Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00013
Version	4.0
Date	30 Apr 2020

A Phase 2, Randomized, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults with Inadequately Controlled Asthma on Inhaled Corticosteroids and at least one additional asthma controller (CASCADE)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2018-002069-21

VERSION HISTORY

Version 4.0, 30 Apr 2020 Changes to the protocol are summarized below
For entire CSP - Updated “From baseline to Week 28” to “from baseline to end of treatment visit (EOT) due to the possibility of additional visits during COVID-19 pandemic Secton 1.1, SoA, Table 1, footnote #3 – Added “During the COVID-19 pandemic unscheduled visits may occur so that sites may perform EOT assessments 4 weeks after last dose of IP at either week 28, 32, 36, 40, 44 or 48(as needed) until the sites are able to resume the EOT assessments." This change is to minimize the risk for subjects being exposed to SARS-CoV-2 with these visits during the pandemic Section 1.1, SoA, Table 1, footnote # 8 – Added “During the COVID-19 pandemic, recording, collecting and dispensing will continue once administration of extra dosing is implemented” to accommodate for extra visits Section 1.1, SoA, Table 1 – Added footnote ‘18’ – “During the COVID-19 pandemic an additional 1 to 6 IP doses may be administered to subjects during unscheduled visits at weeks 28, 32, 36, 40, 44 and 48(as needed) until the sites are able to resume performing all EOT study assessments, including bronchoscopies. All assessments during the unscheduled visit may not be necessarily completed. Please refer to appendix J.” This change is being made because some sites are not able to perform research related bronchoscopies during the COVID-19 pandemic. The change will enable subjects to continue dosing with IP until sites are able to perform bronchoscopy for the EOT visit during the COVID-19 pandemic Section 1.1, SoA, Table 1 – Added “Asterix *** During the COVID-19 pandemic unscheduled visits may occur so that sites may perform EOT assessments 4 weeks after last dose of IP at either week 28, 32, 36, 40, 44 or 48 (as needed) until the sites are able to resume the EOT assessments.” This change is also being made because sites are not able to perform research related bronchoscopies during the COVID-19 pandemic Section 1.1, SoA, Table 1 – Added “X” to include healthcare resource utilization, Urine pregnancy test (dipstick) and distribution and collection of paper diary to the unscheduled visit column. This is to collect/distribute during additional visits during the COVID-19 pandemic Section 1.1, SoA, Table 1 – Under Table 1 added guidance on how to proceed with respect to Schedule of Activities during the Covid-19 pandemic to ensure the safety of the study subjects, to maintain compliance with GCP and to minimize risks to data integrity

Section 1.2, Synopsis, Secondary Objective # 3 – Added "determined by RNAseq of bronchial brushings at baseline" to the end of the sentence under outcome variable to clarify the methodology for determining the T2 status

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Synopsis 1.2, Number of Subjects, - Changed the eosinophil count stratification criteria to match the program specified criteria: Changed the medium group to be *150 - < 300 cells/µL instead of 150 - 300 cells/µL* and the high group to be ≥ *300 cells/µL instead of > 300* at Visit 1 to correct the typographical error and to align with IXRS

Section 1.2, Treatments and treatment duration – Added "(or later due to COVID-19 pandemic)" near the end of the paragraph for clarity

Section 1.2, Synopsis, Treatments and treatment duration, - Added "**Please note**: During the COVID-19 pandemic, the treatment period may be extended and therefore subjects may be given 1 to 6 doses (as needed) every 4 weeks for a longer period than initially planned (please refer to Appendix J). For the last follow up visit, a phone call visit can replace an

on-site visit. Please refer to Appendix J" This change is being made because sites are unable to perform research bronchoscopies during the COVID-19 pandemic. Additional treatments will allow subjects to receive IP up until 4 weeks before the EOT visit and bronchoscopy

Section 1.2, Statistical methods, - Added "During the COVID-19 pandemic, all subjects with EOT assessments performed after unscheduled visits will be summarized and analyzed together with all subjects with EOT assessments performed during the scheduled EOT visit at week 28 and will be reported as having completed the EOT assessments" Please refer to Appendix J. This change is to accommodate for extra visits to minimize the risk for subjects during the COVID-19 pandemic

Section 1.2, Statistical methods, - Changed the eosinophil count stratification criteria to match the program specified criteria: Changed the medium group to be *150 - < 300 cells/µL instead of 150 - 300 cells/µL* and the high group to be ≥ *300 cells/µL instead of > 300* at Visit 1 to correct the typographical error and to align with IXRS

Section 1.3, Schema, Figure 1, Study Design – Week 28 is now EOT and Week 40 is now EOS. Figure has been updated to align with implemented changes during COVID-19 (ie) extra dosing

Section 3, Objectives and Endpoints, Secondary Objective #3 - Added "determined by RNAseq of bronchial brushings at baseline" to the end of the sentence under outcome variable to clarify the methodology for determining the T2 status

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Section 4.1, Overall Design – Added "**Please note:** During the COVID-19 pandemic, there is an option for patients to have an extra dose every 4 weeks up to 6 additional doses, as needed. (please refer to Appendix J). For the last follow up visit, a phone call visit can replace an on-site visit. Please refer to Appendix J

Section 4.1, Overall Design – Changed "activities" to "Spectrum" in the first sentence of the 6th paragraph to provide more clarity to the sentence

Section 4.1, Overall Design - Changed the eosinophil count stratification criteria to match the program specified criteria: Changed the medium group to be *150 - < 300 cells/µL instead of 150 - 300 cells/µL* and the high group to be ≥ *300 cells/µL instead of > 300* at Visit 1 to correct the typographical error and to align with IXRS

Section 5.1, Inclusion Criteria - Under Inclusion #2 added wording that outlines re-consenting of subjects during the COVID-19 pandemic to accommodate the changes made to the protocol

Section 6.2, Preparation/handling/storage/accountability, Dose Administration – Added "**Please Note: During the COVID-19 pandemic, if allowed by local/regional guidelines, IP preparation and administration can be performed at the subject's home by a qualified HCP. Please refer to Appendix J for further details"** at the end of the section to accommodate for home visits

Section 6.2, Preparation/handling/storage/accountability, Dose Administration, Table 4 - Investigational product dose preparation – Added "2 or" within footnote as pertaining to the syringe size

Section 6.3, Measure to minimize bias: randomization and blinding, Methods for assigning treatment groups - Changed the eosinophil count stratification criteria to match the program specified criteria: Changed the medium group to be *150 - < 300 cells/µL instead of 150 - 300 cells/µL* and the high group to be ≥ *300 cells/µL instead of > 300* at Visit 1 to correct the typographical error and to align with IXRS

Section 6.6, Dose Modification - Added "During the COVID-19 pandemic an additional 1-6 IP doses may be administered to subjects during unscheduled visits at weeks 28, 32, 36, 40, 44 and 48 (as needed) until the sites are able to resume performing all study assessments,

including bronchoscopies, in accordance to local regulations/guidelines. Please refer to Appendix J"

Section 6.7, Treatment after the end of the study – Changed "Subjects who complete week 40 should be given standard of care at the discretion of the Investigator" to "Subjects who complete the study should be given standard of care at the discretion of the Investigator" as there may be additional weeks during the COVID-19 Pandemic

Section 7.1.1, Procedures for discontinuation of study treatment – Point # 2 and # 3 – Added "(or later due to COVID-19 pandemic)" near the end of the paragraph

Section 7.1.1, Procedures for discontinuation of study treatment – Added "(or later due to COVID-19 pandemic)" at the end of the sentence in the first paragraph

Section 7.1.1, Procedures for discontinuation of study treatment – Added "or had an EOT visit date greater than 12 weeks after date of last dose of IP" to paragraph as some patients will now be receiving additional doses beyond the dose of week 24 during COVID-19 pandemic

Section 7.1.1, Procedures for discontinuation of study treatment – Added "For more information related to COVID-19 please refer to eCRF instructions" as the last sentence of the section for more clarity on instructions

Section 7.3, Withdrawal from the Study – Added "For more information related to COVID-19 please refer to eCRF instructions" near the end of the section for more clarity on eCRF instructions

Section 8.0, Study Assessment and Procedures – Added "Additional data to assess the impact of COVID-19 pandemic will be collected." at the end of paragraph # 2

Section 8.1.18.1, Paper Diary – Added "**Please note:** During the COVID-19 pandemic, once extra dosing and/or home IP administration is implemented, recording, collection, and dispensation of the subject's paper diaries will continue" to accommodate for extra visits

Section 8.8, Biomarkers, - Changed " 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. To "Selected results of this biomarker research may be reported in the CSR (as per section 8.1.6). Biomarkers not reported in the CSR may be reported in an addendum, or separately in a scientific report or publication." since there are certain biomarkers that may be included in the CSR

Section 8.8.3, Transcriptomics – Changed "preparation" to "collection" in second sentence to provide more clarity

Section 9.2, Populations for analyses, Table 8, Evaluable Analysis Set - Changed the description from "All subjects randomized to study treatment and completed at least 20 weeks of study treatment" to "All subjects randomized to study treatment who completed at least 20 weeks of study treatment and had an EOT visit date not greater than 8 weeks after date of last dose of IP" This change is that some patients will now be receiving additional doses beyond the dose of week 24 during COVID-19 pandemic

Section 9.3.2, Primary outcome measure, Removed "week 28 (Visit 11(V11)) i.e (V11/V3b)" added "EOT/V3b" due to the possibility of additional visits

Section 9.3.4.2, Effect on large airways remodeling – Added "structure and function" to the exploratory objective to provide more clarity and specificity

Section 9.3.4.2, Effect on large airways remodeling – Removed bullet point #2 "Large airway dimensions and estimated airway resistance determined from computed tomography (CT)" and bullet point # 4 "Airway resistance for airway generations 3, 4 and 5 estimated based on lumen area" to clarify the analysis and remove duplication

Section 9.3.4.2, Effect on large airways remodeling – Removed the following wording from bullet point # 3 "segmental, sub-segmental, sub sub-segmental" to simplify the explanation for analysis

Section 9.3.4.2, Effect on large airways remodeling - Added "wall thickness", "and 3 & 4 combined" and "as evaluated by computed tomography (CT)"to bullet point # 3 to provide more clarity and specificity for these variables

Section 9.3.4.2, Effect on large airways remodeling – added Bullet point # 4 "Mucus score as evaluated by CT" as another variable for analysis

Section 9.3.4.3, Effect on small airways obstruction – Removed bullet point #2 "Regional matching of the inspiratory/expiratory CT scans to assess air trapping/small airway obstruction" as it will be replaced with fSAD

Section 9.3.4.3, Effect on small airways obstruction – Added bullet point # 2 "Functional small airway disease (fSAD), air trapping index and expiratory-to-inspiratory (E/I) ratio as evaluated by CT" as another variable for analysis

Section 9.3.4.8, Pharmacokinetics and immunogenicity of tezepelumab – Changed first sentence in second paragraph from **"**ADA status (positive vs. negative) at each visit will be summarized by treatment group" to "ADA status(positive vs. negative) and titers at

specified visits will be summarized by treatment group" because the ADA assessment is not done for every visit

Section 9.4, Statistical Analyses – Added "EOT assessments done at either week 28 or later will be discussed in the Statistical Analysis Plan (SAP)." to specify how analyses will be conducted with subjects receiving extra doses

Section 9.4.1, Efficacy analyses – Removed "For the primary endpoints only, only those subjects who complete at least 20 weeks of treatment will be included in the analysis" from the second paragraph, as some subjects will have additional doses after week 28 during the COVID-19 pandemic

Section 9.4.2, Analysis of the primary variable(s) - Changed the eosinophil count stratification criteria to match the program specified criteria: Changed the medium group to be *150 - < 300 cells/µL instead of 150 - 300 cells/µL* and the high group to be ≥ *300 cells/µL instead of > 300* at Visit 1 to correct the typographical error and to align with IXRS

Section 9.4.4, Supportive analysis – Updated second paragraph from "For the primary variables, the analysis may be repeated using the full analysis set, hence including assessments in subjects who complete between 16 and 20 weeks of treatment as a supportive analysis to "For the primary variables, the analysis may be repeated using the full analysis set, hence including assessments in subjects who complete at least 16 weeks of study treatment and had an EOT visit date not greater than 12 weeks after date of last dose of IP as a supportive analysis" Change has been made due to the COVID-19 pandemic

Section 9.4.4, Supportive analysis – Added the following wording "Additional analyses assessing the impact of COVID-19 may be included in the SAP"

Section 9.4.7, Other Analyses - Removed "To assess consistency of treatment effect across T2 activity as a continuum, a similar model will be fitted as for the primary analysis with additional factors for the subgroup variable (i.e. T2 quartiles) and its interaction with treatment." as this is a repeat of the analysis for one of the secondary variables

Appendix A 3 – Added "During the COVID-19 pandemic, re-consenting remotely may be obtained if local/regional guidelines allow" to accommodate the changes made in the protocol

Appendix J, - Added Appendix J to describe in more detail the changes made during the COVID-19 pandemic

Various typographical and grammatical corrections have been made
Version 3.0, 03 May 2019 Changes to the protocol are summarized below
Section 1.1, SoA, Table 1 – Added "☎" symbol and subsequent footnote to V4, V12, and V13 further clarifying these visits can be conducted via telephone. Section 1.1, SoA, Table 1 – Added "Blood for" prior to Tezepelumab PK clarifying tezepelumab PK will be assessed via blood sample analysis. Section 1.1, SoA, Table 1 – Added "Proposed order of assessments as follows: Visit 11 Day 1 - ACQ-6, paper diary completion, vital signs, ECG, FeNO, AO, physical exam, and AHR; Visit 11 Day 2 - vitals signs, pre-BD spirometry, blood draw, and bronchoscopy (biopsy, brushing, then BAL). Pre-BD spirometry can be done 1 day prior to bronchoscopy if there is a safety concern" to footnote '3' to provide recommended order of procedures if Visit 11 is performed over more than one day. Section 1.1, SoA, Table 1 – Updated footnote '6' from "Blood samples for PK and blood samples for ADA/nAb, biomarker and transcriptomics evaluations will be collected before the administration of IP." to "Blood *and BAL* samples for PK and blood samples for ADA *and* nAb*,* biomarker and transcriptomics evaluations will be collected before the administration of IP. *Samples with confirmed positive ADAs will be archived for possible testing for nAb*." This change is to clarify that both blood and BAL PK samples are intended to be collected, not only PK blood and that nAb samples will be archived for possible future testing. Section 1.1, SoA, Table 1 – Added "The morning diary will include: questions about rescue medications, night-time awakening, and use of maintenance medications. The evening diary will include: questions about rescue medications." to footnote '8' and corrected the corresponding inclusion criteria referenced to 14 & 15 as opposed to 15 & 16. This change is to detail the information that is captured on the paper diaries. Section 1.1, SoA, Table 1 – Updated footnote '9' from "ACQ-6 will not be done at Visit 2 except if the criterion was not met at Visit 1" to "ACQ-6 will *be performed* at Visit 2 *only* if the *eligibility* criterion *is* not met at Visit 1." This change is to better clarify when it is acceptable to complete ACQ-6 at V2. Section 1.1, SoA, Table 1 – Updated footnote '12' from "At EOT visit, AO, BAL, brushing, CT, and AHR will be performed only if baseline assessment is performed successfully, as confirmed by investigator." to "At EOT visit, AO, BAL, *brushings*, CT, and AHR will be

performed only if baseline assessment is performed successfully, as confirmed by investigator." This change is to clarify that bronchial brushing will also not be completed if the baseline measurement is unsuccessful.

Section 1.1, SoA, Table 1 – Updated footnote '13' from "…All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the baseline spirometry *(Visit 3b)* was performed." to "…All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the baseline spirometry *(Visit 1 and/or Visit 2)* was performed." in order to be in line with details in Table 1.

Section 1.1, SoA, Table 1 – Removed footnote '15' and updated the numbering of subsequent footnotes as no longer required due to update to footnote #6 as described above.

