pandemic and social distancing.

Section 1.2 Synopsis, Section 3 Objectives and Endpoints: updated the estimated date of last subject completed to Q2 2023 based on revised estimated date of Q1 2022 for last subject enrolled.

Section 1.2 Synopsis and Section 3 Objectives and Endpoints, Table Table 4, Exploratory Objectives: added clarification 'during treatment phase' to the objective 'to evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome, in subjects participating in sub-study, at baseline, end of treatment, and at the start of all exacerbations.'

Section 1.3 Schema, Figure 1: revised sample size to '169' per treatment arm per sample size revision in Section 9.2.

Appendix I 1 Pre-visit assessment during COVID-19 pandemic: added clarification, 'During the call, subject should be instructed to contact site prior to on-site study visit, if subject experiences any COVID-19 symptoms or was exposed to someone diagnosed with COVID-19'.

Section 4.1 Overall Design, Screening Period (Enrolment and Run-in):

added clarification to the 35-day run-in can be extended by: ‘waiting time required to obtain Visit 1 SARS-CoV-2 naso/oropharyngeal swab test (or rapid test) result’ and ‘28 days for patients receiving COVID-19 vaccine during screening’.

Added clarification to the 35-day run-in can be extended by: ‘28 days for waiting time required to receive central lab kits’ if central laboratory kits are unavailable.

Section 4.1 Overall Design, Randomization, Treatment and Follow-up: added clarification on requirements of signing COVID-19 addendum to informed consent prior to starting alterative options of on-site IP administration; option of phone call visit is included in the main informed consent

Section 5.2 Exclusion Criteria:

updated Exclusion 5: removed ‘or screening period’ to be consistent with Section 5.4. Also added clarification, ‘Note: Refer to Exclusion criteria 19 for restriction with maintenance systemic steroid treatment.’

updated Exclusion 19: added ‘systemic’ to ‘Use of systemic immunosuppressive medication’ to further clarify.

updated Exclusion 24: ‘Chronic use of macrolide or other antibiotics for prophylactic use of COPD exacerbation if duration of treatment is < 9 months prior to enrolment (Visit 1) or re-screening visit. If the patient was previously on prophylactic treatment but is no longer taking it, the patient cannot be randomized until 6 weeks after the last dose. Chronic macrolide or other antibiotic therapy is allowed provided the patient has been on a stable dose/regimen for ≥ 9 months prior to enrolment (Visit 1) or re-screening visit and have had at least 2 historical COPD exacerbations while on prophylactic treatment.’ This reference was updated from randomization to enrolment visit to correct inconsistency between Inclusion 6 and Exclusion 24.

updated Exclusion 39: added ‘naso/oropharyngeal’ and ‘or positive rapid antigen test’ to SARS-CoV-2 testing methods, to be consistent with other protocol updates concerning allowable methods of testing.

added Exclusion 41 ‘Receipt of any COVID-19 vaccine 28 days prior to date of randomization.

Section 6.1.2 Preparation/Handling/Storage/Accountability:

added ‘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 8.2.10, Table Table 8 cannot be followed,' to be consistent with COVID-19 vaccination restrictions added to other sections.

added visual characteristics of the IP to specify more details related to appearance and clarity of the IP.

Section 6.3 Measures to Minimize Bias: Updated vendor name for randomization code provider, from PPD to PPD due to company name change.

Section 6.5 Concomitant Therapy:

Added 'follow-up period' to paragraph describing subject's usual pre-study triple inhaled therapy, to align with Section 6.5.1.

Added for eCRF entry, 'COVID-19 vaccine given at any time', to align with Table Table 6 revisions.

Table Table 6 – Allowed, Restricted, and Prohibited Medications:

systemic corticosteroids (tablets or injections), revised details to 'Allowed to treat a COPD exacerbation or an AE where there is no alternative treatment available, for no more than 14 days' to further clarify the restrictions on use of systemic corticosteroids.

added 'COVID-19 vaccinations' restrictions

replaced 'any' with 'systemic' in Systemic immunomodulators and immunosuppressive medication and removed 'maintenance systemic steroid treatment' from 'any immunomodulators and immunosuppressive medication (including but not limited to methotrexate, cyclosporine, any experimental anti-inflammatory therapy)'. Also in details, added 'refer to Systemic corticosteroids (tablets or injections) for further restrictions'. This is to further clarify the restrictions on use of systemic corticosteroids.

Section 7.3 Withdrawal from the Study, Section 8.8.1 Storage, Re-use and Destruction of Biomarker Samples: For the statement that indicates, if the subject only withdraws consent for retention of biological samples for future exploratory use, it has been revised to include a broadened definition of future use.

Section 8.1.1.5 COPD Exacerbation Visit: added section 'Only for sputum sub-study subjects: Performing COPD Exacerbation visit (EXA) for sputum sub-study patients is essential to evaluate exploratory sputum and nasal sub-study endpoints during treatment phase. Refer to Section 3. Patients participating in sputum sub-study are required to perform pre-BD and sputum post-BD spirometry as part of sputum induction, at EXA visits during treatment. Induced sputum is preferred however spontaneous sputum is acceptable if patient

cannot provide induced sputum sample or if the collection of induced sputum is not permitted per local Healthy and Safety regulations or guidance during the COVID-19 pandemic. Please refer to applicable sub-study manual for more information.' for clarification.

Section 8.1.2.2 Post-BD Spirometry: updated to allow SABA administration to start earlier (less than 15 minutes of the final pre-BD spirometry) if needed for safety reasons.

Section 8.1.2.3 Sputum Post-BD Spirometry, Section 8.8.4 Nasal Epithelial Cell and Sputum Cell Transcriptomics, Section 8.8.5 Sputum Induction, Section 8.8.6 Nasal Lining Fluid:: added 'applicable' to manual to allow for full or partial processing manual.

Section 8.2.1 Clinical Safety Laboratory Assessments: added language to allow for local laboratory testing of safety samples (clinical chemistry, hematology and urinalysis) at the discretion of the PI if central laboratory kits are unavailable. Also indicated that all laboratory assessments for Visit 1, Visit 3, and EoT or IPD Visit (as per SoA) must be analysed at the central laboratory. Also, added sub-section 'Maintaining the blind to the patient's blood immunoglobulin, eosinophil, basophil and monocyte counts' with procedures to mitigate unblinding.

Section 8.2.5 Vital Signs, 9.4.3.7 Vital signs: removed 'pre-dose' from vital signs description as vital signs assessments are also required at follow-up visits.

Section 8.2.10 Vaccination Restrictions: updated section name from 'Pneumococcal and Annual Influenza Vaccination' to 'Vaccination Restrictions' and added sub-section 'COVID Vaccination' to include COVID-19 vaccination restrictions.

Section 8.4.2.1 Maternal Exposure, 8.4.2.2 Paternal Exposure, B 2 Definitions of Serious Adverse Event: revised wording related to congenital anomalies ('congenital anomaly' instead of 'congenital abnormality') to be consistent with wording provided in new clinical study protocol template.