Section 1.2, Synopsis, Treatments and treatment duration – Updated "After initial enrolment and confirmation of entry criteria (Visit 1) subjects will proceed to a run-in period of 4 weeks during which their suitability for randomization will be confirmed." to "After initial enrolment and confirmation of entry criteria (Visit 1) subjects will proceed to a *screening/run-in* period of 4 weeks during which their suitability for randomization will be confirmed.". This change was to clarify that the screening & run-in period together constitute 4 weeks as opposed to run-in alone.

Section 1.2, Synopsis, Statistical Methods – Added "expressed as a ratio" when discussing change from baseline to week 28 in the number of airway submucosal inflammatory cells to clarify that the change is reported as a ratio.

Section 1.2, Synopsis, Statistical Methods – Updated "Covariates and factors included in the model will include at least treatment, and baseline number of airway submucosal eosinophils" to "Covariates and factors included in the model will include at least *screening blood eosinophil strata (screening blood eosinophil count < 150 cells/µL, 150 - 300*

cells/µL, and > 300 cells/µL at Visit 1), treatment, and baseline value" to specify the exact stratification factor.

Section 1.2, Synopsis, Statistical Methods – Added "across the spectrum of T2 status" to clarify that this will be across the entire spectrum of T2 status as opposed to within the T2 spectrum.

Section 1.2, Synopsis, Statistical Methods – Updated "To account for this, 55 subjects will be randomized in each treatment arm" to "To account for this *and subject dropouts*, 55 subjects will be randomized in each treatment arm" to clarify that the total number of randomized subjects per treatment arm has also taken subject dropouts into consideration.

Section 2.2, Background – Updated "We believe that tezepelumab will be efficacious in both T2 low and T2 high subjects (based on the Phase 2b data) so the effect of tezepelumab across the T2 continuum as determined by the three gene mean signature, will be explored" to "We believe that tezepelumab will be efficacious in both T2 low and T2 high subjects (based on the Phase 2b data) so the effect of tezepelumab across the T2 *spectrum* as determined by the three gene mean signature, will be explored" to indicate that this will be across the entire spectrum of T2 status.

Section 2.2, Background – Updated "These results are similar to those observed in the overall ITT population (AERR of 61%..." to "These results are similar to those observed in the overall ITT population (*AAERR* of 61%..." This change was made to clarify that the results are of the Annual Asthma Exacerbation Reduction Rate.

Section 2.3, Benefit/risk assessment – Updated "Risks of the study include those associated with invasive study assessments like the bronchoscopy, bronchial biopsy, and bronchoalveolar lavage (BAL)." to "Risks of the study include those associated with invasive study assessments *such as* bronchoscopy, bronchial biopsy*, bronchial brushing* and bronchoalveolar lavage (BAL)." This change is to correct an oversight in the previous wording as bronchial brushing is also considered an invasive procedure with potential associated risks.

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Section 4.1, Overall Design – Corrected “Table 4 and Table 5” to “Table 5 and Table 6” when reference the list of medication restrictions and prohibitions.

Section 4.2, Scientific rationale for the study design – Updated “In the present study, to ensure recruitment of adequate numbers of T2 low and T2 high subjects for analysis, subjects will be enrolled based on baseline blood eosinophil counts.” to “In the present study, to ensure recruitment of adequate numbers of T2 low and T2 high subjects for analysis, subjects will be enrolled based on *screening* blood eosinophil counts.” This change was to clarify that the baseline blood eosinophil counts will be collected at the screening visit.

Section 5.1, Inclusion criteria #13 – Further defined abstinence requirement and clarified that bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system are acceptable methods of female contraception.

Section 5.1, Inclusion criteria #15 – Added “with a minimum of 4 days of compliance during the last 7 days of the run-in period” to clarify the period within the background asthma medication compliance must be maintained.

Section 5.1, Inclusion criteria #18 – Updated to indicate that “Successful BAL *and brushings are* not inclusionary.” to clarify that brushings are also not inclusionary as was inadvertently omitted from this inclusion criterion.

Section 5.2, Exclusion criteria #7 and Section 5.3.2, Alcohol, tobacco, and other – Updated from “Current smokers or subjects with smoking history ≥ 10 pack-years. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months prior to Visit 1 to be eligible.” to “Current smokers or subjects with smoking history ≥ 10 pack-years, *including the use of vaping products, such as electronic cigarettes*. Former smokers with a smoking history of <10 pack years, *including vaping or e-cigarette users,* must have stopped for at least 6 months prior to Visit 1 to be eligible.” to clarify that tobacco restrictions also apply to vaping and e-cigarette products.

Section 5.4, Screen Failures – Added “If the timeframe between screening and re-screening exceeds 30 days, the subject will not be permitted to rescreen without repeating Visit 1 assessments, as per PI discretion.” to reduce the risk of not identifying the status change in HIV 1, HIV 2, Hepatitis B, Hepatitis C and FSH prior to rescreening, if initial screening visit 1 was more than 30 days ago.

Section 6.2, Preparation/handling/storage/accountability – Clarified that the acceptable syringe size can be 2 or 3mL as opposed to strictly 3mL, as it meets requirements for dose preparation and administration.

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

Section 6.3. Measure to minimize bias: randomization and blinding, Methods for assigning treatment groups – Updated "Randomization will be stratified by baseline blood eosinophil level." to "Randomization will be stratified by *screening* blood eosinophil level." to clarify that the baseline blood eosinophil counts will be collected at the screening visit.

Section 6.3, Measure to minimize bias: randomization and blinding, Ensuring blinding – Added "Applicable DSMB members" and removed "ADA, nAb, and biomarker" at 'Ensuring blinding' to clarify that the laboratory does not require the randomization list for performing biomarker, ADA and nAb sample analysis and that DSMB members may require access to the randomization list.

Section 6.3. Measure to minimize bias: randomization and blinding, Ensuring blinding – Updated "No other member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study" to "No other member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomization scheme during the conduct of the study and until database lock" to clarify that access to the randomization scheme will not be available until after database lock.

Section 6.3, Measure to minimize bias: randomization and blinding, Methods for unblinding – Updated "Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacist at the study sites from the IVRS/IWRS." to "Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or *delegate* at the study sites from the IVRS/IWRS." to clarify that any individual properly delegated by the PI may have access to individual treatment codes.

Section 6.5, Concomitant therapy, Table 5 – Updated "No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP" to "No changes in either dose or regimen are allowed from V1 and *until at least the EOT visit, unless there is a medical need as judged by the Investigator*." for 'Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)', 'Short-acting beta-agonists (SABA)', 'Additional maintenance controllers',

and 'Short-acting anticholinergics (e.g. ipratropium)'. This change is to further detail the restriction period and permit use of the aforementioned medication if needed medically.

Section 6.5, Concomitant therapy, Table 6 – Updated "No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP" to "No changes in either dose or regimen are allowed from V1 and *until at least the EOT visit, unless there is a medical need as judged by the Investigator*." for 'Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)', 'Suplatast tosilate (T2 cytokine inhibitor)', 'Anticoagulants', 'Any immunomodulators or immunosuppressives (except for OCS used in the treatment of asthma/asthma exacerbations)', 'Immunoglobulin or blood products', 'Other IPs (including investigational use of an approved drug)', 'Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases' and 'Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care'. This change is to further detail the restriction period and permit use of the aforementioned medication if needed medically.

Section 7.1, Discontinuation of study treatment – Added "except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided the malignancy is excised and determined to have clean margins" when discussing discontinuation due to any malignancy to align with the updated IB version 4.2.

Section 7.1.1, Procedures for discontinuation of study treatment – Updated "If the last IP administration was after week 16 for options 1 or 2, the subject will return to the clinic for an EOT visit at week 28 (+/- 3 days)." to "If the last IP administration was *at or* after week 16 for options 1 or 2, the subject will return to the clinic for an EOT visit at week 28 (+/- 3 days)." to clarify that the EOT visit will be completed for subjects who complete at least week 16 of IP administration.

Section 7.1.1, Procedures for discontinuation of study treatment – Updated "Development of study specific discontinuation criteria' on the termination form in the eCRF." to "Development of study specific discontinuation criteria' on the *Discontinuation of Investigational Product* form in the eCRF." to be in line with eCRF guidelines.

Section 8.1.2, Bronchial brushing – Added "The brushings at the EOT Visit will be performed only if the baseline visit brushing is performed successfully, as judged by the Investigator." to clarify that the bronchial brushing will only be collected if a successful baseline brushing is obtained.

Section 8.1.4, Airwave Oscillometry – Removed "AO evaluation will be performed in accordance with the schedule provided in Table 1. Assessment at week -1 will be a training maneuver for the subjects.", as training is not conducted and there is no week -1 visit.

Section 8.1.5, Airway hyper-responsiveness – Clarified that the mannitol challenge will also be performed in accordance to the vendor's manual and added "Medication washouts should be followed as per the mannitol vendor's manual detailed in Appendix I"

Section 8.1.13, Computed tomography – Removed "of procedures" and "Principal" and updated "EOT CT will be performed only if baseline CT is performed successfully, as judged by the investigator." to "EOT CT will be performed only if baseline CT is performed successfully, as *confirmed by imaging QC review by the imaging vendor*." This change is to clarify that the imaging vendor will confirm proper baseline CT scan assessment.

Section 8.1.18, Patient reported outcomes – Replaced "The questionnaires will be administered at home in the following order…" to "The questionnaires will be *completed* at home in the following order…" and corrected the corresponding inclusion criteria referenced to 14 & 15 as opposed to 15 & 16, due to typographical error.

Section 8.2.2, Weight and height – Added "Body Mass Index (BMI) will be automatically calculated in the eCRF."

Section 8.2.4, Vital signs – Replaced "Pulse rate will be obtained before blood pressure." with "Pulse rate will be obtained before blood pressure *only if the manual measuring technique is used*". to specify that the order of measurements is only applicable when manually measurement occurs.

Section 8.2.5, Electrocardiograms – Updated "A 12-lead ECG will be taken in supine position, prior to blood draw, spirometry, BD administration, and IP administration" to "A 12- *or 15*-lead ECG will be taken in supine position, prior to blood draw, spirometry, and BD administration" to be in line with the ECG timepoints detailed in the SoA and to clarify that either 12- or 15-lead ECGs are acceptable.

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

Section 8.5.1, Collection of samples and drug concentration – Added "Urea concentration will be measured in blood and BAL samples to correct for the dilution factor of the BAL samples" to clarify that correction for the dilution factor for PK measurements in BAL will occur.

Section 8.5.2, Collection of samples to measure the presence of ADAs – Removed "and ADA-neutralizing antibodies" and updated "Samples with confirmed positive ADAs will be analyzed for the presence of neutralizing antibodies (nAb)." to "Samples with confirmed

positive ADAs will be *archived for possible testing for* neutralizing antibodies (nAb)." as nAb samples will be archived for possible future testing.

Section 8.7.1, Optional exploratory genetic sample – Removed "Healthy volunteers and pediatric patient samples will not be collected for optional genetic research." as no healthy volunteers or pediatric patients are permitted on this study.

Section 9, Statistical considerations – Updated "The null hypothesis H0: The ratio (tezepelumab/placebo) equals 1 and will be tested vs. H1: The ratio is not equal to 1." to "The null hypothesis H0: The ratio (tezepelumab/placebo) *of the change, expressed as a ratio, from baseline to week 28 for each primary and secondary endpoint between tezepelumab and placebo* equals 1 and will be tested *versus the alternative hypothesis* H1: The ratio *(tezepelumab/placebo) of the change, expressed as a ratio, from baseline to week 28 for each primary and secondary endpoint between tezepelumab and placebo* is not equal to 1." and removed "For the primary endpoints only, one-sided tests will be conducted against the alternative hypothesis H1: The ratio tezepelumab/placebo is < 1". This change is to clarify the hypotheses definitions.

Section 9.1, Sample size determination – Updated "It is estimated that 50 subjects in each treatment arm will provide (using a nominal 10% significance level for each endpoint)" to "It is estimated that 50 subjects in each treatment arm will provide (using a *2-sided test with a* nominal 10% significance level for each endpoint)" to clarify that all results will be presented as 2-sided tests.

Section 9.2, Populations for analyses, Table 8 – Defined additional analysis population set "Evaluable analysis set" to account for subjects in the full analysis set with at least 20 weeks of treatment.

Section 9.2, Populations for analyses – Replaced "For analysis of efficacy variables, subjects will be assigned to the full analysis set (defined above) according to their randomized treatment. For consistency, demographic and baseline characteristics will be presented using the full analysis set." with "For analysis of efficacy variables, subjects will be assigned to the *evaluable* analysis set (defined above) according to their randomized treatment. For consistency, demographic and baseline characteristics will be *confirmed by presenting using both the evaluable analysis set (to correspond to the primary efficacy analysis population) and full analysis set*." This change was made to be consistent with safety and efficacy analysis populations.

Section 9.3.3, Secondary outcome measures – Updated "The change, expressed as a ratio, in airway inflammatory cells/mm^2 from baseline up to week 28 within T2 spectrum" to "The change, expressed as a ratio, in airway inflammatory cells/mm^2 from baseline up to week 28 *across the spectrum of T2 status*" to clarify that this will be across the entire spectrum of T2 status as opposed to within the T2 spectrum.

Section 9.3.4.5, Rescue use – Removed "Total rescue medication use defined as the average number of inhalations (puffs) per day will be calculated as the outcome variable. The number of inhalations (puffs) per day will be calculated as follows: Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times]. Biweekly mean number of inhalations (puffs) per day will be calculated as the outcome variable" as this information is captured via paper diaries and outcome variable analysis will not be possible.

Section 9.3.4.6, Nights with awakening due to asthma – Removed sub-section and subsequent subsection numbering adjusted accordingly as this information is captured via paper diaries and outcome variable analysis will not be possible.

Section 9.3.4.7, Effect on lung function and bronchial hyper-responsiveness – Removed "…and post-BD" when discussing the change in baseline to week 28 for FEV_1, FVC, $FEF_{25-75\%}$ as post-BD spirometry measurement is not performed at EOT.

Section 9.3.4.8, Calculation or derivation of pharmacokinetics and immunogenicity variables – Removed "These validated methods are conducted using a bridging assay format and statistically determined floating screening assay cut point factor and confirmatory assay cut point. The minimal sample dilution is 1:13. Titer values are reported as the reciprocal of the highest dilution that yields a value above the cut point." and added "Details of the method will be provided in validation reports as well as in bioanalytical reports.". This change was made to clarify where the details of the method will be maintained.

Section 9.3.4.8, Calculation or derivation of pharmacokinetics and immunogenicity variables – Updated "Samples that confirm positive for ADA will also be tested for nAb activity." to "Samples *with confirmed* positive ADAs will be *archived for possible testing for nAb*.". This change was to clarify that nAb samples will be archived for possible future testing.

Section 9.3.4.8, Calculation or derivation of pharmacokinetics and immunogenicity variables – Added "The prevalence and incidence of ADA over the course of the study will be calculated and tabulated by treatment group." and removed "Neutralizing antibody evaluations will be conducted on those serum samples that test positive for ADA at end of treatment and also during the study follow up period. The test sample is deemed positive or negative for the presence of nAb to tezepelumab relative to a predetermined (in assay validation), statistically derived cut point. Samples positive for nAb to tezepelumab are then titered to determine relative amounts of nAb present in each test sample." This change was

made to clarify how ADA results will be presented and that nAb samples will be archived for possible future testing.

Section 9.3.5, Calculation or derivation of safety variables – Updated "The following safety data will be collected: vital signs, physical examination, 12-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs." to "The following safety data will be collected: vital signs, physical examination, 12- *or 15*-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs." to clarify that either 12- or 15-lead ECGs are acceptable.

Section 9.3.5.3, Laboratory variables – Corrected "Table 3" to "Table 7" when referencing the lab parameters to be collected.

Section 9.4.1, Efficacy analyses – Replaced "Efficacy analyses will be based on the full analysis set (FAS) population, and subjects will be classified according to their randomized treatment." with "Efficacy analyses will be *primarily* based on the *evaluable analysis set*, and subjects will be classified according to their randomized treatment." to account for subjects in the full analysis set with at least 20 weeks of treatment.

Section 9.4.1, Efficacy analyses – Removed "%change" when discussing outcome measure for primary/secondary outcomes as this will only be presented as a ratio.

Section 9.4.1, Efficacy analyses – Updated "All hypothesis testing will be reported using 2-sided tests at the nominal 10% significance level. For the primary endpoints only, hypothesis tests with a nominal 5% significance level using 1-sided tests will also be reported. The alternative hypothesis for the 1-sided tests is that the ratio tezepelumab/placebo is lower than 1." to "All hypothesis testing will be reported using 2-sided tests *with a* nominal 10% significance level *and 90% confidence intervals (CIs)*. For the primary endpoints only, *2-sided 95% CIs* will also be reported. The *direction of interest* for *each of the primary endpoints* is that the ratio tezepelumab/placebo is lower than 1." This change is to clarify the method of reporting the testing of the hypotheses.

Section 9.4.2, Analysis of the primary variable(s) – Added "expressed as a ratio" when discussing change from baseline to week 28 and updated "The primary variable of within subject change from baseline to week 28 (expressed as a ratio) in numbers of each of the airway submucosal inflammatory cells will be analyzed using an analysis of covariance (ANCOVA) including at least baseline value and treatment as covariates." to "The primary variable of within subject change from baseline to week 28 (expressed as a ratio) in numbers of each of the airway submucosal inflammatory cells will be analyzed using an analysis of covariance (ANCOVA) including at least *screening blood eosinophil strata (screening blood eosinophil count < 150 cells/µL, 150 - 300 cells/µL, and > 300 cells/µL at*

Visit 1), baseline value, and treatment as covariates." to clarify that the change is expressed as a ratio change and to specify the exact stratification factor.

Section 9.4.2, Analysis of primary variable(s) – Removed "Patients that discontinue IP prior to week 20 visit will be excluded from the primary analyses." as contained in the evaluable analysis set definition.

Section 9.4.3, Analysis of the secondary variable(s) - Added "expressed as a ratio" when discussing change from baseline to week 28 to clarify that the change is expressed as a ratio change.

Section 9.4.4, Supportive analysis – Updated "For the primary and secondary variables, non-parametric analysis methods will be applied as supportive analyses. For the primary analysis, the same method will be used including subjects who complete at least 16 weeks of treatment as a supportive analysis." to "For the primary and secondary variables, *alternative transformations or* non-parametric analysis methods *may* be applied as supportive analyses *if substantial deviations from the parametric assumptions are observed. This will be assessed and documented prior to unblinding*. For the primary *variables, the analysis may be repeated using the full analysis set, hence including assessments in subjects who complete between 16 and 20 weeks of treatment as a supportive analysis.*" This change was made to further clarify the supportive analysis, including the definition of the supportive analysis set.

Appendix A, Regulatory, ethical and study oversight considerations – Added details regarding the sponsor's right to close a study site or terminate the study and potential reasons for early closure of a study site to A9 and Publication Policy shifted to A10. This change was made as per new AstraZeneca guidelines.

Appendix E, Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law – Added "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 AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events." to E1. The appendix has been updated in conjunction with sponsor's routine pharmacovigilance activities/processes.

Appendix E, Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law – Removed "Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section E 6 Actions Required When Potential Hy's Law

Criteria are Met Before and After Starting Study Treatment) from E4.2. The appendix has been updated in conjunction with sponsor's routine pharmacovigilance activities/processes.

Appendix E, Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law – Updated "Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined." to "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." at E5. The appendix has been updated in conjunction with the sponsor's routine pharmacovigilance activities/processes.

Appendix E, - Updated "Update the previously submitted PHL SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined." to "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." at E5.The appendix has been updated in conjunction with sponsor's routine pharmacovigilance activities/processes. .

Appendix E, Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law – Removed subsection E6 and E7 and renumbered subsequent subsections. The appendix has been updated in conjunction with the sponsor's routine pharmacovigilance activities/processes.

Appendix F, Maintenance therapy equivalence table – Updated to include ICS/LABA combination therapies and changed footnote 'a' to confirm the source of the ICS/LABA combination therapy dose details. This change was made to provide Investigators additional information when assessing eligibility.

Appendix F, Maintenance therapy equivalence table – removed the low dose references for ICS-LABA medication as low dose is not applicable to this study.

Added Appendix I, Medication washout period for airway hyper-responsiveness, as these restrictions are more stringent than the medication washout for the study and are required to be withheld for safety and pharmacokinetic purposes.

Various typographical and grammatical corrections have been made.

Version 2.0, 12 Nov 2018

Changes to the protocol are summarized below

Section 1.1, SoA, Table 1 – Removed Pre-BD spirometry from V3a.

Section 1.1, SoA, Table 1 – Added Safety Spirometry (optional) to V3b.

Section 1.1, SoA, Table 1 –Removed FeNO from V3b and added to V3a.

Section 1.1, SoA, Table 1 –Removed AO from V3b and added to V3a.

Section 1.1, SoA, Table 1 – Updated footnote '*' from "Order of assessments at V3a would be ACQ-6, vital signs, *spirometry*, physical exam." to "Order of assessments at V3a would be ACQ-6, vital signs, *FeNO, AO,* physical exam." and added "*A compliance check for background medication and paper diary completion to be completed.*".

Section 1.1, SoA, Table 1 – Updated footnote '**' from "Order of assessments at V3b would be *FeNO, AO*, vital signs, blood draw, bronchoscopy, then IP administration. Visit 3a and 3b should be performed within 7 days of each other." to "Order of assessments at V3b would be vital signs, *spirometry*, blood draw, bronchoscopy *(biopsy, brushing, then BAL),* then IP administration. *Per PI discretion, the IP can be administered on the day after V3b if there is any safety concern.* Visit 3a and 3b should be performed within 7 days of each other."

Section 1.1, SoA, Table 1 – Updated footnote '8' from "Paper diary will capture rescue medication, night time awakening, and use of maintenance medications from the evening of V2 to the morning of V14. Paper diary will be distributed at V2 to V11 (sufficient paper diaries will be distributed at V11) and collected at V3 to V11 and V14." to "Paper diary will capture rescue medication, night time awakening, and use of maintenance medications from the evening of V2 to the morning of V14. Paper diary will be distributed at V2 to V11 (sufficient paper diaries will be distributed at V11 *for follow-up phase*) and collected at V3 to V11 and V14. *The diary dispensed at V2 will be re-used for both V3a and V3b. Diary and background medications compliance for inclusion criteria numbers 15 and 16 will be performed at V3a.*" to indicate that the diary dispensed at V2 will be re-used for both V3a and V3b. Diary and background medications compliance for inclusion criteria 15 and 16 will be performed at V3a.

Section 1.1, SoA, Table 1 – Changed "baseline spirometry (Visit 3b)" to "baseline spirometry (Visit 1 or 2)".

Section 1.1, SoA, Table 1 – Added footnote '16' to indicate that CT is to be performed between V3a and V3b.

Section 1.1, SoA, Table 1 – Added footnote '17' to indicate that "In case of repeat of spirometry at V2, the AHR will be rescheduled to be done within 3 days of V2."

Section 1.1, SoA, Table 1 – Added ADA testing at Unscheduled along with footnote '18' to indicate that "ADA sample should be collected in case of any suspected immunologically-related AEs."

Section 1.1, SoA, Table 1 – Updated "Tezepelumab PK" to "*Blood for* Tezepelumab PK"

Section 1.1, SoA, Table 1 – Added "(except for spirometry which should be done pre-BD at V11)" to footnote '3'.

CCI

Section 1.2, Synopsis – Added information regarding the Data Safety Monitoring Board

Section 2.2, Background – Updated with additional published information regarding Study CD-RI-MEDI9929-1146.

CCI

CCI

[redacted]

Section 5.1, Inclusion criteria #7 – Replaced "Subjects on OCS are allowed in the study, provided they are on a stable dose for at least 6 months before V1." with "Subjects on OCS are allowed in the study, provided they are on a stable *maintenance* dose for at least 6 months before V1."

Section 5.1, Inclusion #9 – Replaced "15-*30* min" with "15-*60* min"

Section 5.1 - Removed Inclusion #14 which stated "Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from enrolment through 16 weeks after receipt of the final dose of IP. In the countries where the abovementioned method of contraception is not available a condom can be used alone. Male subjects must not donate or bank sperm during this same time period"

Section 5.1, Inclusion criteria #16 – Corrected "Subjects must have demonstrated a minimum 70% compliance with background asthma medication *the during* run-in period." to read as "Subjects must have demonstrated a minimum 70% compliance with background asthma medication *during the* run-in period."

Section 5.1, Inclusion #19 – Added "at Visit 3b"

Section 5.2, Exclusion #21 – Removed "the current study or"

Section 5.4, Screen failures – Added "Subjects who experience an asthma exacerbation during run-in period may be re-screened after 14 days of complete resolution of the asthma exacerbation, and when the subjects return to their baseline, at Investigator discretion." and removed typo "X`"

Section 6.4, Treatment Compliances – Removed "as well as any missed doses"

Section 6.5, Table 5 – Updated "Use of SABA should be avoided within 6 hours before ECG assessments." to "Use of SABA *or SAMA* should be avoided within 6 hours before ECG assessments."

Section 6.5.2, Rescue medication – Added "or SAMA" and removed "When possible, home lung function should be taken at least 6 hours after the last dose of SABA rescue medication."

Section 7.1.1, Procedures for discontinuation of study medication – Corrected "…post last IP administration for the EOT visit at Week 28 (+/-3 days)." to "…post last IP administration *and* for the EOT visit at Week 28 (+/-3 days)."

Section 7.3, Withdrawal from the study – Added "AstraZeneca reserves the right to discontinue a subject's participation in the study for any safety reasons."

Section 8.1.1, Bronchial biopsy – Updated "Subjects will receive a sedative and local anesthetic to reduce any discomfort." to "Subjects will receive a sedative and local anesthetic to reduce any discomfort, local guidelines to be followed."

Section 8.1.1, Bronchial biopsy – Added "Bronchial biopsy, being the primary endpoint, will be conducted first followed by bronchial brushing then BAL." to clarify the order of assessments.

Section 8.1.5, Airway hyper-responsiveness – Added "In case of repeat spirometry at V2, AHR will be rescheduled within 3 days of Visit 2."

Section 8.1.6, Biomarkers – Updated "Blood samples should be collected pre-dose at the pre-specified scheduled visit in the SoA" to "All biomarker samples should be collected pre-dose at the pre-specified scheduled visit in the SoA"

Section 8.1.7, Blood eosinophils and neutrophils – Added "All blood eosinophils and neutrophils results will be redacted from the laboratory reports except for Visit 1 and Visit 3." and removed "Results will be blinded after randomization."

Section 8.1.9, Serum IgE – Added "All total serum IgE results will be redacted from the laboratory reports except for Visit 3."

Section 8.1.11, DNA for genetics – Added "This data will be reported separately from the CSR in an addendum or in a scientific report or publication."

Section 8.1.12, Urine Biomarkers – Removed "which may include, but not limited to, lipids such as thromboxane."

Section 8.1.16.1, General requirements – Updated "SABAs should be withheld at least 6 hours prior to scheduled spirometry at site." to "SABAs *and SAMAs* should be withheld at least 6 hours prior to scheduled spirometry at site."

Section 8.1.16.1, General requirements – Removed "and at randomization visits (Visit 3b (V3b))" and replaced "randomization spirometry" with "enrolment spirometry".

Section 8.1.16.2, Figure 3 – Replaced "Wait 15-*30* min" with "Wait 15-*60* min"

Section 8.1.16.2, FeNO – Moved to new section 8.1.17

Section 8.1.17 (formerly section 8.1.16.2), FeNO – Updated "Subjects should not use their rescue SABA medication (e.g. albuterol/salbutamol) within 6 hours of the measurement." to "Subjects should not use their rescue SABA medication (e.g. albuterol/salbutamol) *or SAMA medications* within 6 hours of the measurement."

Section 8.1.17 (formerly section 8.1.16.2), FeNO – Updated "All FeNO measurements will be blinded for sites and subjects throughout." to "All *post-randomization* FeNO measurements will be blinded for sites and subjects throughout *the study*."

Section 8.1.17, Patient Reported Outcomes – Updated to section 8.1.18

Section 8.2.2, Weight and height – Removed "BMI will be automatically calculated in the eCRF."

Section 8.2.5, Electrocardiograms – Removed "overall data and"

Section 8.3.2, Time period and frequency for collecting AE and SAE information – Added "AEs and SAEs should still be collected after IP discontinuation for subjects that prematurely discontinue from IP and will be encouraged to undergo appropriate study visits/procedures for the full 40-week period."

Section 8.3.3, Follow-up of AEs and SAEs – Updated "All SAE/non-serious AEs/AEs of special interest will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up." to "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."

Section 8.3.7, Adverse events based on examinations and tests – Updated to include ECG and removed "unless unequivocally related to the disease under study".

Section 8.4.2, Pregnancy – Added "Any cases of pregnancy during the study period or follow up will be recorded in the specific CRF module."

Section 8.4.2.1, Maternal Exposure – Updated "The PREGREP module in the CRF is used to report the pregnancy and PREGOUT is used to report the outcome of the pregnancy." to "The PREGREP module in the CRF is used to report the pregnancy and the *paper-based pregnancy outcome report* is used to report the outcome of the pregnancy." Section 8.4.2.2, Paternal Exposure – Removed "Male subjects should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose." Section 8.4.6, Data Safety Monitoring Board – section was added with details regarding the scope of the DSMB Section 8.5.1 Collection of samples and drug concentrations – Removed "and BAL" and added "Samples for determination of tezepelumab concentration in BAL will be analyzed by a designated third party on behalf of AstraZeneca using a qualified bioanalytical method. Samples for determination of urea will be analyzed by a designated third party on behalf of AstraZeneca using qualified bioanalytical methods." Section 8.5.2, Collection of samples to measure the presence of ADAs – Added "ADA sample should be collected in case of any suspected immunologically-related AEs." Section 8.8.2, Serum IgE – Added "All total serum IgE results will be redacted from the laboratory reports except for Visit 3." Section 9.2, Populations for analyses – Added "and PK BAL" Section 9.3.4.4, Effect on restoring peripheral pulmonary vasculature – Removed "Exploratory biomarker of tissue vascularity in bronchial biopsy specimens assessed by histology, IHC, or ISH." Appendix E, Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law – Appendix has been updated including addition of section E6, E7, and E8. Appendix F, Maintenance Therapy Equivalence Table – Updated as per GINA 2018 guidelines. Appendix F, Maintenance Therapy Equivalence Table – Added "Breo®" as example of Fluticasone furoate. Various typographical and grammatical corrections have been made.
Version 1.0, 20 Jul 2018
Initial Creation

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

For detailed schedule of activities (SoA) please see section 1.1 below.