Section 8.8.5 Sputum Induction

added new guidance for partial sputum processing, 'Depending on individual site capability, sputum processing will follow one of two sputum processing protocols (full processing or partial processing). Sputum sample processing will result in the production of cytospin slides (for full sputum processing only), microbiome sample, cell pellets for RNA transcriptome, and aliquots of sputum supernatant. The clinical sites performing full sputum processing procedures will also generate and record total cell count and cell viability data on their sputum processing worksheets.'

added clarification, 'For other sub-study visits, sputum sub-study samples will be collected if sub-study laboratory kits and supplies are available within visit window. In the event of missing supplies, sites should make reasonable effort to collect and process samples where feasible, and with the approval of Study Physician.'

Section 8.8.6: added clarification for nasal lining fluid samples that will be obtained in accordance with the schedule provided in Table 2 in a subset of subjects only participating in the sub-study, 'if nasal lining fluid sampling supplies are available.'

Section 9.2 Sample Size Determination: revised into two sections, 'Original Sample Size' and 'Updated Sample Size' and added 'The sample size has been reassessed due to the potential for reduced exacerbation rates due to limited person-to-person contact and exposure to respiratory infections during the COVID-19 pandemic. Assuming the same treatment effect (0.7) and dispersion parameter (0.6) as originally assumed, a sample size of 169 subjects per treatment arm (338 overall) will maintain the study power if the placebo exacerbation rate is as low as 1.2 exacerbations/subject-year.'

Section 9.2.1 Estimands: presentation of the primary and supplemental estimands has been updated to more clearly specify the 4 attributes of an estimand. The handling of IP discontinuation as an intercurrent event in the supplemental estimand has been amended (previously addressed by an on-treatment estimand detailed in the SAP only).

Section 9.4.2.5 Forced Expiratory Volume in 1 Second: removed, 'If the Visit 3 pre-bronchodilator measurement is missing, the last non-missing pre-bronchodilator value before Visit 3 will be used as baseline instead.' to be consistent with Section 9.4.1.

Appendix A 7 Data Quality Assurance: Added clarification describing details of monitoring strategy, including remote monitoring.

Appendix F Maintenance Therapy Equivalence Table: added to support Inclusion 7 criterion assessment.

Appendix H Abbreviations: added 'EUA: Emergency Use Authorization' as newly referenced in Section 8.2.10.

Throughout CSP:

removed references associating baseline assessments with Visit 3. The association has been redefined as follows, "randomization" or "randomization visit" for efficacy related assessments, and "first IP administration" for safety related assessments, to remove ambiguity.

various typographical and grammatical corrections have been made.
Version 4.0, 11 August 2020 Changes to the protocol are summarized below.
Section 1.1 SoA, Table 1: Added pre-visit assessment: telephone assessment of possible COVID-19 symptoms, to visits 1 and 2. Also, added footnote k 'During the COVID-19 pandemic, subjects must be contacted by telephone for COVID-19 screening assessments within 24 hours prior to every study visit (except remote visits). Refer to Appendix I for details.' This is to minimize the risk of subject performing study visits with active COVID-19 infection. Added study procedure: COVID-19 addendum to ICF (if applicable). Also, added footnote m 'During re-consenting of subjects during the COVID-19 pandemic, local and regional guidelines must be followed. Refer to Appendix I for further details'. This is to minimize the risk of enrolling subject who do not agree to any alternatives when on-site visit is not possible due to COVID-19 pandemic'. Added laboratory assessment: SARS-CoV-2 nasopharyngeal swab test to Visit 1. Also, added footnote l 'Central laboratory SARS-CoV-2 nasopharyngeal swab test result must be available and negative prior to performing screening lung function assessments and ECG (refer to 1.1 footnote a)'. This is to minimize the risk of subject completing lung function assessments with active COVID-19 infection. Footnote a: updated to 'The screening lung function assessments and ECG must be postponed until the Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative. At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed. Visit 2 should be scheduled, if the post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 nasopharyngeal swab test result. Lung assessments can only be done if there are no restrictions to medications (refer to Section 6.5.5 and 8.1.3).' This is to minimize the risk of subject completing lung function assessments with active COVID-19 infection. Footnote c: removed 'Sponsor and' from 'the Sponsor and sites will be blinded to the FeNO values for the whole study duration' and added 'The sponsor will be blinded to the FeNO values except at screening visit, at any repeat testing that is performed during the screening

period and prior to Investigational Product (IP) administration at Visit 3.' Sponsor only needs to be blinded to the FeNO values after randomization.

Footnote f: added 'IMPORTANT: Applicable during COVID-19 pandemic: the suggested order of assessments: vital signs, ePRO, blood draws and SARS-CoV-2 nasopharyngeal swab testing. The lung function assessments and ECG must be postponed and scheduled after Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative.' This is to minimize the risk of subject completing lung function assessments with active COVID-19 infection.

Footnote g: updated to specify that for all subjects enrolled during COVID-19 pandemic, a chest X-ray must be done at Visit 1, or at any time that allows the chest X-ray assessment prior to randomization. This is to minimize the risk of enrolling subjects with COVID-19 pneumonia or other lung pathology.

Section 1.1 SoA, Table 2:

Added pre-visit assessment applicable during COVID-19 pandemic: telephone assessment of possible COVID-19 symptoms, to every visit. Also, added footnote p 'During the COVID-19 pandemic, subjects must be contacted by telephone for COVID-19 screening assessments within 24 hours prior to every study visit (except remote visits). Refer to Appendix I for details.' This is to minimize the risk of subject performing study visits with active COVID-19 infection.

Added assessment applicable during COVID-19 pandemic: SARS-CoV-2 serology test to Visit 3 and footnote q to clarify that 'SARS-CoV-2 serology test at Visit 3 is applicable for newly enrolled subjects. For remaining ongoing active subjects, the test should be done as soon as possible but preferably at the next site visit'. This is to determine whether subjects have been previously infected with SARS-CoV-2 for safety reasons (e.g. assessment of adverse events during study participation).

Footnote c: removed 'Sponsor and' from 'the Sponsor and sites will be blinded to the FeNO values for the whole study duration' and added 'The sponsor will be blinded to the FeNO values except at screening visit, at any repeat testing that is performed during the screening period and prior to Investigational Product (IP) administration at Visit 3.' Sponsor only needs to be blinded to the FeNO values after randomization.

Footnote k: updated to clarify that during the COVID-19 pandemic, sputum and nasal sampling will not be collected from subjects in treatment phase until the pandemic normalizes and AZ approves the continuation of sampling.

Added footnote r: 'Randomization transaction in IWRS should be completed after confirmation of subject eligibility'. This is to further clarify the order of assessments and prevent randomization in error.

Section 1.2 Synopsis: updated the estimated date of last subject completed to Q4 2022 as delays have occurred due to putting recruitment on hold during COVID-19 pandemic.

Section 4.1 Overall design:

Added 'Pre-visit assessment during COVID-19 pandemic: Subjects must be contacted by telephone for assessment of possible COVID-19 symptoms within 24 hours prior to every study visit (except remote visits). Please refer to Appendix I for details'. This is to minimize the risk of subject completing study procedures with active COVID-19 infection.