1.1 SoA

Table 1 – Schedule of Activities

Assessment/ activity	Screening	Run-in	Randomization		Treatment period							EOT ***/ IPD	FU			UNS visit[1]	Details in CSP Section or Appendix
Visits **Visit number**	**1**	**2**	**3a***	**3b****	**4[2]☎**	**5**	**6**	**7**	**8**	**9**	**10**	**11[3]**	**12[2] ☎**	**13[2] ☎**	**14**		Details in CSP Section or Appendix
Weeks **Visit week**	**-4**	**-2**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**		
Visit window (days)[4]	**N/A**	**±3**	**±3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Routine Clinical Procedures																	
Informed consent	X																See Section 5.1
Inclusion/exclusion criteria	X	X	X	X													See Section 5.1& 5.2
Demographics	X																See Section 5.1& 5.2
Medical/surgical and asthma history	X															X	See Section 5.1
Height	X																See Section 8.2.2
Weight	X			X								X			X		See Section 5.1 & 8.2.2
Hematology	X			X				X				X			X	X	See Section 8.2.1
Serology (Hepatitis B, C; HIV-1,2)	X																See Section 8.2.6
Serum pregnancy test	X											X					See Section 8.2.1
Urine pregnancy test (dipstick)				X		X	X	X	X	X	X					X	See Section 5.1
FSH	X[5]																See Section 8.2.1
Blood for Tezepelumab ADA and nAb[6]				X				X				X			X	X[17]	See Section 8.5.2 & 9.3.4.8
Serum IgE				X				X				X			X		See Section 8.1.9
IgE (FEIA)				X													See Section 8.1.15
Healthcare resource utilization[7]				X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.9

Assessment/ activity	Screening	Run -in	Randomization		Treatment period							EOT ***/ IPD	FU			UNS visit[1]	Details in CSP Section or Appendix
Visits **Visit number**	**1**	**2**	**3a***	**3b****	**4[2]☎**	**5**	**6**	**7**	**8**	**9**	**10**	**11[3]**	**12[2] ☎**	**13[2] ☎**	**14**		Details in CSP Section or Appendix
Weeks **Visit week**	**-4**	**-2**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**		
Visit window (days)[4]	**N/A**	**±3**	**±3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Routine Safety Procedures																	
Distribution and collection of paper diary[8]		X	X	X		X	X	X	X	X	X	X			X	X	See Section 8.1.18.1
Clinical chemistry	X			X				X				X			X	X	See Section 8.2.1
Urinalysis (dipstick)	X			X				X				X			X		See Section 8.2.1
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 5.2 & 6.5
Vital signs	X	X	X	X		X	X	X	X	X	X	X			X	X	See Section 8.2.4 & 9.3.5.6
Local ECG	X											X					See Section 5.2 & 8.2.5
Complete physical examination	X		X									X					See Section 9.3.5.5
Brief physical exam								X							X	X	See Section 9.3.5.5
Efficacy Measurements																	
ACQ-6	X	X[9]	X					X				X					See Section 8.1.18.2 & 9.3.4.6
Urine for biomarker				X				X				X			X		See Section 8.1.12
Asthma exacerbation reporting[10]				X	X	X	X	X	X	X	X	X	X	X	X	X	See Section 8.1.14
Blood for serum and plasma biomarkers[6]				X				X				X			X		See Section 8.1.6
Blood for RNA transcriptomics[6,11]				X				X				X			X		See Section 8.8.3
Fractional exhaled nitric oxide (FeNO)			X					X				X			X		See Section 8.1.17
Computed tomography (CT)			X[15]									X[12]					See Section 8.1.13
Pre- BD, spirometry	X	X[13]						X				X			X		See Section 8.1.16
Post-BD, spirometry	X	X[13]															See Section 8.1.16.2
Safety spirometry, optional				X													See Section 8.1.16.1
Airwave oscillometry (AO)			X									X[12]					See Section 8.1.4
Airway hyperresponsiveness (AHR)		X[16]										X[12]					See Section 8.1.5
Bronchoscopy/biopsy/brushing and bronchoalveolar lavage (BAL) [6, 11]				X								X[12]					See Section 8.1
Pharmacokinetic Measurements																	

Assessment/ activity	Screening	Run -in	Randomization		Treatment period							EOT ***/ IPD	FU			UNS visit[1]	Details in CSP Section or Appendix
Visits **Visit number**	**1**	**2**	**3a***	**3b****	**4[2]☎**	**5**	**6**	**7**	**8**	**9**	**10**	**11[3]**	**12[2] ☎**	**13[2] ☎**	**14**		Details in CSP Section or Appendix
Weeks **Visit week**	**-4**	**-2**	**0**		**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**		
Visit window (days)[4]	**N/A**	**±3**	**±3**		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Blood for Tezepelumab PK[6]				X				X				X			X		See Section 8.5
Pharmacogenetic Sampling																	
Blood for DNA (optional)			X														See Section 8.7.1
Study Treatment Administration																	
Randomization				X													See Section 6.3
IP administration[14]				X		X	X	X	X	X	X					X[18]	See Section 6.2

* Order of assessments at V3a would be ACQ-6, vital signs, FeNO, AO, physical exam. A compliance check for background medication and paper diary completion to be completed.

** Order of assessments at V3b would be vital signs, spirometry (if performed), blood draw, bronchoscopy (biopsy, brushing then BAL), then IP administration. Per PI discretion, the IP can be administered on the day after V3b if there is any safety concern. Visit 3a and 3b should be performed within 7 days of each other.

*** During the COVID-19 pandemic unscheduled visits may occur so that sites may perform EOT assessments 4 weeks after last dose of IP at either week 28, 32, 36, 40, 44 or 48 (as needed) until the sites are able to resume the EOT assessments.

☎ Telephone Visit

1 PI can add more assessments as needed to unscheduled visits.

2 Visits 4, 12 and 13 are phone visits.

3 Based on investigator's judgement and site resources, EOT assessments (V11) will be performed over more than one day, within a 7-day window. The sequence of assessments during Visit 11 should be performed in the same order as completed at Visits 3a, 3b (except for spirometry which should be done pre-BD at V11). Proposed order of assessments as follows: Visit 11 Day 1 - ACQ-6, paper diary completion, vital signs, ECG, FeNO, AO, physical exam, and AHR; Visit 11 Day 2 - vitals signs, pre-BD spirometry, blood draw, and bronchoscopy (biopsy, brushing, then BAL). Pre-BD spirometry can be done 1 day prior to bronchoscopy if there is a safety concern. During the COVID-19 pandemic unscheduled visits may occur so that sites may perform EOT assessments 4 weeks after last dose of IP at either week 28, 32, 36, 40, 44 or 48(as needed) until the sites are able to resume the EOT assessments.

4 All visits are to be scheduled from the date of randomization, not from the date of the previous visit.

5 FSH will be done only for women < 50 years old, if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment.

6 Blood and BAL samples for PK and blood samples for ADA and nAb, biomarker and transcriptomics evaluations will be collected before the administration of IP. Samples with confirmed positive ADAs will be archived for possible testing for nAb.

7 Asthma specific resource utilization (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).

8 Paper diary will capture rescue medication, night time awakening, and use of maintenance medications from the evening of V2 to the morning of V14. The morning diary will include: questions about rescue medications, night-time awakening, and use of maintenance medications. The evening diary will include: questions about rescue medications. Paper diary will be distributed at V2 to V11 (sufficient paper diaries will be distributed at V11) and collected at V3 to V11 and V14. The diary dispensed at V2 will be re-used for both V3a and V3b. Diary and background medications compliance for inclusion criteria numbers 14 and 15 will be performed at V3a. During the COVID-19 pandemic, recording, collecting and dispensing will continue once administration of extra dosing is implemented.

9 ACQ-6 will be performed at Visit 2 only if the eligibility criterion is not met at Visit 1.

[10] Any asthma exacerbation before randomization will be reported as an AE/SAE. Any asthma exacerbation that will occur during treatment and FU will be reported in the exacerbation page in the eCRF.

[11] RNA samples will be obtained from the peripheral blood and bronchial brushings. RNA may also be collected from lung biopsies and BAL cells if sufficient sample remains after the other assessments on these cells are completed.

[12] At EOT visit, AO, BAL, brushings, CT, and AHR will be performed only if baseline assessment is performed successfully, as confirmed by investigator. EOT biopsy will only be performed if baseline biopsy meets pathology QC.

[13] Pre- and post-BD spirometry to assess FEV_1 and its reversibility will be performed at Visit 2 only if eligibility criteria is not met at Visit 1. The spirometry will be rescheduled if the subject did not withhold their BD at V1. Pre-BD spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM. All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the baseline spirometry (Visit 1 and/or Visit 2) was performed.

[14] IP will be administered after performing all the visit-specific assessments.

[15] CT to be performed during the period between V3a and V3b.

[16] In case of repeat of spirometry at V2, the AHR will be rescheduled to be done within 3 days of V2.

[17] ADA sample should be collected in case of any suspected immunologically-related AEs

[18] During the COVID-19 pandemic an additional 1 to 6 IP doses may be administered to subjects during unscheduled visits at weeks 28, 32, 36, 40, 44 and 48 (as needed) until the sites are able to resume performing all EOT study assessments, including bronchoscopies. All assessments during the unscheduled visit may not be necessarily be completed. Please refer to Appendix J.

CHANGES REQUIRED DURING COVID-19 PANDEMIC

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

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

● The option of providing home-administration of Investigational Product (IP) performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV), if possible. More information related to the visit can be obtained via phone call and/or virtual visits. The rationale for this change is to ensure that subjects are not missing any scheduled visits due to inability/unwillingness to visit the site during COVID-19 pandemic.

●Adding 1-6 extra IP doses every 4 weeks after week 24 (possibly through weeks 28, 32, 36, 40, 44 and 48) The rationale for this change is to ensure that the duration between the last IP dose and end of treatment assessments is within the protocol specified duration. Adding additional doses will give the subject a chance to resume bronchoscopies and other assessments when the pandemic is over.

●Phone call and/or virtual visits to replace the last on-site follow up visit, if subjects cannot attend the visits at the study site where necessary. The rationale for this change is to ensure that we collect the safety information if the last follow up cannot be done at the site.

●Re-consent will be obtained verbally if allowed by local and regional guidelines. The rationale is to ensure that the subject agrees to the changes implemented to the COVID-19 pandemic.

For further details, please refer to Appendix J

1.2 Synopsis

International Co-ordinating Investigator:

Professor Chris Brightling
NIHR Senior Investigator
University of Leicester
Leicester, United Kingdom
LE3 9QP

Protocol Title: A Phase 2, Randomized, Double-Blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults with Inadequately Controlled Asthma on Inhaled Corticosteroids and at least One Additional Asthma Controller (CASCADE)

Short Title:

Bronchoscopy Mechanistic Study

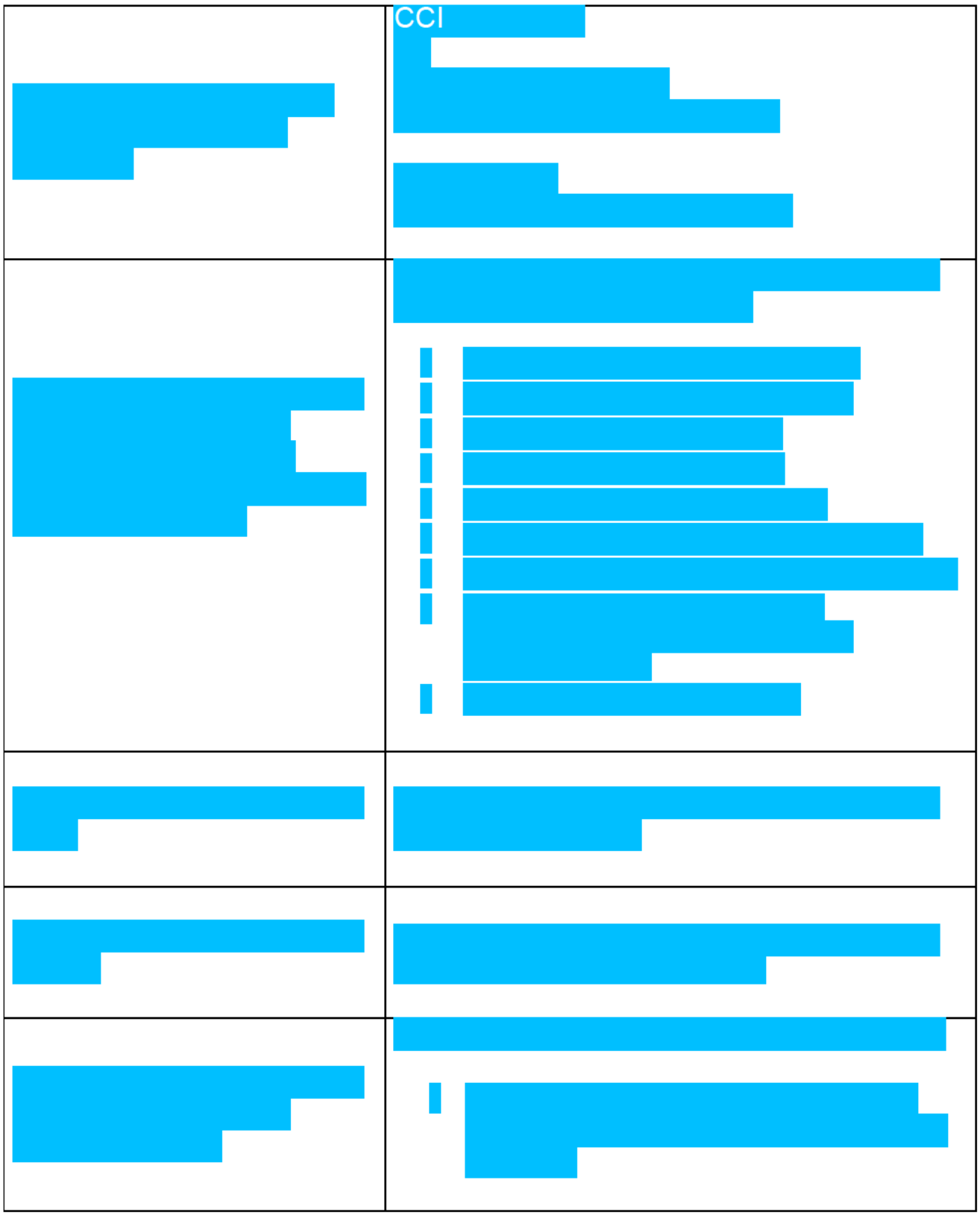
Rationale:

Tezepelumab has been shown to significantly reduce exacerbation rates in severe asthma. It is assumed that this effect was achieved by tezepelumab effectively controlling airway inflammation, but this has not been previously confirmed. This study is intended to explore the mechanism of a tezepelumab airway anti-inflammatory effect in improving asthma outcomes. Of particular interest in this study, is the action of tezepelumab across the spectrum of Type 2 (T2) activity, including the effect of tezepelumab in the T2 low population. The primary objective of this study is to directly explore the airway anti-inflammatory effect of tezepelumab. The secondary objectives will explore whether tezepelumab treatment (1) reduces reticular basement membrane (RBM) thickness, (2) improves airway epithelial integrity, (3) benefits subjects across the spectrum of T2 airway inflammation. In addition, this study will address several exploratory questions. First, it will explore the effect of tezepelumab on large airway remodeling and small airway obstruction. Second, it will explore the effect of tezepelumab on various biomarkers in the lung, bronchoalveolar lavage (BAL), blood, and urine. Third, the relationship between improvement in airway inflammation, lung function and bronchial hyper-responsiveness will also be assessed. Fourth, the relationship between tezepelumab and the effect on different inflammatory cells in the blood will be explored. Finally, the effect of tezepelumab on the pulmonary vasculature will be assessed.