Screening Period (Enrolment and Run-in): removed 'Run-in Visit 2 should be initiated no later than 1 week after Enrolment at Visit 1' and added 'The screening lung function assessments and ECG must be postponed until the Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative. At the postponed Visit 1, the spirometry equipment will allow pre-BD, post-BD spirometry, FeNO and ECG (combined Visit 1 and Visit 2) to be performed. Visit 2 should be scheduled, if the post-BD spirometry and FeNO were not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 nasopharyngeal swab test result.'

Section 4.1 Overall design and Section 5.1 Inclusion 6: Added a note from section 5.4 on how historical COPD exacerbations should be reported in case of re-screening, for further clarifications.

Section 5.1 Inclusion 12: removed with version 4.0 of Clinical Study Protocol and replaced with Exclusion criterion 40.

Section 5.2 Exclusion Criteria: added Exclusion criterion 38 applicable during COVID-19 pandemic to exclude subjects with suspected COVID-19 infection based on signs and symptoms assessed by Investigator. This is to minimize the risk of enrolling subject with active COVID-19 infection.

Section 5.2 Exclusion Criteria: added Exclusion criterion 39 during COVID-19 pandemic to exclude subjects with positive SARS-CoV-2 nasopharyngeal swab test for active infection at Visit 1. This is to minimize the risk of enrolling subject with active COVID-19 infection.

Section 5.2 Exclusion Criteria: added Exclusion criterion 40 during COVID-19 pandemic to exclude subjects with chest X-ray performed during the screening period which shows

abnormalities or evidence of COVID-19 pneumonia that precludes the patient's ability to complete the study.

Section 5.4 Screen Failures and Re-screening: Added situations, applicable during COVID-19 pandemic, when subject must be screen failed:

'Judgement by the Investigator that the subject should not participate in the study based on assessment of COVID-19 signs and symptoms for active infection. Subject can be re-screened within 2 to 4 weeks upon approval of the AZ Study Physician (exclusion criterion 38)'.

'Subject who had positive SARS-CoV-2 nasopharyngeal test at Visit 1 for active infection during screening should be screen failed. They may be re-screened once recovered from the infection, upon approval of the AZ Study Physician (exclusion criterion 39)'.

Section 5.4 Screen Failures and Re-screening: Removed 'and only once' under re-screening requirements as subject screen failed due to COVID-19 can be re-screened additionally. Re-screening of a subject for any reason will be allowed only upon approval of the AZ Study Physician.

Section 6.1.2 Preparation/handling/storage/accountability, Dose Administration – added situations, applicable during COVID-19 pandemic, when IP should not be administered: if the subject has suspected or confirmed active COVID-19 infection. Also added that AZ Study Physician should be contacted to discuss further subject participation if the subject has been diagnosed with an active COVID-19 infection. This is to minimize the risk of subjects completing study assessments with COVID-19 infection.

Section 6.4 Compliance to IP: added 'with the reason for drug interruption' to 'The date and time of all IP administrations, as well as any missed doses with the reason for drug interruption, should be recorded in the appropriate section of the eCRF' to further clarify eCRF reporting requirements.

Section 6.5.5 COPD Medication Restrictions on the Days of Scheduled Spirometry and FeNO Visits: updated instructions for Screening Visit 1 and Visit 2 to 'the screening lung function assessments must be postponed until the Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative (refer to SoA Table 1)' At the postponed Visit 1, the spirometry equipment will allow pre- and post-BD spirometry and FeNO (combined Visit 1 and Visit 2) to be performed. Visit 2 should be scheduled, if the post-BD spirometry was not done at the postponed Visit 1. Preferably, Visit 2 should be scheduled no later than 1 week after Visit 1 but the enrolment can be extended to accommodate additional waiting time required to obtain Visit 1 SARS-CoV-2 nasopharyngeal swab test result. The subject must meet the COPD medications restrictions in order to perform the lung assessments.'

This is to minimize the risk of a subject completing lung assessments with active COVID-19 infection.

Section 6.5.7 COPD Medication Restrictions at Centre Visits with Scheduled ECG Assessment: removed 'Medications do not have to be withheld for the ECG performed at any time between Visit 1 and Visit 2 inclusive' as medication wash out during enrolment is a requirement.

Section 8 Study Assessments and Procedures: added 'During COVID-19 pandemic, the suggested order of screening assessments is: Vital signs (starting with body temperature measurement), ePRO, blood draws and SARS-CoV-2 nasopharyngeal swab testing. The screening lung function and ECG assessments must be postponed and scheduled after Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative'. This is to minimize the risk of subjects completing study assessments with COVID-19 infection.

Section 8.1.2.1 Spirometry, General Requirements: added sub-section 'Applicable during COVID-19 pandemic: The screening lung function assessments must be performed only when Visit 1 SARS-CoV-2 nasopharyngeal swab test result is available and negative (refer to footnote a and footnote l under Table 1, section 1.1 and to section 6.5.5). SARS-CoV-2 testing should be performed prior to lung function assessments at subsequent visits, if required per local regulations and guidance. If SARS-CoV-2 testing is conducted, a negative result must be obtained before conducting visit assessments' This is to minimize the risk of a subject completing lung function assessments with active COVID-19 infection.

Section 8.1.2.2 Post-BD Spirometry: added 'postponed' to 'Visit 1' for clarification.

Section 8.1.3 FeNO: removed visit 1 from list of visits prior to randomization, for which the FeNO values will be unblinded for the sponsor.

Section 8.1.4 COPDCompEx: added 'systemic' replacing 'oral' to corticosteroids to further clarify medication type. Also, removed 'wheeze' as a diary variable as it is not used in the analysis of COPDCompEx.

Section 8.1.6.5 St. George's Respiratory Questionnaire (SGRQ) and Section 8.1.6.6 COPD Assessment Test (CAT): Removed 'during the COVID-19 pandemic due to local restrictions' and added reference to Appendix I.

Section 8.2.5 Vital Signs: added instructions that 'body temperature should be done as the first study assessment (at Visit 1 when ICF is obtained)' and 'Subject with fever (≥ 38°C; ≥ 100.4°F) suspected due to COVID-19 infection during screening or at randomization (Visit 3) should be screen failed (Exclusion criterion 38). IP should not be administered if the

subject is febrile (≥ 38°C; ≥ 100.4°F) or is suspected of having COVID-19. Refer to section 6.1.2'.

Section 8.2.9 Chest-X-ray, CT scan or MRI: section title update to 'Section 8.2.9 Chest-X-ray. The section was updated to 'a chest X-ray done during the screening period before randomization visit (Visit 3) is required to ensure there are no abnormal radiological findings as per exclusion criterion 14 and exclusion criterion 40.' This is to minimize the risk of enrolling subjects with COVID-19 pneumonia.

Section 8.2.11.2 SARS-CoV-2 testing: added a new section to describe tests that are applicable during the COVID-19 pandemic, for subjects enrolling into the study after recruitment is resumed and for subjects ongoing in the study.

Section 8.8.5 Sputum Induction:

updated to clarify spontaneous sputum may also be used as a secondary option for outcome measures if induced sputum is not permitted per local regulations or guidance during COVID-19 pandemic.

added 'additional local or national regulations or guidance must be followed for sputum processing during COVID-19 pandemic'.