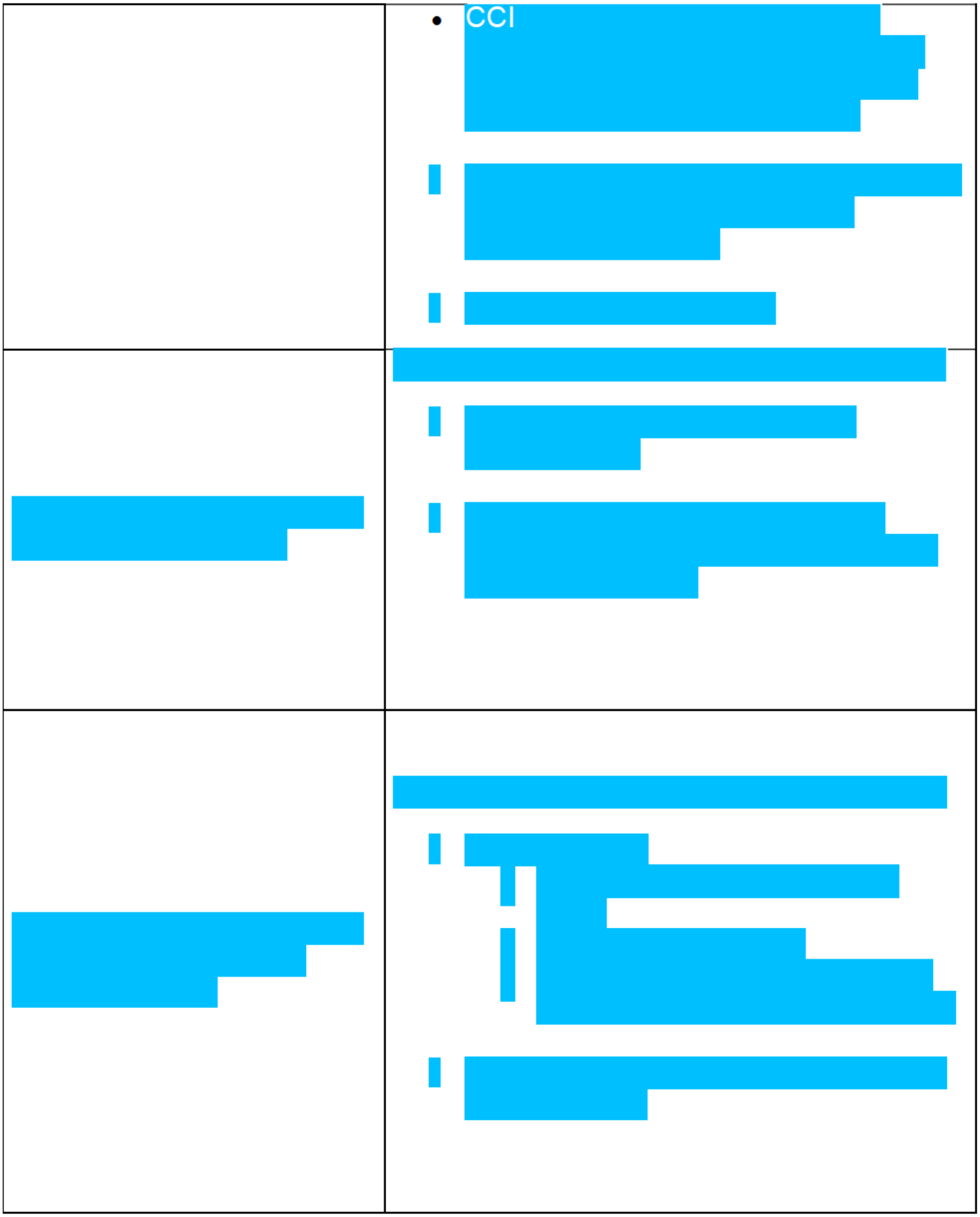
Objectives and Endpoints

Primary Objective	**Outcome Measure:**
To explore the airway anti-inflammatory effect of tezepelumab	Outcome Variable: The change, expressed as a ratio, in the number of airway submucosal inflammatory cells/mm^2 of bronchoscopic biopsies from baseline to end of treatment (EOT). Airway submucosal inflammatory cells will include eosinophils, neutrophils, T cells and mast cells Outcome Measure: Ratio of tezepelumab to placebo at EOT
Secondary Objective:	**Outcome Measure:**
To explore the effect of tezepelumab on RBM thickening	Outcome Variable: The change, expressed as a ratio, in RBM thickness determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the effect of tezepelumab on airway epithelial integrity	Outcome Variable: The change, expressed as a ratio, in % airway epithelial integrity determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the airway anti-inflammatory effect of tezepelumab across the spectrum of T2 status by three gene mean derived from bronchial brushing RNA transcriptomics	Outcome Variable: The change, expressed as a ratio, in number of airway submucosal inflammatory cells per mm^2 determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT in subjects across the spectrum of T2 status determining by RNAseq of bronchial brushings at baseline Outcome Measure: Ratio of tezepelumab to placebo at EOT across the spectrum of T2 status.
Safety Objectives:	**Outcome Measures:**
To evaluate the safety and tolerability of tezepelumab	Adverse events (AEs)/serious adverse events (SAEs)/adverse events of special interest (AESIs) Clinical chemistry/hematology/urinalysis Vital signs Electrocardiograms (ECG)
Exploratory Objectives:	**Outcome Measure:**

Objectives and Endpoints



Objectives and Endpoints



Objectives and Endpoints

	CCI

Overall design:

This is a Phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of tezepelumab on airway inflammation in adults with inadequately controlled moderate-to-severe asthma. Patients will have background asthma therapy of medium- or high dose ICS plus at least one additional asthma controller medication, such as a long-acting β2 agonist (LABA), leukotriene receptor antagonist

(LTRA), long-acting anti-muscarinic (LAMA), cromone, and theophylline, with or without maintenance oral corticosteroids (OCS) from screening and throughout the study including the follow-up period.

The study will consist of a screening/run-in period of up to 4 weeks, a treatment period of 28 weeks and a post-treatment follow-up period of 12 weeks. One dose level of tezepelumab, 210 mg will be compared with placebo administered subcutaneously (SC) every 4 weeks (Q4W) over the treatment period. Subjects who discontinue investigational product (IP) during the study will be encouraged to undergo appropriate study visits/procedures for the full 40-week period. Any new treatments that are initiated will be recorded.

Subjects who complete the 28-week study visit will complete a 12 week off-treatment follow-up period.

Study period:

Estimated date of first patient enrolled: Q4 2018

Estimated date of last patient completed: Q1 2021

Number of subjects:

Approximately 110 subjects will be randomized 1:1 to the following groups:
Tezepelumab 210 mg administered SC Q4W or
Matching placebo administered SC Q4W

The study aims to randomize subjects across the spectrum of T2 low and high activation. Approximately 30% of randomized subjects will have < 150 blood eosinophils/μL, approximately 30% of subjects with 150 – <300 blood eosinophils/μL and approximately 40% of subjects with ≥ 300 blood eosinophils/μL. When the target percentage of subjects for each eosinophil subgroup in the study is reached, consideration will be given to closing the IWRS/IVRS randomization for that subgroup, which may be done on the study level irrespective of the region. Once a subgroup is closed, subjects in the screening/run-in period in the closed subgroup will not be allowed to be randomized and will be screen failed.

Treatments and treatment duration:

After initial enrolment and confirmation of entry criteria (Visit 1) subjects will proceed to a screening/run-in period of 4 weeks during which their suitability for randomization will be confirmed. The subjects' currently prescribed ICS and additional asthma controller medication will remain unchanged during the run-in and treatment period. Subjects who meet the eligibility criteria at week -2 and randomization criteria at day 0 will be randomized to a 28-week treatment period and will receive either tezepelumab or placebo as an IP in addition to

their existing asthma controller medications. IP will be administered at weeks 0, 4, 8, 12, 16, 20 and 24. End of treatment (EOT) visit will be at week 28 (or later due to COVID-19 pandemic). A safety follow-up period for all subjects will be for 12 weeks from EOT.

Please note: During the COVID-19 pandemic, the treatment period may be extended and therefore subjects may be given 1 to 6 doses (as needed) every 4 weeks for a longer period than initially planned (please refer to Appendix J). For the last follow up visit, a phone call visit can replace an on-site visit. Please refer to Appendix J

Data safety monitoring board:

A Data Safety Monitoring Board (DSMB) is an external independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety data at regular intervals and making appropriate recommendations based on the available data. The DSMB will periodically review unblinded safety summary tables and listings and evaluate for subject safety and make appropriate recommendations.

DSMB 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 if and as required. 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 DSMB. The committee will operate in accordance with a DSMB Charter.

Statistical methods:

During the COVID-19 pandemic, all subjects with EOT assessments performed after unscheduled visits will be summarized and analyzed together with all subjects with EOT assessments performed during the scheduled EOT visit at week 28 and will be reported as having completed the EOT assessments" Please refer to Appendix J.

The primary analysis of the efficacy endpoints will include all data captured during the double blind, treatment period (intent-to-treat approach). However, only subjects with complete data for an endpoint will be included in the primary analysis of that endpoint.

The primary efficacy objective will be evaluated through statistical testing of the within subject change, expressed as a ratio, from baseline to EOT in number of airway submucosal inflammatory cells. The null hypothesis test H0 will be: The ratio tezepelumab/placebo equals 1 and will be tested vs. H1: The ratio is not equal to 1. The test will be based on an analysis of covariance model. Covariates and factors included in the model will include at least screening

blood eosinophil strata (screening blood eosinophil count <150 cells/μL, 150 – <300 cells/μL, and ≥300 cells/μL at Visit 1), treatment, and baseline value.

The secondary variables of within subject change from baseline up to EOT in the RBM thickness and epithelial integrity will be analysed using a similar model as for the primary variable. The secondary variable of within subject change from baseline up to EOT across the spectrum of T2 status in airway submucosal inflammatory cells will be assessed by using a similar model as for the primary variable with additional terms for T2 quartiles and their interactions with treatment and by visual data displays.

The analyses will be performed by using log-transformed data and estimated geometric means and the ratio of geometric means with 90% confidence intervals will be presented.

The study is sized to explore reductions in airway submucosal inflammation, from baseline to EOT, for tezepelumab versus placebo in the overall study population and across the T2 continuum.

The sample size is based on the primary endpoint: change from baseline to EOT in number of airway submucosal inflammatory cells. Given the assumed standard deviation of the log values of change in number of eosinophils in the two treatment groups are 1.87 and 2.06, it is estimated that 50 subjects in each treatment arm will be sufficient to achieve 80% power to detect a 2.7-fold difference in number of eosinophils versus placebo using a two-sided test at 10% significance level. Given the assumed standard deviation of the log values of change in number of neutrophils in the two treatment groups are 0.71 and 0.97, it is estimated that 50 subjects in each treatment arm will be sufficient to achieve > 90% power to detect a 2.7-fold difference in number of neutrophils versus placebo using a two-sided test at 10% significance level.

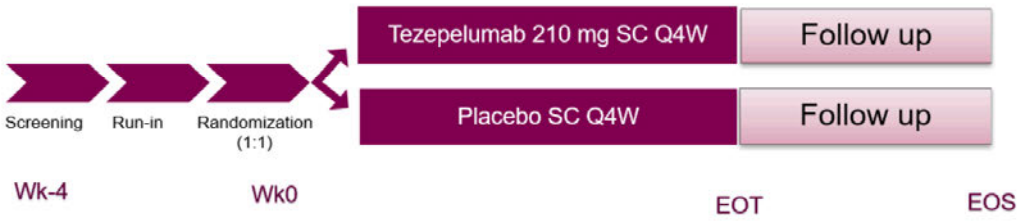
It is assumed that a non-neglectable proportion of the subjects will not have an evaluable primary endpoint value due to failed biopsies. To account for this and subject dropouts, 55 subjects will be randomized in each treatment arm.

The results for the exploratory variables will be summarized using descriptive statistics and graphical displays by treatment group. All safety parameters will be analyzed descriptively. The safety analyses will be based on the safety analysis data set, defined as all subjects who received at least one dose of IP.

1.3 Schema

The general study design is summarized in Figure 1

Figure 1 Study design



2. INTRODUCTION

Asthma is a chronic inflammatory airway disorder caused by the interaction of genetic and environmental factors. It is characterized by widespread, variable reversible airflow obstruction, airway inflammation, excessive mucus production, and airway hyperresponsiveness that lead to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (The Collaborative Study on the Genetics of Asthma (CSGA) 1997, GINA 2018).

Progressive pathologic airway remodeling and scarring may occur in persistent asthma resulting in only partially reversible or irreversible airway obstruction (Pascual and Peters 2005). The etiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise when a person becomes hypersensitive to allergens. Despite the availability of multiple therapeutic options, asthma continues to be a major health problem. Worldwide, asthma currently affects approximately 300 million people and by 2020, it is predicted to affect 400 million people (Partridge 2007). Each year in the US, asthma accounts for an estimated 8.9 million outpatient visits, 1.9 million emergency room visits, 479,000 hospitalizations (Corren et al 2017), and 3,400 deaths (Centers for Disease Control and Prevention 2017).

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

2.1 Study rationale

Tezepelumab is a human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against thymic stromal lymphopoietin (TSLP). It binds to human TSLP and prevents its interaction with thymic stromal lymphopoietin receptor (TSLPR). A Phase 1b study (Gauvreau et al 2014) provided indirect evidence that tezepelumab acts as an airway anti-inflammatory by showing attenuation of both the late asthmatic response (LAR) and the early asthmatic response (EAR) after allergen challenge; tezepelumab also reduced the expected increases in blood and sputum eosinophilia after this allergen challenge. A Phase 2b study (CD-RI-MEDI9929-1146) showed doses of 70 mg and 210 mg administered every 4 weeks (Q4W) and 280 mg of tezepelumab administered every 2 weeks resulted in reduction of annualized asthma exacerbation rates (AAER) by 61%, 71% and 66% respectively in the all-comer population (Corren et al 2017). Analysis of subgroups in the Phase 2b study also showed that tezepelumab benefited subjects with low and high baseline eosinophil counts and

a low and high T2 profile. These analyses suggest that tezepelumab, unlike other currently available biologics on the market used to treat severe asthma, is effective in subjects with T2 high and T2 low airway inflammation. It is assumed that tezepelumab reduces the AAER by acting as an airway anti-inflammatory. However, information directly supporting this assumption is currently not available and this study will investigate this further.

2.2 Background

Biologic therapies used to treat asthma have been shown to reduce the AAER in severe asthma patients who are uncontrolled with medium-to-high dose ICS and additional asthma controller medications. Omalizumab provided benefit for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2016). Three additional biologics, mepolizumab, reslizumab, and benralizumab have recently been approved for severe asthma with an eosinophilic phenotype (XOLAIR US PI 2016; CINQAIR US PI 2016; FASENRA US PI 2017). Benralizumab is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype (FASENRA US PI 2017). Biologics targeting IL-5 and IgE are now included in international treatment guidelines (GINA 2018) as an add-on treatment to patients uncontrolled with ICS/LABA treatment. However, when using the currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2016, Froidure et al 2016, Swedin et al 2017). These approved biologic therapies show efficacy mainly in the T2 high subpopulation, but there are no current biologic therapies that address the need of the T2 low patients. Tezepelumab is the first biologic that has shown promising data in a Phase 2b study for both T2 high and T2 low population (Corren et al 2017). This mechanistic study is designed to understand how tezepelumab works in the T2 low population. Therefore, despite these additional therapeutic options, there is still a clear unmet medical need among patients with severe asthma, independently of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that acts as a danger signal and is produced in response to numerous proinflammatory stimuli (e.g., infectious, allergic and environmental agents) and trauma. TSLP has a central role in the initiation of immune responses and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, ILC-2 cells and basophils (Watson and Gauvreau 2014). Classically, TSLP is believed to be a critical component in the initiation and perpetuation of the T2 response and the resulting cascade of cytokines associated with T2 driven asthma (Kaur and Brightling 2012). Asthma is recognized as a heterogeneous disease. There are subsets of patients that do not exhibit T2-associated disease (Wenzel 2012), and there is existing data that TSLP may also mediate non-allergic (non-T helper cell 2)

inflammation (Tanaka et al 2009, Ziegler et al 2013). The three gene mean, derived from epithelial expression levels of periostin (POSTN), chloride channel accessory 1 (CLCA1), and serpin family B member 2 (SERPINB2), has been demonstrated as a surrogate marker of T2-driven inflammation in mild to moderate asthmatics (Woodruff et al 2009, Choy et al 2011, Bhakta et al 2013). This epithelial gene expression signature will be used to retrospectively determine the degree of T2 activity of each individual at randomization (Visit 3b). We believe that tezepelumab will be efficacious in both T2 low and T2 high subjects (based on the Phase 2b data) so the effect of tezeplumab across the T2 spectrum as determined by the three gene mean signature, will be explored.

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with TSLP receptor (TSLPR). Owing to the central role of TSLP in initiating and maintaining a T2 response, anti-TSLP therapy may provide an opportunity to treat the upstream underlying mechanisms of asthma by reversing the established inflammatory responses to asthma triggers.

Results of a completed inhaled allergen challenge study in 31 adult subjects with mild atopic asthma (Study 20101183) demonstrated that tezepelumab attenuated the LAR and EAR to allergen challenge, as measured by the Area Under the Curve (AUC) for the percent fall in FEV_1 and the maximum percent fall in FEV_1. Tezepelumab also attenuated the expected increase in FeNO value as well as sputum and blood eosinophils on the post-allergen day compared with the pre-allergen day. Multiple doses of 700 mg IV tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed ADA after receiving tezepelumab in this exploratory study.

Study CD-RI-MEDI9929-1146 was a Phase 2b multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of tezepelumab on the AAER in adult subjects with inadequately controlled, severe asthma. Subjects were randomized in a 1:1:1:1 ratio to 1 of 3 dose levels of SC tezepelumab (280 mg Q2W, 210 mg Q4W, 70 mg Q4W) or placebo (Q2W) for 52 weeks. A total of 584 subjects received at least 1 dose of tezepelumab or placebo. One site was excluded from all analysis due to GCP noncompliance making the total number of subjects analyzed to 550. A post-hoc sensitivity analysis excluding these subjects (38 subjects in the active treatment arms and 13 subjects in placebo arm) was performed for the primary and selected secondary endpoints. Results from the post-hoc analysis showed that reductions in AAER at Week 52 of 62% ($p<0.001$), 71% ($p<0.001$), and 66% ($p<0.001$) for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W doses, respectively, compared with placebo were observed. These results are similar to those observed in the overall ITT population (AAERR of 61%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups, respectively, compared with placebo. After repeated SC administration, mean serum trough concentration

increased over time and achieved steady-state by week 12. Tezepelumab exhibited linear pharmacokinetics (PK) across 3 doses. A low incidence of ADA was observed across all treatment subjects. The ADA incidences were 9.4%, 3.7%, 0.8%, and 2.3% for placebo, 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W, respectively and no subjects tested positive for neutralizing antibodies. There was no impact of ADA on tezepelumab PK. The results of this study did not identify safety concerns associated with tezepelumab for any dosing regimen. The overall incidence of TEAEs were similar between the placebo (65.9%) and the tezepelumab (66.0%) dose groups. A majority of subjects had TEAEs that were Grade 1 (mild) or Grade 2 (moderate) in severity and not related to IP. TEAEs that resulted in permanent discontinuation of IP occurred in few subjects, and at a similar incidence between the tezepelumab (5 subjects [1.2%] overall) and placebo (1 subject [0.7%]) groups. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no identified safety risks were noted.

2.3 Benefit/risk assessment

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

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

The potential benefits of the study are expected to be Category IIB as described in the guidance document aimed directly at the diagnosis, cure, or prevention of disease.

Biopsies will be performed by qualified pulmonologists experienced in research bronchoscopies, and all due precautions will be taken to minimize the risk to subjects. Risks of the study include those associated with invasive study assessments such as bronchoscopy, bronchial biopsy, bronchial brushing and bronchoalveolar lavage (BAL). Although rare, complications of bronchoscopy and biopsy include pneumothorax and the risks associated with anesthesia. BAL has some possible complications like cough, transient fever, transient chills and myalgias, bronchospasm, or transient decrease of lung function. Also, there is a minor risk of exposure to radiation by the CT scans, the use of CT may cause an increase in the risk of radiogenic tumors in subjects.

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

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

3. OBJECTIVES AND ENDPOINTS

Table 2 – Objectives and Endpoints

Objectives and Endpoints

Primary Objective	**Outcome Measure:**
To explore the airway anti-inflammatory effect of tezepelumab	Outcome Variable: The change, expressed as a ratio, in the number of airway submucosal inflammatory cells/mm^2 of bronchoscopic biopsies from baseline to EOT. Airway submucosal inflammatory cells will include eosinophils, neutrophils, T cells and mast cells Outcome Measure: Ratio of tezepelumab to placebo at EOT
Secondary Objective:	**Outcome Measure:**
To explore the effect of tezepelumab on RBM thickening	Outcome Variable: The change, expressed as a ratio, in RBM thickness determined by microscopic evaluation of bronchoscopic biopsies from baseline toEOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the effect of tezepelumab on airway epithelial integrity	Outcome Variable: The change, expressed as a ratio, in % airway epithelial integrity determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the airway anti-inflammatory effect of tezepelumab across the spectrum of T2 status by three gene mean derived from bronchial brushing RNA transcriptomics	Outcome Variable: The change, expressed as a ratio, in number of airway submucosal inflammatory cells per mm^2 determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT in subjects across the spectrum of T2 status determined by RNAseq of bronchial brushings at baseline

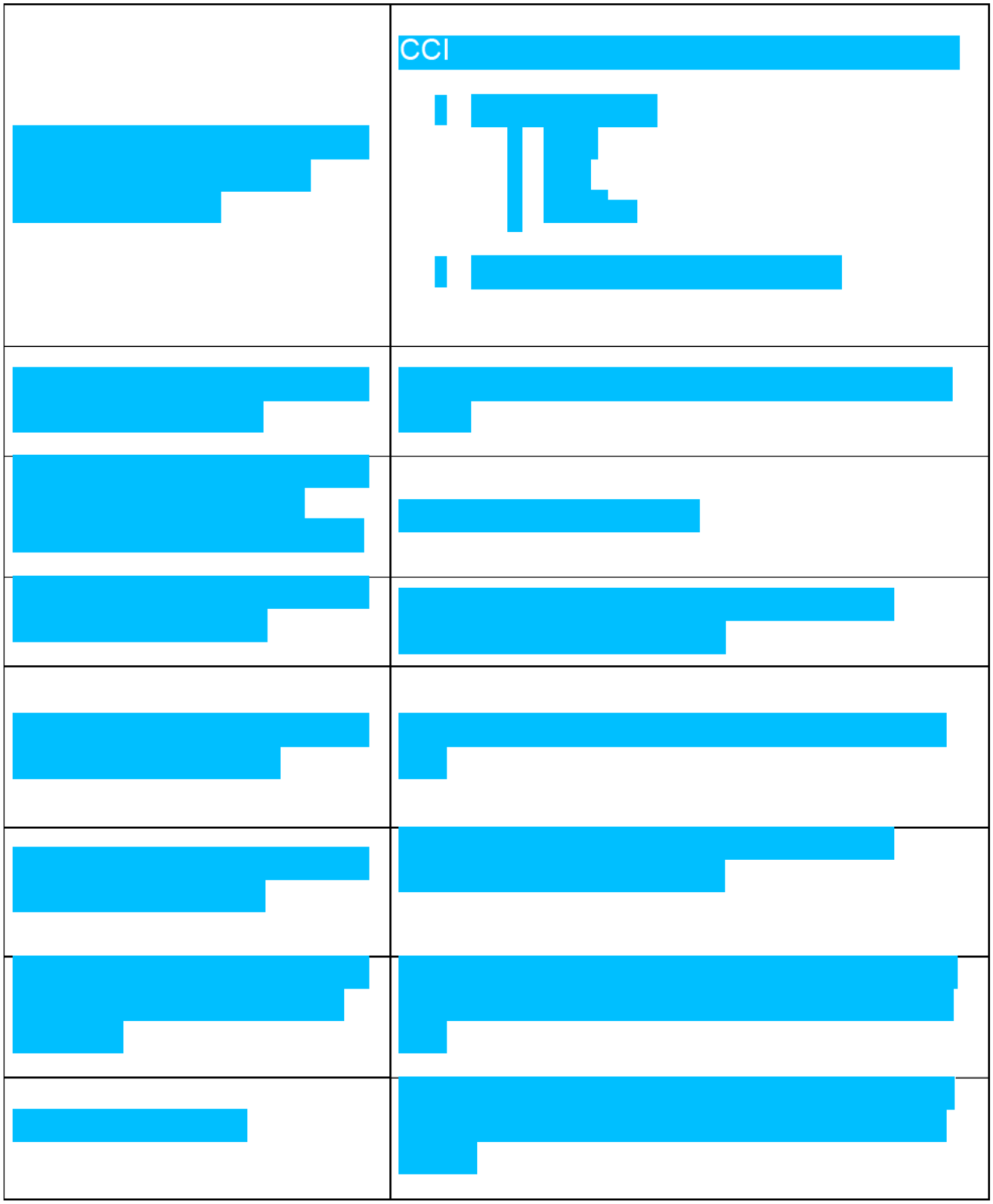
Objectives and Endpoints

	Outcome Measure: Ratio of tezepelumab to placebo at EOT across the spectrum of T2.
Safety Objectives:	**Outcome Measures:**
To evaluate the safety and tolerability of tezepelumab	AEs/SAEs/AESIs Clinical chemistry/hematology/urinalysis Vital signs ECG
Exploratory Objectives:	**Outcome Measure:**
[redacted]	CCI [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives and Endpoints

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

Objectives and Endpoints



4. STUDY DESIGN

4.1 Overall design

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

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

This is a Phase 2, multicentre, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of tezepelumab on airway inflammation in approximately 110 adults with inadequately controlled moderate-to-severe asthma. Patients will have background asthma therapy of medium- or high dose ICS plus at least one additional asthma controller medication, such as a long-acting β2 agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting anti-muscarinic (LAMA), cromone, and theophylline, with or without maintenance oral corticosteroids (OCS) from screening and throughout the study including the follow-up period.

The study will consist of a screening/run-in period of up to 4 weeks, a treatment period of 28 weeks and a post-treatment follow-up period of 12 weeks. One dose level of tezepelumab, 210 mg will be compared with placebo administered SC Q4W over the treatment period. Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 40-week period. Any new treatments that are initiated will be recorded. Subjects who complete the 28-week study visit will complete a 12-week post-treatment follow-up period.

Please note: During the COVID-19 pandemic, there is an option for patients to have an extra dose every 4 weeks up to 6 additional doses, as needed. (please refer to Appendix J). For the last follow up visit, a phone call visit can replace an on-site visit. Please refer to Appendix J

The study aims to randomize subjects across the T2 spectrum. To ensure this, the study will randomize approximately 30% of subjects with < 150 blood eosinophils/µL, approximately 30% of subjects with 150 - <300 blood eosinophils/µL and approximately 40% of subjects with ≥ 300 blood eosinophils/µL.

When the target percentage of subjects for each blood eosinophil subgroup in the study is reached, consideration will be given to closing the IWRS/IVRS randomization for that subgroup, which may be done on the study level irrespective of region. Once a subgroup is closed, subjects in the screening/run-in period in the closed subgroup will not be allowed to be randomized and will be screen failed.

Section 6.5 (Table 5 and Table 6) provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial.

4.2 Scientific rationale for the study design

Given that TSLP is an upstream and pleiotropic cytokine, TSLP blockade is anticipated to have broad impact on the spectrum of inflammatory responses observed in asthma. Due to the mechanism of action it is expected that severe asthmatics, irrespective of their phenotype of asthma, would benefit from treatment with tezepelumab.

To better understand the effect of tezepelumab on airway inflammation, the study will assess multiple airway anti-inflammatory cells (eosinophils, neutrophils, T cells and mast cells) by microscopic evaluation of bronchoscopic biopsies.

These cells have been chosen as they are the typical airway inflammatory cells of asthma and represent both T2 and non-T2 driven inflammatory cell types. Published literature supports a potential role for TSLP, and therefore tezepelumab, on all of these cell types; eosinophils (Wong et al 2010, Cook et al 2012), neutrophils (Li et al 2018), T cells (Soumelis et al 2002, Torii et al 2008, Tanaka et al 2009, Rochman et al 2007) and mast cells (Allakhverdi et al 2007). This mechanistic study is designed to investigate the efficacy of tezepelumab in T2 high and T2 low subjects, hence we will examine the anti-inflammatory effects of tezepelumab on a broad array of airway inflammatory cells. Bronchoscopic biopsies will be also used to assess the effect of tezepelumab on airway epithelial integrity and reticular basement membrane thickness. As an epithelial barrier alarmin, TSLP is predicted to be involved in epithelial homeostasis and wound healing. TSLP has also been reported to play a role in airway smooth muscle proliferation (Redhu et al 2013). Therefore, we believe the remodeling end points of airway epithelial integrity and reticular basement membrane thickness may be impacted by tezepelumab and this will be explored in this study.

The BAL will be used to assess different biomarkers and tezepelumab PK. The study is also assessing the effect of tezepelumab on large airways using CT and the effect of tezepelumab on the small airways using AO and CT.

Bronchial epithelial brushings will be used to assess the T2 status of the subjects using the three gene mean. In addition, exploratory biomarkers in blood and urine will also be assessed.

The treatment period of 28 weeks allows ample time for tezepelumab to show effect on airway epithelial integrity and RBM thickness.

In the Phase 2b trial subgroups, those with low and high baseline blood eosinophil counts and low and high T2 profile, clearly improved with tezepelumab treatment (CD-RI-MEDI9929-1146). In the present study, to ensure recruitment of adequate numbers of T2 low and T2 high

subjects for analysis, subjects will be enrolled based on screening blood eosinophil counts. Blood eosinophils are not sufficient to determine T2 status, but are a convenient approach to use during the screening process. At study end, epithelial expression of periostin (POSTN), chloride channel accessory 1 (CLCA1), and serpin family B member 2 (SERPINB2); a gene signature demonstrated as a surrogate marker of T2-driven inflammation in mild to moderate asthmatics (Woodruff et al 2009, Choy et al 2011, Bhakta et al 2013), will be assessed to confirm that a range of subjects spanning the T2 continuum was included in this study.

In order to avoid bias, this study will be randomized and double-blinded. A placebo group will be included to ensure a control for comparison effects.

4.3 Justification for dose

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

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

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

4.4 End of study definition

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

A subject is considered to have completed the study when he/she has completed his/her last scheduled 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 of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to section 5.4.

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

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

5.1 Inclusion criteria

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

Informed consent

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

2. Provision of signed and dated written genetic informed consent prior to collection of optional sample for genetic analysis.

The ICF process is described in Appendix A 3.

Please note: During COVID-19 pandemic, ongoing patients in the study may need to be re-consented. Local/regional guidelines must be followed with regard to informed consent. Please refer to Appendix J .

Age

3. Subject must be 18 to 75 years of age inclusive, at the time of signing the informed consent form.

Type of subject and disease characteristics

4. Documented physician-diagnosed asthma for at least 12 months prior to Visit 1 (V1).

5. Subjects who have received a physician-prescribed asthma controller medication with medium or high dose ICS as per GINA guideline (GINA 2018) for at least 12 months prior to V1.

6. Subjects who have received a physician-prescribed asthma controller medication with medium- or high-dose ICS must have been on a stable dose for at least 3 months prior to V1.

- High-dose ICS is defined as total daily dose of >500 µg fluticasone dry powder inhaler or a total daily dose of 440 µg fluticasone metered dose inhaler or equivalent
- Medium-dose ICS is defined as a total daily dose of >250-500 µg fluticasone dry powder inhaler or a total daily dose of >220-440 µg fluticasone metered dose inhaler or equivalent
- Equivalent ICS doses will be based upon GINA guidelines (GINA 2018), as detailed in Appendix F.

7. At least 1 additional maintenance asthma controller medication is required according to standard practice of care; e.g. LABA, LTRA, theophylline, LAMA, cromone etc. Use of additional asthma controller medications must be documented for at least 3 months prior to V1.

Notes:

- Patients who are on triple background medication, e.g. ICS plus LABA plus LAMA, will be eligible for enrolment.
- The ICS and LABA can be parts of a combination product or given by separate inhalers.
- Subjects on OCS are allowed in the study, provided they are on a stable maintenance dose for at least 6 months before V1.

8. The subject must have a predicted normal value (PNV) for the morning pre-bronchodilator (BD) FEV_1 >50% and more than 1 L at V1. If this is not met at V1, this criterion must be met at V2.

   NB: If the subject did not withhold their morning BD dose, all other V1 study assessments may be completed, except for the spirometry procedure, which should be scheduled within 3 days of V1.

9. Subjects must have evidence of asthma as documented by post-BD (albuterol/salbutamol) reversibility of FEV_1 ≥12% and ≥200 mL (15-60 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 12 months prior to V1, at V1, or at V2.