Section 9.3 Populations for Analyses: revised PK analysis set description from 'all subjects who received at least one dose of tezepelumab and have PK blood samples…' to 'all subjects who received at least one dose of tezepelumab and have at least one detectable serum concentration post first dose…' to be consistent with other studies in tezepelumab clinical program.

Appendix H Abbreviations: added SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 20 and CDC (Centers for Disease Control and Prevention)

Appendix I Coronavirus (COVID-19) Pandemic Guidance:

Clarified that sputum and nasal samples will not be collected from subjects in treatment until the pandemic normalizes and AZ approves the continuation of sampling. Sputum and nasal sampling will be performed, if allowed per local regulations and guidance.

Added a new section I 1 to describe the pre-visit assessment applicable during COVID-19 pandemic.

Updated sections I 2, I 3 and I 4 to include telephone assessment of possible COVID-19 symptoms.

Added a new section I 6 to describe the benefit/risk assessment of re-starting recruitment during COVID-19 pandemic. Various typographical and grammatical corrections have been made.
Version 3.0, 26 May 2020 Changes to the protocol are summarized below.
Section 1.1 SoA, Table 1: Footnote b: clarified that screening phase can be extended up to 14 days to meet FeNO restrictions (refer to section 5.4). Footnote c: clarified that the sponsor and site will be blinded to the FeNO values for the whole study duration to minimize the possibility that changes in FeNO levels might unblind the subject, ie indicate to the site/sponsor that the subject was on tezepelumab rather than placebo. Footnote j: added that inactive/killed vaccinations e.g. influenzae should be withheld 3 weeks prior to EOT visit for patients in the sub study (if no safety concerns) as it might influence exploratory sputum analysis. Section 1.1 SoA, Table 2: Added 'Healthcare resource utilization' to Follow up visits 17 and 18 to correct a typographical error in the SoA. Footnote b: clarified that exacerbation (EXA) visit is an optional visit and may be initiated when patient experiences COPD exacerbation.' Footnote c: clarified that the sponsor and site will be blinded to the FeNO values for the whole study duration to minimize the possibility that changes in FeNO levels might unblind the subject, ie indicate to the site/sponsor that the subject was on tezepelumab rather than placebo. Footnote e: clarified that during COVID-19 pandemic, spirometry may not be completed as per local regulations and guidance. Footnote k: clarified that during COVID-19 pandemic, sputum and nasal samples will not be collected from subjects that have consented to the sub study until the pandemic stabilizes and AZ approves the continuation of sampling. This is to limit the possibility of COVID-19 spread to subjects and site staff.

Footnote l: clarified that during COVID-19 pandemic: IP administration can be performed at the subject's home or alternative location along with study assessments. This step is taken to limit subject exposure to COVID-19. Also, the laboratory assessments can be completed post IP administration, to allow additional time for processing of the safety samples at site according to the laboratory manual.

Added Footnote m: to clarify that during re-consenting of trial subjects during the COVID-19 pandemic, local/regional guidelines must be followed with regard to verbal informed consent. Pleases refer to Appendix I. Also, added 'COVID-19 addendum to ICF (if applicable)' as assessment to Table 2.

Added Footnote n: to clarify that during the COVID-19 pandemic for at home IP administration visits, where possible study assessments should be conducted according to the SoA. However, the qualified HCP is expected to collect a minimum information as detailed in Appendix I. This is to minimize the risk of subject exposure to COVID-19.

Added Footnote o: These assessments can be replaced by a phone visit during COVID-19 pandemic. Please refer to Appendix I. This is to limit the possibility of COVID-19 spread to subjects and site staff.

Section 1.2 Synopsis and Section 3 Objectives and Endpoints: Evaluating the effect of tezepelumab on the frequency, duration and severity of EXACT-PRO defined events has been added as an exploratory objective (with the rate of EXACT-PRO defined exacerbations and the EXACT-PRO defined exacerbation rate ratio (tezepelumab vs placebo) as the outcome variable and measure respectively). Previously these data were being recorded but not analysed.

Section 1.2 Synopsis and Section 4.1 Overall design, Section 6.3 Measures to minimize Bias: Corrected typo in the target of subjects based on eosinophils count to: approximately 20% of the subjects with ≥300 eosinophils/µL, 40% of the subjects between ≥150 to <300 eosinophils/µL and a maximum of approximately 40% of the subjects with <150 eosinophils/µL at enrolment.'

Section 1.2 Synopsis, Overall design and Section 4.1 Overall design: clarified that 'During the COVID-19 pandemic, sputum and nasal samples will not be collected from subjects in treatment phase, until the pandemic normalizes, and AZ approves the continuation of sampling. Please refer to Appendix I.' This is to limit the possibility of COVID-19 spread to subjects and site staff.

Section 4.1 Overall design:

Screening Period (Enrolment and Run-in): added ECG as assessment that cannot be performed during screening without meeting wash-out requirement due to ECG device settings to 'If the subject does not meet the COPD medications restrictions at Visit 1, the lung function assessments (Spirometry, FeNO) and ECG should be postponed and performed no later than one week after Visit 1.'.

Randomization, Treatment and Follow-up: clarified that 'If allowed by local/regional guidance during the COVID-19 pandemic, a phone call visit can replace an on-site visit and on-site IP administration can be replaced with home/alternative location IP administration. Patient must sign the COVID-19 addendum to informed consent form prior to starting these alternative options. If obtaining signed addendum is not feasible, patient can follow alternative options after verbal consenting. Please refer to Appendix I for details.' These steps are being taken to limit subject exposure to COVID-19 with clinic visits.

Randomization, Treatment and Follow-up: clarified that COPD exacerbation visit (EXA) is optional visit.

Section 4.1 Overall Design, Section 9.2 Sample Determination, 9.6 Interim Analysis: The futility analysis was originally planned to occur when 182 patients had been randomized. As a result of the pause in recruitment due to COVID-19, the futility analysis is now planned to occur when approximately 30% of information has been achieved. This time point has been chosen on the recommendation of the Independent Data Monitoring Committee (IDMC) chair.

Section 5.1 Inclusion 6: updated to clarify that in case of re-screening, historical COPD exacerbation from period within 2 to 52 weeks prior to re-screening Visit 1 should be included.

Section 5.1 Inclusion 8 and 18: updated to clarify that CAT score only based on ePRO questionnaire should be used for assessing patient eligibility.

Section 5.1 Inclusion 19: updated to clarify that only screening Visit 1 pre-BD result can be used for assessing FEV1 screening variability due to spirometer device settings 'Stable FEV1 during the screening period, defined as a change in pre-BD FEV1 ≤400 mL and/or ≤25% compared to baseline pre-BD (Visit 1) assessment' (i.e. Inclusion 19 requirements have not changed).

Section 5.4 Screen Failures and Re-screening:

Updated to clarify in which situations, the screening may be extended without prior approval form AstraZeneca Study Physician and added that 'Extension of the screening

period for any other reason will be allowed only upon approval of the AstraZeneca Study Physician.'

Added clarification that 'Subjects with respiratory infection (excluding pneumonia) NOT requiring antibiotics or antiviral medication during the screening period: May remain in screening and the screening period may be extended up to 14 days to allow subject to meet FeNO restrictions.'

Added guidance on how to proceed with re-screening of subjects that were screened failed due to the COVID-19 pandemic and were re-screened once since re-screening is only allowed once.

Section 6.1.2 Preparation/handling/storage/accountability, Dose Administration – added "Please Note: During the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration may be performed at the subject's home/alternative location by a qualified HCP. Please refer to Appendix I for further details" at the end of the section to accommodate for home/alternative location visits. This option is being included to limit subject exposure to COVID-19 with clinic visits.

Section 6.5 Concomitant Therapy Table Table 6:

SABA and SAMA combination products are added as 'Allowed for rescue medication and treatment of acute COPD exacerbation and prohibited if administered as maintenance medication or in a scheduled dose' as patients might be on SABA and SAMA combination product.

For omalizumab, denosumab or any other monoclonal or polyclonal antibody therapy, added clarification that medications are prohibited during the study even if the subject has discontinued IP.

For clarification, added Immunomodulators as prohibited medication to 'Any Immunomodulators and immunosuppressive medication (…)'. Also, updated restrictions conditions: medications 4 weeks after the last dose.

For inactive/killed vaccinations, added restriction '3 weeks prior to EOT visit for sub-study subjects only' as it might influence exploratory sputum analysis.

Section 6.5.5 COPD Medication Restrictions on the Days of Scheduled Spirometry and FeNO Visits:

For clarification, added note that screening (Visit 1 and Visit 2) and randomization (Visit 3) spirometry and FeNO are not allowed without proper medication wash out.

For clarification added FeNO in various places in the section to include with scheduled Spirometry assessments.

Section 6.5.7 COPD Medication Restrictions at Centre Visits with Scheduled ECG Assessment: For clarification added note that screening and randomization ECG are not allowed without proper medication wash out due to ECG device settings.

Section 8 Study Assessment and Procedures: Added 'Due to COVID-19 pandemic, it may not be possible to complete all study assessments, such as spirometry, according to SoA. Please refer to SoA and Appendix I for further details.' This is added to limit the risk of COVID-19 exposure to subject and site staff.

Section 8 Study Assessments and Procedures: Added 'Additional data to assess the impact of COVID-19 pandemic will be collected.'

Section 8.1.1.2 Duration of COPD Exacerbations:

For clarification, updated COPD exacerbation start date: 'The start date will be defined as the start date of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital admission, which occurs earlier.' by including hospital admission.

For clarification, updated COPD exacerbation stop date: 'The stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid and/or systemic antibiotic or hospital discharge, which occurs later.'

Section 8.1.1.3.2 Symptom Reporting: added clarification that 'If COPD exacerbation is associated with ePRO worsening alert, symptoms should not be reported in the COPD exacerbation eCRF. If COPD exacerbation is not associated with ePRO worsening alert, please refer to section 8.1.1.4 for further guidance'

Section 8.1.2.1 Spirometry, General Requirements: Added that 'During the COVID-19 pandemic, spirometry assessments should be performed only as allowed per local regulations and guidance.' This is to provide guidance on how to proceed with respect to Schedule of Activities during the COVID-19 pandemic.

Section 8.1.6 Patient Reported Outcomes: Added clarification that subject can be trained at home use of eDiary also at Visit 1, if Visit 1 and Visit 2 are combined.

Section 8.1.6.5 St. George's Respiratory Questionnaire (SGRQ): added clarification 'If the subject is not able to visit the site during the COVID-19 pandemic due to local restrictions, SGRQ may be completed by the subject at home/alternative location.'

Section 8.1.6.6 COPD Assessment Test (CAT): added clarification 'If the subject is not able to visit the site during the COVID-19 pandemic due to local restrictions, CAT may be completed by the subject at home/alternative location.'

Section 8.2.2 Clinical Safety Laboratory Assessments: added clarification 'During the COVID-19 pandemic, it may not be possible to collect clinical safety laboratory tests at the site due to local restriction. If the subject has re-consented to home/alternative location IP administration visits, it is possible that the HCP can collect clinical safety laboratory tests in the subject's home/alternative location.' This change is to minimize the subject's risk of COVID-19 exposure with clinic visits.

Section 8.3.2 Time Period and Frequency for Collecting AE and SAE Information: Clarified that Adverse Events and Serious Adverse Events have to be collected from the time of informed consent and throughout the duration of the study. The AE/SAE collection requirements have not changed.

Section 8.7.1 Optional Exploratory Genetic Sample, Section 8.8.1 Storage, Re-use and Destruction of Biomarker Samples: For clarification added that the results of any analyses will not be reported in the CSR itself but as an addendum, or separately in a scientific report or publication for clarification.

Section 8.8.4 Nasal Epithelial Cell and Sputum Cell Transcriptomics: added clarification 'During the COVID-19 pandemic, nasal and sputum samples will not be collected from treatment subjects to minimize the risk of subject and site staff exposure to the virus.

Section 8.8.5 Sputum Induction: Added that during the COVID-19 pandemic, sputum samples will not be collected from subjects in treatment phase to reduce the risk of subject and site staff exposure to the virus.

Section 8.8.6 Nasal Lining Fluid: Added that during the COVID-19 pandemic, nasal samples will not be collected from subjects in treatment phase to reduce the risk of subject and site staff exposure to the virus.

Section 9 Statistical considerations: For clarification of the analysis plan added that additional estimands (Section 9.2.1) and additional analyses (Section 9.5) to assess the impact of COVID-19 will be detailed in the SAP.

Appendix A 3 Informed Consent Process: Added 'During the COVID-19 pandemic, re-consenting of subjects must follow local/regional guidelines with regard to informed consent. It is critical that where written re-consent cannot be obtained, and local and regional guidance allows, the subject's verbal consent via phone or teleconference is obtained before conducting any patient related changes implemented during COVID-19

pandemic. Confirmation of subject's re-consent needs to be documented in the source documents.' This step is taken to minimize the risk of subject exposure to COVID-19 with site visits. Appendix H Table of Abbreviations: For clarification added COVID-19 and TPV. Appendix I Coronavirus (COVID-19) Pandemic Guidance: Added Appendix I to describe in more detail the changes made during the COVID-19 pandemic. Various typographical and grammatical corrections have been made.
Version 2.0, 16 December 2019 Changes to the protocol are summarized below.
Section 1.1, SoA – Table 1- Schedule of Assessments: corrected visit windows days. Section 1.1, SoA – Table 1- Schedule of Assessment, footnotes: 'a': Updated to clarify that Visit 1 and Visit 2 can occur on the same day when all restrictions to medications for Visit 1 assessments are met, not only spirometry. Added wording clarifying that if the medication restrictions are not meet at Visit 1 then the lung function assessments (Spirometry and FeNO) should be postponed and done within a week after Visit 1. At the postponed visit, spirometry equipment will allow to combined Visit 1 and Visit 2 pre-BD and post BD Spirometry. The remaining Table 1 (Visit 1 and Visit 2) assessments should be done at Visit 1, if combined Visit 1 and Visit 2 spirometry is planned at the postponed visit. 'b': Updated to align with changes made in Section 5.4 as patients with respiratory infection may remain in screening and the run-in period may be extended up to 14 days to allow the completion of therapy if deemed suitable by the Investigator. 'c': Added 'Visit 1' to clarify that sponsor is also unblinded to FeNO values from enrolment (Visit 1) when Visit 1 and Visit 2 are combined; added 'The site will be blinded to the FeNO values for the whole study duration,' to clarify that sites do not have access to FeNO central results for the whole study duration. 'g': Added Magnetic Resonance Imaging (MRI) to 'If a historical (not older than 6 months) chest x-ray (posterior/ anterior and lateral) is not available, historical (not older than 6 months) Computed Tomography (CT) scan/ MRI is acceptable,' as an acceptable historical MRI could replace chest x-ray during screening.