10. ACQ-6 score ≥ 1.5 at V1. If patient does not meet criterion at V1, ACQ-6 score ≥ 1.5 must be met at V2.

Weight

11. Weight ≥ 40 kg at V1.

Reproduction

12. Negative serum pregnancy test for female subjects of childbearing potential at V1.

13. Females of childbearing potential who are sexually active must use a highly effective method of contraception from screening and must agree to continue using such precautions for 16 weeks after the final dose of IP. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

- A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Highly effective forms of birth control methods include: true sexual abstinence [periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not permitted], a vasectomized sexual partner, Etonogestrel (e.g. Implanon™), bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system,, Medroxyprogesterone (e.g. Depo-Provera™) injections, oral contraceptive, Norelgestromin/ Ethinyl Estradiol patch (e.g. Evra Patch ™) or etonogestrel/ethinyl estradiol vaginal ring (e.g. Nuvaring™).

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of randomization without an alternative medical cause. The following age specific requirements apply:

    - Women < 50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

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

Inclusion criteria at randomization:

14. Subjects must have demonstrated a minimum 70% compliance with diary completion during the run-in period with a minimum of 4 days of compliance during the last 7 days of the run-in period

A compliant day requires completion of evening diary and subsequent morning diary

- The run-in period for this criterion is defined as the period between diary assignment (evening assessment) of Visit 2 (V2) and Visit 3a (morning assessment).

15. Subjects must have demonstrated a minimum 70% compliance with background asthma medication during the run-in period with a minimum of 4 days of compliance during the last 7 days of the run-in period.

16. For WOCBP only: have a negative urine pregnancy test prior to administration of the IP.

17. Subjects must have the ability to perform acceptable inhaler and spirometry techniques as judged by the Investigator.

18. Subjects must have a successful bronchial biopsy procedure at Visit 3b as judged by the Investigator. Successful BAL and bronchial brushing are not inclusionary.

5.2 Exclusion criteria

Medical conditions

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

2. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

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

3. History of cancer:

Subjects who have had basal cell carcinoma, 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 V1.

Subjects who have had other malignancies are eligible provided that curative therapy was completed at least 5 years prior to V1.

4. Subjects who had been hospitalized or required OCS for an asthma exacerbation event within 6 weeks of enrolment or who had more than 3 asthma exacerbations requiring OCS or hospitalization in the year prior to V1 or who had either been intubated or admitted to the ICU for an asthma exacerbation in the year prior to enrolment will be excluded. For this study, an asthma exacerbation is defined as a worsening of asthma that either:

- required treatment with a burst of systemic corticosteroids for at least 3 days or a single IM depo-injectable dose of corticosteroids will be considered equivalent to a 3-day burst of systemic corticosteroids

OR

- resulted in an emergency department visit (defined as evaluation and treatment for <24 hours in an ER or urgent care center) which required systemic corticosteroids (as per above)

OR

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

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

5. History of a clinically significant infection, including upper (URTI) or lower respiratory tract infection (LRTI), requiring treatment with antibiotics or antiviral medications finalized < 2 weeks before V1 or during the run-in period.

6. A helminth parasitic infection diagnosed within 6 months prior to V1 that has not been treated with, or has failed to respond to, standard of care therapy.

7. Current smokers or subjects with smoking history ≥ 10 pack-years including the use of vaping products, such as electronic cigarettes. Former smokers with a smoking history of <10 pack years, including former vaping or e-cigarette users, must have stopped for at least 6 months prior to Visit 1 to be eligible.

8. History of chronic alcohol or drug abuse within 12 months prior to V1.

9. Tuberculosis requiring treatment within the 12 months prior to V1.

10. History of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at V1, or the subject taking antiretroviral medications as determined by medical history and/or subject's verbal report.

11. Major surgery within 8 weeks prior to V1 or planned surgical procedures requiring general anesthesia or in-patient status for > 1 day during the conduct of the study.

Prior/concomitant therapy

12. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to V1 or receipt of any investigational non-biologic agent within 30 days or 5 half-lives (whichever is longest) prior to V1.

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

13. Treatment with the following medications within the last 12 weeks prior to randomization: Systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, etc.) except for OCS used in the treatment of asthma/asthma exacerbations or receipt of the T2 cytokine inhibitor suplatast tosilate within 15 days prior to V1.

14. Receipt of immunoglobulin or blood products within 30 days prior to V1.

15. Receipt of live attenuated vaccines 30 days prior to the date of randomization

16. Subjects that have been treated with bronchial thermoplasty in the last 24 months prior to V1.

17. Known or suspected history of immunosuppression, immune dysfunction or immune dysregulation which may include but is not limited to conditions such as: Guillain-Barré syndrome, invasive opportunistic infections (e.g. histoplasmosis,

listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), or unusually frequent, recurrent, or prolonged infections, per Investigator judgment

Prior/concurrent clinical study experience

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

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

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

21. Subject randomization in previous tezepelumab studies.

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

Diagnostic assessments

23. Any clinically meaningful abnormal finding in physical examination, vital signs, ECG, hematology, clinical chemistry, or urinalysis during the run-in 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 the entire duration of the study.

24. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2 times the upper limit of normal (ULN) at V1.

25. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology at screening, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without a history of hepatitis B and subjects with hepatitis C who have been cured are allowed to participate.

Other exclusions

26. 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.

27. 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

28. Previous allogeneic bone marrow transplant.

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

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 center.

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 V1 and throughout the conduct of the study is restricted.

Current smokers or subjects with smoking history ≥ 10 pack-years, including the use of vaping products such as electronic cigarettes at V1 are not allowed.
Former smokers with a smoking history of <10 pack years, including former vaping or e-cigarette users, must have stopped for at least 6 months to be eligible. Smoking is not allowed throughout the course of the study

The use of e-cigarettes is also not allowed during the course of the study.

5.3.3 Activity

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

5.4 Screen failures

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

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

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

- Subjects with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to the screening/run-in period may be re-screened 14 days after recovery, i.e., completion of the therapy.
- Subjects who experience an asthma exacerbation during run-in period may be re-screened after 14 days of complete resolution of the asthma exacerbation, and when the subjects return to their baseline at Investigator discretion.

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

Any re-screened subject will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF) and after all V1 assessments have been performed as listed in SoA, Table 1 (with the exception of testing for HIV1 and HIV2, hepatitis B and C, and FSH). If the timeframe between screening and re-screening exceeds 30 days, the subject will not be permitted to re-screen without repeating Visit 1 assessments, as per PI discretion.

Subjects who experience an asthma exacerbation before the EOT assessments should have their EOT visit rescheduled to be after 14 days after the complete resolution of the asthma exacerbation, and when the subjects return to their baseline, provided that the Investigator has no safety concerns.

Rescreening should be documented so that its effect on study results, if any, can be assessed.

IMPORTANT: Re-screening for subjects who have screen-failed due to PRO criteria (e.g.

ACQ-6 score <1.5 or did not report adequate compliance with maintenance medications) is not allowed.

Re-screening of a subject for any other reason (transient reasons including, but not limited to study supplies, equipment failures, unforeseen personal event, missed visits, etc.) will be allowed only upon approval of the AstraZeneca study physician. A documented approval for re-screening should be filed in the Investigator Study File (ISF).

6. STUDY 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

Table 3 – Study treatments

	Treatment 1	Treatment 2
Study treatment name:	Tezepelumab	Placebo
Dosage formulation:	CCI	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 6.2	Refer to section 6.2

Packaging and labelling	Study treatment will be provided in 5cc vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.	Study treatment will be provided in 5cc vial. Each vial will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.

6.2 Preparation/handling/storage/accountability

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

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.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorized site staff.

The 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).

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

Dose preparation

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

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

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

Dose preparation steps:

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

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

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

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

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

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

7. Apply the appropriate label to the syringe.

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

The IP will be administered by one SC injection (see Table 4) and must be prepared using disposable plastic syringes and aseptic technique.

Table 4 – Investigational product dose preparation

Dose	Number of vial (s) required	Syringe size required	Total Volume administered
210 mg [a]	1	2 or 3 mL	1.9 mL

Placebo	1	2 or 3 mL	1.9 mL

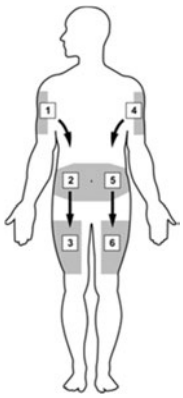
[a] Due to the gradations available on 2 or 3 mL disposable plastic syringe, dose based on 1.9 mL administered volume is 209 mg.

Dose administration

IP will be administered by a qualified healthcare professional (e.g. pharmacist, Investigator or qualified designee) at the site. The injection site must be recorded in the source documents at each treatment visit and in the eCRF. The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90-degree angle approximately halfway into the SC tissue. The IP will be slowly injected (at least 5 second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. It is advised that the site of injection of IP be rotated such that the 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.

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

Figure 2 Suggested schema of rotation of injection sites



Subjects should be observed for a minimum of 2 hours after administration of the first two IP

administrations for the appearance of any acute drug reactions. For the remaining doses, 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 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 subject skips 2 consecutive IP administrations, the AstraZeneca study physician should be contacted to discuss further participation.

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

6.3 Measure to minimize bias: randomization and blinding

The Investigator(s) will:

1. Obtain signed informed consent or assent from the potential subject, or their guardian/legal representative, before any study specific procedures are performed.
2. Assign the potential subject a unique enrolment number (which begins with an ‘E’) via the interactive web response system/interactive voice response system (IWRS/IVRS).
3. Determine subject eligibility.
4. Assign the eligible subject unique randomization code via IWRS/IVRS.
5. Subjects will be allocated to receive tezepelumab or placebo in a 1:1 ratio and stratified by baseline eosinophil level (< 150, 150 - 300, > 300). 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/IVRS 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.

If 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. In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about IP, all randomized patients should remain in the study and the subjects should continue to be followed up in accordance with defined study procedures.

Methods for assigning treatment groups

Randomization will be stratified by screening blood eosinophil level. Approximately 30% of subjects with < 150 blood eosinophils/μL, approximately 30% of subjects with 150 - <300 blood eosinophils/μL, and approximately 40% of subjects with ≥300 blood eosinophils/μL.

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 PAREXEL Informatics on behalf of AZ (AZRand).

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, Investigator or qualified designee) 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 IXRS company
- Supply Chain Management department
- Bioanalytical lab performing PK sample analysis.
- Patient Safety department at AstraZeneca
- Applicable DSMB members

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 CRO handling data, will have access to the randomization scheme during the conduct of the study and until database lock.

Methods for unblinding

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the 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.

6.4 Treatment compliance

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 should be recorded in the appropriate section of the eCRF.

6.5 Concomitant therapy

All ICS asthma medications taken in the 12 months prior to V1 must be recorded in the eCRF along with reason for treatment.

To satisfy inclusion criterion 6, a history of continuous treatment with medium or high dose ICS plus a second controller medication for at least 3 months prior to V1 should be documented in source and recorded in the eCRF prior to the date of randomization.

In order to satisfy inclusion criterion 7, a history of all asthma controller medications for the 3 months prior to V1 until the end of the study should be documented in source and recorded in the eCRF. No changes are allowed to background asthma medications throughout the duration of the study except during the treatment of an asthma exacerbation.

All other medications taken for conditions other than asthma in the 3 months prior to V1 must be recorded in the eCRF along with reason for treatment by the Investigator/authorized delegate at each visit (as shown in Table 1).

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

As theophylline has a narrow therapeutic window, please note that subjects on maintenance treatment with theophylline should have blood concentration levels within therapeutic range. documented before V1. 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 V1 procedures. The sample can be analyzed at the central or local lab as applicable. Investigator can use their clinical judgement about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

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

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

Table 5 – Restricted medications

Medication/class of drug:	**Usage**
Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)	No changes in either dose or regimen are allowed from V1 and until at least the EOT visit, unless there is a medical need as judged by the Investigator. The patients should be instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment (please refer below for long-acting bronchodilator restrictions). Use of SABA or SAMA should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at V1. Twice daily bronchodilators should be withheld for at least 12 hours prior to the scheduled FeNO and spirometry at site. Once daily bronchodilators should be withheld for at least 24 hours prior to the scheduled FeNO and spirometry at site. Subjects will not need a washout of their asthma medications for unscheduled visits due to asthma worsening.
Short-acting beta-agonists (SABA)	Regular scheduled use of SABA is not allowed from V1 and until at least the EOT visit, unless there is a medical need as judged by the Investigator. PRN use is allowed if needed, however attention should be paid to the following restrictions. SABA should be withheld for at least 6 hours prior to scheduled spirometry, FeNO, ECG at site with the exception of any unscheduled visits due to asthma worsening.

Medication/class of drug:	**Usage**
Additional maintenance controllers	No changes in either dose or regimen are allowed from V1 and until at least the EOT visit, unless there is a medical need as judged by the Investigator. Once daily LABA and LAMA should be withheld for at least 24 hours prior scheduled spirometry and FeNO at site visits with the exception of any unscheduled visits due to asthma worsening. Twice daily LABA or LAMA containing therapies should be withheld for at least 12 hours prior to scheduled spirometry and FeNO at site with the exception of any unscheduled visits due to asthma worsening. LTRA should be restricted for at least 24 hours prior to scheduled spirometry and FeNO at site with the exception of any unscheduled visits due to asthma worsening. Subjects on theophylline should have blood concentration levels within therapeutic range documented before proceeding in the study. Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry and FeNO at site with the exception of any unscheduled visits due to asthma worsening. Once daily theophyllines should be withheld for at least 24 hours prior to scheduled spirometry and FeNO at site with the exception of any unscheduled visits due to asthma worsening.
Short-acting anticholinergics (e.g. ipratropium)	These are not allowed as a rescue treatment for worsening asthma symptoms from V1 and until at least the EOT visit, unless there is a medical need as judged by the Investigator. They may be used for managing an asthma exacerbation event.
Inactive/killed vaccinations (e.g. inactive influenza)	Allowed provided they are not administered within 5 days before or after any study visit.

Medication/class of drug:	**Usage**
Allergen immunotherapy	Allowed, if on stable therapy for at least 2 months prior to date of V1 with no anticipated change during the treatment period. These should not be administered on the same day as IP administration.

Table 6 – Prohibited medications

Prohibited medication/class of drug:	**Usage**
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Not allowed 15 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed within 15 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Live attenuated vaccines	Not allowed 30 days prior to the date of randomization, and during the study including the follow-up period.
Anticoagulants	Not allowed 15 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Any immunomodulators or immunosuppressives (except for OCS used in the treatment of asthma/asthma exacerbations)	Not allowed 12 weeks prior to randomization, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Immunoglobulin or blood products	Not allowed 30 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.

Prohibited medication/class of drug:	**Usage**
Any marketed (e.g. omalizumab, mepolizumab, reslizumab, benralizumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of V1, throughout the entire, screening run in period, treatment period (even if the subject has discontinued IP) and until the follow up visit at week 40.
Other IPs (including investigational use of an approved drug)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care	Not allowed 30 days prior to V1, during screening/run-in and until at least the EOT visit, unless there is a medical need as judged by the Investigator.

6.5.1 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 Case Report Form.

6.5.2 Rescue medication

SABA should be withheld for at least 6 hours prior to scheduled site visit spirometry, FeNO, and ECG at site with the exception of any unscheduled visits due to asthma worsening.

Albuterol (US)/salbutamol (ex US) rescue medication will be provided by the sponsor and obtained locally. Rescue use of SABA administered via nebulization is discouraged, except as urgent treatment during an asthma exacerbation. Occasions where SABA is administered via nebulization will be recorded separately from metered dose inhaler inhalations in the paper diary.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.6 Dose modification

During the COVID-19 pandemic an additional 1-6 IP doses may be administered to subjects during unscheduled visits at weeks 28, 32, 36, 40, 44 and 48 (as needed) until the sites are able to resume performing all study assessments, including bronchoscopies, in accordance to local regulations/guidelines. Please refer to Appendix J

6.7 Treatment after the end of the study

Subjects who complete the study should be given standard of care at the discretion of the Investigator.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subject may be discontinued from IP in the following situations.