'f': The order of assessments during the screening period was changed from 'The suggested order of assessments in the clinic should occur as follows: Patient Reported Outcomes (PRO), Vitals, ECG, blood draw, FeNO and spirometry to 'The suggested order of assessments in the clinic: Vital Signs, ECG, FeNO, spirometry and blood draw,' as the blood sampling is not required if the patient does not meet spirometry eligibility criteria.

'h': Added 'immunoglobulin' as sponsor and site are blinded to immunoglobulin results from the central laboratory results except at screening visits, for any repeat testing that is performed during the screening and at Visit 3 prior to IP administration.

'j': Updated to clarify that 'Pneumococcal vaccination can be done at Visit 1 or at any time prior to randomization' and 'Annual influenza vaccination can be done at any other time throughout the study (except for within ±7 days of IP administration) at the discretion of Investigator' and added reference to Section 8.2.10.

Section 1.1, SoA – Table 2 - Schedule of Assessments:

Removed Healthcare resource utilization assessment from COPD Exacerbation (EXA) visit as data is not to be captured in the case report form.

Under section 'Subset of Subjects Participating in Sputum and Nasal Lining Fluid/Epithelial Cells Sub Studies Only' added assessment 'Sputum post-BD spirometry' that is part of the sputum sub-study and is conducted to ensure patient safety during the induction as described in Section 8.1.2.3 and in the sputum manual.

'NOTE' was updated from 'The suggested order of assessments to be completed before IP administration should be as follows: ePRO, Vital Signs, ECG, Blood draws, FeNO, and Spirometry' to 'The suggested order of assessments to be completed prior IP administration: ePRO, Vital Signs, ECG, FeNO, Spirometry and Blood draws' to be consistent with Table 1 footnote 'f'.

Section 1.1, SoA – Table 2- Schedule of Assessments, footnotes:

'b': Added missing reference to Section 8.1.1.5.

'c': Updated to clarify that sponsor is also unblinded to FeNO values from enrolment (Visit 1) when Visit 1 and Visit 2 are combined. Also, added 'The site will be blinded to the FeNO values for the whole study duration' to clarify that the sites should not have access to FeNO central results.

'f': Footnote f is removed from IPD visit as pre- and post-BD spirometry is required for all subjects at IPD visit, and not only for subjects in the sub study.

‘g’: Amended to clarify that ‘sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (Visit 1 and 2), any repeat testing that is performed during the screen visits, and at Visit 3 prior to IP administration.’

‘h’ was removed as footnotes ‘g’ and ‘h’ were merged.

‘k’: Amended to clarify that if subject is not able to produce sputum (spontaneous or induced) at Visit 3, then subject should be withdrawn from the sub-study and nasal samples should be discarded.

Section 1.2 Synopsis: Added International coordinating investigator details.

Section 1.2 Synopsis and Section 3. Objectives and Endpoints, Safety Objectives:

Removed ’Physical examinations’ from Safety Endpoints/Variables as specific details from the assessment will not be captured in the case report form.

Added ‘participating in sub-study’ in ‘To evaluate the effect of tezepelumab on sputum biomarkers, sputum cell counts and sputum microbiome in subjects participating in sub-study at baseline, end of treatment, and at the start of all exacerbations’ to specify the subgroup.

Section 1.2 Synopsis, Section 4.1 Overall design, Section 6.3 Measures to minimize Bias: Updated the target of subjects based on eosinophils count to include approximately 20% of the subjects with >300 eosinophils/µL as ‘Approximately 20% of the subjects will be targeted to have >300 eosinophils/µL, 40% of the subjects between ≥150 to 300 eosinophils/µL and a maximum of approximately 40% of the subjects with <150 eosinophils/µL at enrolment’ to improve distribution of subjects across the range of baseline eosinophils levels.

Section 2.1 Synopsis and Section 8.1.6.5: Updated from ‘proportion of subjects with at least 4 units changed in SGRQ’ to ‘proportion of subjects with at least 4 units decrease in SGRQ’ to clarify the clinically significant change.

Section 4.1 Overall design:

Changed section heading from ‘Screening Period’ to ‘Screening Period (Enrolment and Run-in)’ and added description of enrolment and run-in visits based on Table 1.

Removed ‘In case of an exacerbation within 2 weeks of randomization; run-in period can be extended to allow for recovery,’ as instructions on how to manage a COPD exacerbation are provided in Section 5.4 Screen Failure and Re-screening.

Added ‘If the subject does not meet the COPD medications restrictions at Visit 1, the lung function assessments (Spirometry, FeNO) should be postponed and performed no later than one week after Visit 1. At the postponed visit, spirometry equipment will allow to combined Visit 1 and Visit 2 pre-BD and post BD Spirometry. The remaining Table 1 (Visit 1 and Visit 2) assessments should be done at Visit 1, if combined Visit 1 and Visit 2 spirometry is planned at the postponed visit.’ clarification from Table 1 footnote ‘a’.

Added ‘COPD disease state’ in ’Acceptable Documentation for COPD disease state and Historical COPD Exacerbations and Background Therapy’ to clarify that the section defines the acceptable documentation for COPD disease.

Changed section heading from ‘Treatment’ to ‘Randomization, Treatment and Follow-up’ to align with section content.

Removed ‘If the EXA visit was completed within +/-5 days of as scheduled visit, the same assessment does not need to be repeated at the next scheduled visit, unless at the PI’s discretion’ and added instead reference to Section 8.1.1.5 COPD Exacerbation Visit.

Section 5.1 Inclusion criteria:

#5: Added ‘(Visit 1 if Visit 1 and 2 are combined)’ as the inclusion is applicable at Visit 1 if Visit 1 and Visit 2 are combined.

#6: Added reference ‘See Section 4.1 for required source documentation for this inclusion.’

#7: Removed the reference, ‘Equivalent ICS doses as detailed in Appendix F’ as Appendix F was removed as data included in the Appendix were from GINA Asthma guidance 2018 and were not in congruence with ICS doses for COPD.

#7: Added ‘If an Investigator decides to switch a subject who is on an ICS in a separate single device to a fixed-dose combination device therapy, this should be done at Visit 1 and the ICS component must remain at the same dose and schedule as used in the 3 months prior to Visit 1 (provided dose and regimen are locally approved for COPD)’ from Table 5 for Background (maintenance) COPD medications details pertain to Inclusion #7.

#12: Added Magnetic Resonance Imaging (MRI) and correct double negative wording as it should read that ‘Chest x-ray, computed tomography (CT) scan or Magnetic Resonance

Imaging (MRI) of the chest/lungs must not show suspected lung pathology that precludes the patient's ability to complete the study.'

#19: Added 'pre-BD' to clarify that stable pre-BD FEV1 is expected during the run-in period; updated the run-in period baseline pre-BD definition from 'Visit 1' to 'Visit 1 if visits are combined or Visit 2' as Visit 1 or Visit 2 pre-BD FEV1 result can be used as baseline.

Section 5.2 Exclusion criteria:

#1: Added 'as judged by Investigator' to clarify that patients with clinically important pulmonary disease other than COPD in Investigator's judgement should not be enrolled if it may put the patient at risk or negatively affect the outcome of the study.

#6: Changed from 'History of clinically significant infection (excluding pneumonia), acute upper or lower respiratory infection, requiring antibiotics or antiviral medication within 14 days prior to enrolment (Visit 1) or during the screening period based on the last day of antibiotic/antiviral treatment or hospitalization date, whatever occurred later or during the enrolment and screening' to 'History of clinically significant infection (excluding pneumonia), acute upper or lower respiratory infection, requiring antibiotics or antiviral medication within 14 days prior to enrolment (Visit 1) or 14 days prior to randomization (Visit 3), based on the last day of antibiotic/antiviral treatment or hospitalization date, whatever occurred later,' as patients with respiratory infection can continue with screening as per updated Section 5.4.

#16: Added reference to Section 6.5.1.

#20: Added 'immunoglobulin' to 'Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1)' as we assess the effect of tezepelumab on total serum immunoglobulins in exploratory analysis.

#24: Updated to 'Patients who received ≥6 months of antibiotics treatment (including macrolides or other antibiotic) in the previous year must have a hearing assessment performed as per local standard of care within 3 months prior to randomization' to further clarify when the hearing assessment is applicable.

#32: Added 'with or without ongoing treatment' to further clarify that patients with evidence of active liver disease even on ongoing treatment should be excluded.

Section 5.3.2 Alcohol, Tobacco and Other and Section 8.2.2 Smoking Status: Removed 'Any changes in smoking status between Visit 1 (enrolment) and Visit 3 (randomization) will result in screen failure' as change of smoking status is acceptable throughout the study.

Section 5.3.2 Alcohol, Tobacco and Other and Section 8.1.2.1 General requirements: Added 'Subjects should not smoke on day(s) prior to lung function assessments at the site' to clarify that current smokers should withhold smoking until the lung assessments are completed.

Section 5.4 Screen Failures and Re-screening: Updated 'Subjects with respiratory infection (excluding pneumonia) requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the run-in period: May remain in screening and the run-in period may be extended up to 14 days to allow for the completion of therapy if deemed suitable by the Investigator' to allow patients with respiratory infection to continue with enrolment and be randomized if they managed to complete the treatment within allowed run-in window.

Section 6.1.2 Preparation/Handling/Storage/Accountability, Dose administration: Added clarification that 'IP should be equilibrated to room temperature for at least 60 minutes prior to administration' and that 'The second injection should be administered immediately after the first injection.'

Section 6.3 Measures to Minimise Bias, Randomization and Blinding: Added 'or re-screening Visit 1' to reflect that number of historical exacerbations should be revised in case of re-screening.

Section 6.5 Table 5 Allowed, Restricted and Prohibited Medications:

'Background (maintenance) COPD medications' details: updated from 'The dose of background (maintenance) COPD medications (ICS/LABA/LAMA) should be stable 3 months prior to V1 and throughout the study' to 'The dose of ICS should be stable 3 months prior to V1 and throughout the study' as only ICS stable dose is required 3 months prior to V1 and throughout the study.

'Mucolytics' details: removed 'Allowed if not containing ephedrine' as 'Medications containing ephedrine' were added to Table 5 as prohibited medications.

'Antitussive prn' details: removed 'Allowed if not containing ephedrine and/or opiates and/or other bronchodilator' from as Medications containing ephedrine' were added to Table 5 as prohibited medications.

Updated from 'Antihistamines prn not containing ephedrine or bronchodilators' to 'Antihistamines prn' and removed from details 'Allowed if not containing ephedrine or bronchodilators' as 'Medications containing ephedrine' were added to Table 5 as prohibited medications.

Added ‘Dermal topical steroids, intra-articular, nasal steroids, topical ophthalmic and otic corticosteroids’ to clarify other allowed medications.

Added ‘Immunoglobulin and blood products’ as prohibited medications within 30 days prior to enrolment (Visit 1) as per Exclusion 20 and throughout the treatment period.

added ‘Medications containing ephedrine’ as prohibited medications from Visit 3 throughout the treatment period.

for ‘Allergen immunotherapy,’ added ‘run-in’ to ‘Allowed, if on stable therapy for at least 2 months prior to date of Visit 1 with no anticipated change during the run-in and the treatment period’ to clarify that no change is anticipated also during the run-in.

‘Inactive/killed vaccinations’ details: changed from ‘within 5 days before and after any IP dosing visit’ to ‘within 7 days before or after any IP dosing visit’ to correct inconsistency between Table 5 and Table 1 footnote ‘j’.

‘Long term oxygen therapy (LTOT)’ status changed from ‘Prohibited’ to ‘Restricted’ and details were added, ‘During the treatment phase, any increase in maintenance oxygen therapy up to 4 L/min is allowed, based on investigator’s judgement’ in order to clarify that the increase in maintenance oxygen therapy may be allowed under specific circumstances.

Added ‘Investigational non-biologic products’ as prohibited medications within 30 days or 5 half-lives, whichever is longer prior to Visit 1 and during the study as already prohibited per Exclusion Criterion 22.

Section 6.5.5, COPD Medication Restrictions on the Days of Scheduled Spirometry Visits:

Updated the screening section to clarify that for subject who does not meet the COPD medications restrictions at Visit 1, the spirometry should be postponed no later than 1 week after Visit 1 to allow the patient to follow the COPD medications restrictions. At postponed visit, the spirometry equipment will allow to combined Visit 1 and Visit 2 pre-BD and post BD Spirometry. The remaining Table 1 (Visit 1 and Visit 2) assessments should be done at Visit 1, if combined Visit 1 and Visit 2 spirometry is planned at the postponed visit.’

Removed ‘preferably’ from ‘(preferably should be at least 12 hours prior to the assessment for twice daily medication and for 24 hours prior to the assessment for once daily medications)’ as there is a requirement to withhold triple inhaled medications at least 12 hours for twice daily medications and for 24 hours for once daily medications.

To sub-section ‘Treatment Visits 3-15’ and to Section 8.1.2.1, added ‘or sputum post-BD spirograms (for patients participating in sputum sub-study’ to clarify that for subject

participating in the sputum sub-study, the usual COPD medications may be administered following completion of sputum post-BD assessment.

Added 'The spirometry without proper medication washout is not allowed during the screening period (between Visit 1 and Visit 2 inclusive) and at Randomization Visit 3' to clarify the medication conditions for the screening and randomizations visits.

Section 7.1 Discontinuation of Study Treatment: added 'eosinophilia (≥5% based on local laboratory results)' as sponsor and site staff are blinded to central lab results after IP administration at Visit 3.

Section 7.3.2, Discontinuation or suspension of entire study and site closure – Updated the title of this section and added additional comments about site closure. The rationale for this change is to specify the conditions for closure of sites during and after study completion.

Section 8.1.1.2 'Duration of COPD exacerbations': Added reference to Section 8.1.1.1.

Section 8.1.1.3.1 'COPD Exacerbation eCRF':

Removed 'The investigator should record all pertinent findings and symptoms associated with the exacerbation event and their duration in source documents and in the COPD exacerbation' as symptoms reporting are properly described in Section 8.1.1.3.2 Symptom Reporting.

Added: 'The investigator should record the COPD exacerbation that meets the COPD exacerbation definition (refer to Section 8.1.1) in the COPD exacerbation eCRF (COPDEX)' to clarify when COPD exacerbation should be reported in COPDEX.

Updated the rule for reporting the serious COPD exacerbation, 'The serious COPD exacerbation should be recorded in AE/SAE eCRF and in COPDEX. Other COPD related SAEs should be recorded on the AE/SAE eCRF' to clarify the rules.

Section 8.1.1.3.2 'Symptom reporting': Added timeframe of 5 working days for investigator to document the action taken after an e-diary alert has been triggered.

Added 'Section 8.1.1.5- COPD Exacerbation visit': To describe the COPD exacerbation (EXA) visit from SoA Table 2.

Section 8.1.2.1 General requirements:

Added restrictions for subjects not to smoke/vape on the same day(s) prior to the lung function test is being performed;

Added reference to Section 8.1.2.3.

Section 8.1.2.2 Post-BD Spirometry: The revised text reads, 'Endpoint maximal bronchodilation will be induced using albuterol (90µg metered dose) or salbutamol (100µg metered dose) with or without a spacer device up to a maximum of 4 inhalations administrated between 15 and 45 minutes of the final pre-BD spirometry measurement. SABA administration should start at least 15 minutes after final pre-BD spirometry and should end no later than 45 minutes after final pre-BD spirometry. Post-BD spirometry will be performed 15-30 minutes after last SABA inhalation' to clarify SABA administration details for Post-BD spirometry.'

Added Section '8.1.2.3 Sputum post-BD Spirometry': Sputum post-BD spirometry should be performed per schedule in Table 2 (Visit 3, Visit 16, IPD and EXA) as part of induced sputum procedures if subject is participating in the sputum sub study, after post-BD spirometry (refer to Section 8.1.2.2). It is conducted solely to ensure patient safety in inducing sputum and results will neither be captured for the eCRF, nor for study endpoints. More details will be provided in the sputum sub-study manual to clarify assessment applicability and purpose.

Section 8.1.3 FeNO: Removed 'including ICS/LABA' and added reference to Section 6.5.5. The inhaled BDs should be withheld for the effect duration specific to the BD as described in the Section 6.5.5. Updated to clarify that sponsor is unblinded to FeNO values prior to randomization and blinded for values post-randomization. Sites will be blinded to FeNO values for the whole study duration.

Section 8.2.1 Clinical Safety Laboratory Assessments, Table 7 Laboratory Safety Variables: Added a footnote with clarification on the urinalysis dipstick and added instruction on how site should manage reporting of clinically significant results as, 'Urinalysis (Dipstick) central laboratory report will contain results from variables as listed in the laboratory manual, however only for variables U-Hb/Erythrocytes/Blood, U-Protein/Albumin and U-Glucose is required confirmation in the laboratory eCRF module if the result is clinically significant. If there are any clinically significant results from other variables, it will be the investigator decision to document them in the eCRF as an AE.'

Section 8.2.7 Supplemental Oxygen (O2): Added eCRF reporting instruction, 'Use of oxygen should be recorded as a concomitant medication in the eCRF.'

Section 8.2.9: Updated section, 'Chest X-ray, CT Scan or MRI' to include MRI as an acceptable historical scan.

Section 8.3.2 Time Period and Frequency for Collecting AE and SAE Information: Updated to clarify that Adverse Events (AEs) are to be collected only for randomized patients and

Serious Adverse Events (SAEs) should be recorded and reported from the time of signing of ICF throughout the duration of the study for all patients.

Section 8.8.4 Nasal Epithelial Cell and Sputum Cell Transcriptomics and Section 8.8.5 Sputum Induction: Added 'In a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before spontaneous/sputum induction' to clarify that the assessment is only applicable for patients participating in the sub-study and the nasal sampling should be done prior to sputum sampling. Also added 'If subject is not able to produce sputum (spontaneous or induced) at Visit 3 then subject should be withdrawn from the sub-study and nasal samples should be discarded.' Nasal samples will not be analyzed if the subject cannot produce sputum sample at Visit 3.

Section 8.8.6 Nasal Lining Fluid: Added 'In a subset of subjects only participating in the sub-study. If sputum and nasal collections occur at the same visit, nasal sampling should occur before spontaneous/sputum induction' to clarify that assessment is only applicable for patients participating in sub-study and the nasal sampling should be done prior to sputum sampling.

Section 9.2 Sample Size Determination: Added 'In the absence of the interim analysis for futility, this design would provide 81.2% power, and only 136 subjects per treatment arm would be required for 80% power. This power statement accounts for the power loss associated with the futility interim analysis that will occur when 182 subjects have been randomized. In simulated results, 1.2% of simulated trials were stopped early for futility but would have been successful at the final analysis of the primary endpoint had they been allowed to continue. Therefore, the overall power for this trial accounting for the interim analysis is 80%.' This section was added to explain how the sample size was adjusted to account for the futility analysis, so that the sample size calculations could be fully reconstructed.

Section 9.4.2.1 Exacerbation rate: Added 'The number of days that the subject experiences an exacerbation during the follow-up time, including the subsequent 7 days (when a further exacerbation would not be considered a separate event (and if within the follow-up time) will be subtracted from the follow-up time to give the time at risk of exacerbation' and updated the formula to calculate the annual exacerbation rate to be, 'Annual exacerbation rate=Number of exacerbations*365.25 / (Time at Risk of Exacerbation).' Using time at risk rather than total follow-up time (i.e. taking into account the duration of exacerbation & recovery) when estimating annual exacerbation rates, can avoid an under-estimation of the treatment effect.

Section 9.5.2.1 Primary Analysis Methods and Section 9.4.2.1 Exacerbation rate: Amended from 'corresponding follow up time' to 'corresponding time at risk of exacerbation'. Appendix A1, Regulatory and Ethical Considerations: Added Regulatory Reporting Requirements for SAEs in accordance with the European Directive 2001/20/EC. Appendix F Maintenance Therapy Equivalence Table: Appendix F removed as data included in the appendix were from GINA Asthma guidance 2018 and were not in congruence with ICS doses for COPD.
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