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

- Subject decision. The subject is at any time free to discontinue IP, without prejudice to further treatment
- An adverse event considered to jeopardize the safety of a subject participating in the study
- Pregnancy or breastfeeding
- Severe non-compliance with the CSP.
- Development of any study specific criteria for discontinuation, including:
    - An anaphylactic reaction to the IP
    - A helminth parasitic infestation requiring hospitalization
    - An asthma-related event requiring intubation
    - Any malignancy except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided the malignancy is excised and determined to have clean margins

- Development of one or more of the following:

  Confirmed ALT or AST increase of ≥ 8 x ULN

  Confirmed ALT or AST increase of ≥ 5 x ULN for more than 2 weeks

  Confirmed ALT or AST increase of ≥ 3 x ULN and total bilirubin of ≥ 2 x ULN

  ALT or AST of ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%)

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

7.1.1 Procedures for discontinuation of study treatment

Subjects are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Discontinuing study treatment is not the same as study withdrawal. Procedures to follow for study withdrawal are detailed below. If the subject decides to withdraw consent, then the reason for this must be recorded separately in the eCRF. A subject that decides to discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Subjects permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until week 40 even if the subject has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. For additional information regarding pharmacokinetic and pharmacodynamic effects of tezepelumab reference should be made to the Investigator brochure.

All subjects who prematurely discontinue IP should return to the study center and complete the procedures described for the premature IP Discontinuation visit (IPD) at 4 weeks (+/-7 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 until he/she completes a total of 28 weeks treatment period.

2. The subject will be offered follow-up on a monthly basis via telephone calls until the subject completes 28 weeks in the study. The subject should return for a follow-up visit 16 weeks (+/- 3 days) post last IP administration and for the EOT visit at Week 28 (or later due to COVID-19 pandemic) (+/-3 days).

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 diary, they will complete a follow-up visit at 16 weeks (+/-7 days) (refer to SoA, Visit 14 – week 40) post last IP administration. After this visit the Investigator will only contact the subject at 28 weeks post-randomization (or later due to COVID-19 pandemic) No other study assessments will be performed prior to this contact.

If the last IP administration was at or after week 16 for options 1 or 2, the subject will return to the clinic for an EOT visit at week 28 (or later due to COVID-19 pandemic) (+/- 3 days). The PI will not perform the EOT bronchoscopy assessment unless the subject has had IP administered at least through the week 16 dose. Any subjects who discontinues IP before week 16 (V8) or had an EOT visit date greater than 12 weeks after date of last dose of IP will not have the EOT bronchoscopy assessment performed. For option 3, the Investigator will contact the subject at 28 weeks post randomization. For all options 1, 2 and 3, subjects will then return for a follow-up Visit 16 weeks (+/- 7 days) post-last IP administration (refer to SoA, V14 – Week 40). The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2. Subjects who do not wish to have any follow-up contacts will be discontinued from the study. All discontinued subjects must return the paper diaries at the EOT visit. If the subject chooses option 1, all assessments will be completed as per the SoA as indicated in Section 1.1. If the subject chooses 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, health care utilization, and asthma exacerbation information.

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).

If a subject discontinues IP due to a study-specific discontinuation criterion, this should always be recorded as ‘Development of study specific discontinuation criteria’ on the Discontinuation of Investigational Product form in the eCRF. For more information related to COVID-19 please refer to eCRF instructions.

7.2 Lost to follow-up

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

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

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

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

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g. withdraw consent), at any time (IP and assessments) at his/her own request, without prejudice to further treatment. A subject who 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 AEs. 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, Section 1.1.

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

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

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

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF. For more information related to COVID-19 please refer to eCRF instructions.

AstraZeneca reserves the right to discontinue a subject's participation in the study for any safety reasons.

7.3.1 Withdrawal due to recruitment completion

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

7.3.2 Discontinuation or suspension of the whole study program

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1).

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

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

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 amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will be approximately 220 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 Bronchial biopsy

Facilities for the management of medical emergencies and cardiopulmonary resuscitation will be available. Biopsies will be performed by qualified pulmonologists experienced in research bronchoscopies, and all due precautions will be taken to minimize the risk to subjects.

Subjects will receive a sedative and local anesthetic to reduce any discomfort and local guidelines to be followed. Subjects will be informed of the risks associated with bronchoscopy and bronchial biopsy procedure before participating in the study.

The biopsy at the EOT Visit will be performed only if the baseline biopsy tissue passes quality control, as judged by the study pathologist. QC criteria include tissue area, quality and architecture which must all be sufficient to allow quantification of inflammatory cells, RBM and epithelium to enable primary and secondary endpoints to be quantified.

Details for conducting bronchial biopsies will be described in a separate manual. Samples will be analyzed at a central facility designated by AstraZeneca. Details of assessment and analysis parameters will be described in a separate manual.

Bronchial biopsy, being the primary endpoint will be conducted first followed by bronchial brushing then the BAL.

8.1.2 Bronchial brushing

During bronchoscopy, bronchial brushings will be obtained. Details for sample collection, handling, processing, storage and transportation will be described in a separate manual. Samples will be analyzed at a central facility designated by AstraZeneca. Details of

assessment and analysis parameters and transporting samples will be described in a separate manual. The periostin (POSTN), chloride channel accessory 1 (CLCA1), and serpin family B member 2 (SERPINB2) three gene mean gene signature for each subject will be reported in the CSR, but additional transcriptomics data will be analyzed separately and will be reported separately from the CSR in a scientific report or publication.

The brushings at the EOT Visit will be performed only if the baseline visit brushing is performed successfully, as judged by the Investigator.

8.1.3 Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) will be obtained during bronchoscopy. BAL will be mandatory for all subjects (unless if there is any safety concern by the Investigator), but it is not an inclusion criterion for patients to be randomized in the study. BAL samples should be collected pre-dose at the pre-specified scheduled visit in the SoA. Details for sample collection, handling, processing, storage and transportation will be described in a separate manual. The results of the exploratory BAL biomarker analyses may be reported separately from the CSR in a scientific report or publication.

The BAL at the EOT Visit will be performed only if the baseline visit BAL is performed successfully, as judged by the Investigator.

8.1.4 Airwave oscillometry

AO is a non-invasive lung function test included in this study to evaluate treatment effect on small airway physiology. AZ will provide the equipment for testing.

A calibrated system will be used for measurements. Detailed procedures for performing, recording and analyzing AO data will be described in a separate manual.

By measuring subject's airflow and response to sound waves, frequency-dependent resistance and reactance will be calculated by the AO system software. A signed and dated copy of the results printout from the equipment must be kept at the study site for source data verification (SDV). The printout must be marked with the study code, subject enrolment code, date and time of measurement, and visit number. Number of parameters including (but not limited to) R5, R20 and AX for each trial will be recorded and analyzed.

The AO assessment at EOT Visit will be performed only if the baseline visit AO is performed successfully, as judged by the Investigator.

8.1.5 Airway hyper-responsiveness

AHR measured by mannitol challenge testing (MCT) will be assessed in a subgroup of patients according to the schedule provided in Table 1. MCT will be performed in accordance

to GINA guidelines (GINA 2006), vendor's manual, and applicable SOP and clinical standards of care at investigational sites. Medication washouts should be followed as per the mannitol vendor's manual detailed in Appendix I.

Signed and dated worksheets from the measurements will be kept in the ISF for SDV. If a worksheet cannot be printed, required measurements will be recorded in the subject's medical records for SDV. Sponsor will provide the mannitol kits to the sites.

The AHR assessment at EOT Visit will be performed only if Visit 2 AHR is performed successfully, as judged by the Investigator.

In case of repeat spirometry at V2, AHR will be rescheduled within 3 days of Visit 2.

8.1.6 Biomarkers

Multiple sample types (blood, plasma, serum, BAL, bronchoscopic biopsies, bronchial brushings and urine) will be collected according to the Table 1 for exploratory analyses to investigate the effect of tezepelumab on biomarkers of inflammation, asthma, remodeling, pharmacology of tezepelumab and for potential predictors of response. All biomarker samples should be collected pre-dose at the pre-specified scheduled visit in the SoA. Instructions for sample collection, processing, storage, and shipment can be found in the separate manual provided to the sites. Samples may be analyzed separately. The results of the exploratory biomarker analyses may be reported separately from the CSR in an addendum, in a scientific report or publication.

8.1.7 Blood eosinophils and neutrophils

Samples for assessment of blood eosinophils and neutrophils will be collected as hematology samples according to the schedule in Table 1. Blood eosinophil and neutrophil counts will be obtained from the total and differential white blood cell (WBC) counts. All blood eosinophil and neutrophil results will be redacted from the laboratory reports except for Visit 1 and Visit 3. Instructions for sample collection, processing, storage, shipment and analysis will be provided in a separate laboratory manual provided to the sites.

8.1.8 Airway inflammatory cells

Lung biopsy tissue will be collected by bronchial biopsy at baseline and EOT to evaluate the effect of tezepelumab on inflammatory cell infiltrate.

8.1.9 Serum IgE

Testing for Serum IgE will be performed as per schedule in Table 1. The analysis for this test will be managed by the central laboratory. All total serum IgE results will be redacted from

the laboratory reports except for Visit 3. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

8.1.10 RNA transcriptomics

Transcriptomic analysis will be performed on the RNA sample obtained from bronchial brushing as per schedule in Table 1. Details for bronchial brushing collection will be as described above (8.1.2). Three gene mean gene signature will be reported in the CSR but additional transcriptomics data from bronchoscopic brushings will be reported separately from the CSR in an addendum, scientific report or publication.

In addition, other samples including whole blood, BAL cells and bronchial biopsies will be collected, stored and may be processed for RNA transcriptomics. Instructions for sample collection, processing, storage, shipment and analyses will be provided in a separate manual of procedures provided to the sites. Samples may be analyzed separately. Any exploratory transcriptomics analyses on BAL cells, whole blood and biopsy tissue, will be reported separately from the CSR in an addendum, in a scientific report or publication.

8.1.11 DNA for genetics

An optional blood sample will be collected as per schedule in Table 1 for genetic analysis. Instructions for sample collection, processing, storage, shipment and analyses will be provided in a separate manual of procedures provided to the sites. This data will be reported separately from the CSR in an addendum, in a scientific report or publication.

8.1.12 Urine biomarkers

Urine will be collected and stored as per schedule in Table 1 for exploratory biomarker analysis of inflammatory markers. Instructions for sample collection, processing, storage, shipment and analyses will be provided in a separate manual of procedures provided to the sites. Samples may be analyzed separately. The results of the exploratory biomarker analyses will be reported separately from the CSR in an addendum, in a scientific report or publication.

8.1.13 Computed tomography

Chest CT will be performed in accordance with the schedule provided in Table 1. Prior to CT scan, subject will be asked to inhale 100 µg of salbutamol using a metered dose inhaler and a valve spacer device. This procedure will be repeated 4 times. CT scan procedure should be within 10-60 minutes post-bronchodilation. Scans will be performed in both full inspiration and full expiration. Detailed procedures for the acquisition, storage, anonymization and transfer of the CT image data will be described in a separate manual.

Details for the analysis of the CT image data to obtain parameters for large airway morphometry, air trapping, vascular pruning and functional imaging will be described in a

separate imaging biomarker document. The CT scans will be assessed clinically at each site, and the Investigator is responsible for the clinical reporting of findings and its subsequent management. Clinically significant findings not related to asthma will be reported as medical history or AEs by the Investigator.

EOT CT will be performed only if baseline CT is performed successfully, as confirmed by imaging QC review by the imaging vendor.

8.1.14 Assessment of asthma exacerbation

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

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

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

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

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

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

Subjects are required to report any of the following in the paper diary:

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

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

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

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

The start of an exacerbation is defined as the start date of systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visits requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier.

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

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

All asthma exacerbations that occur during the treatment period and follow up, must be recorded in the exacerbation eCRF. See section 8.3.7 for additional information on recording asthma exacerbations as an AE/SAE during the study.

8.1.15 Allergen specific IgE (FEIA)

Testing for Phadiatop in blood (allergy screening test) will be performed as per schedule in Table 1. The analyses for these tests will be managed by the central laboratory. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

8.1.16 Spirometry

8.1.16.1 General requirements

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

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

Important!

- Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the center.
- Subjects should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the center.
- Subjects should withhold their usual maintenance therapies on the day(s) when lung function testing is being performed as below:
    - SABAs and SAMAs should be withheld at least 6 hours prior to scheduled spirometry at site.
    - Twice daily LABA or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at site.
    - Once daily LABA or LAMA-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at site.
    - LTRA should be restricted for at least 24 hours prior to scheduled spirometry at site.
    - Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry at site.

- Once daily theophyllines for at least 24 hours prior to scheduled spirometry at site.

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

Time of day for scheduled center visit spirometry

Spirometry testing should be done according to the SoA. For all subjects, spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the screening or re-screening period.

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

Spirometry technique

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

Spirometry references

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

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

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

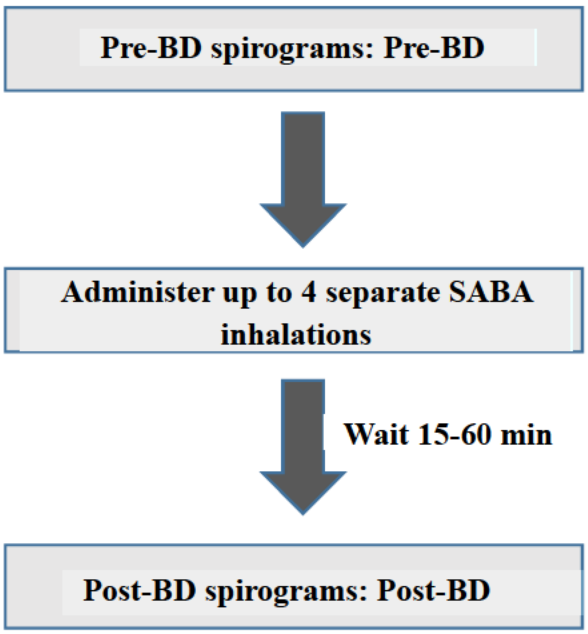
8.1.16.2 Post-BD spirometry and FEV_1 reversibility assessment

All subjects must meet inclusion criteria 9 either by having documented historical reversibility or by demonstrating reversibility either at V1 or V2.

Even if documented historical reversibility is available, the post-BD spirometry procedures must be performed at V1 to categorize subjects (establish baseline characteristic) prior to randomization. The documented historical reversibility must be recorded in the eCRF/spirometer prior to randomization. Further details will be provided in a separate instruction manual.

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

Figure 3 Reversibility algorithm



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

V2 is an optional visit at which the reversibility testing/ post BD spirometry can be repeated, if the inclusion criteria were not met or the patient was unable to perform good quality spirometry.

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

Reversibility is calculated as follows:

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

Record keeping

A signed and dated copy of the pre- and post-BD printout must be kept at study center 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.

8.1.17 Fractional exhaled nitric oxide

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 (Allakhverdi et al 2007, Alving et al 2017).

Subjects will be asked whether they have had a respiratory infection in the 2 weeks prior to the measurement. The FeNO measurements will not be performed within 2 weeks of a respiratory infection. The FeNO test will be performed prior to spirometry. Subjects should not eat or drink 1 hour prior to having the FeNO test. Subjects should not use their rescue SABA medication (e.g. albuterol/salbutamol) or SAMA medications within 6 hours of the measurement. Inhaled BDs (including ICS/LABA) should be withheld for the effect duration specific to the BD as described in the spirometry section. If not, the assessment should be postponed till after the required time has passed since the meal or drink or 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.

All post-randomization FeNO measurements will be blinded for sites and subjects throughout the study. The sponsor will be unblinded to the FeNO values prior to randomization and blinded to the FeNO values post randomization.

8.1.18 Patient reported outcomes

Patient reported outcomes (PRO) data will be captured by paper diaries at home and at the site. Subjects will be trained on at-home use of the diary at V2. Training will emphasize the importance of completing the paper diary assessments as scheduled to capture the subject's experience and meet the objectives of the study. The questionnaires will be completed at home in the following order: Rescue medication, nocturnal awakening, maintenance medication. At every visit, subjects will be asked to return their paper diaries to be filed with the source documents. Site will give the subject a new diary booklet every visit, as specified in the SoA.

At-home paper diary assessments will start the evening of V2. Subjects will complete assessments twice daily at timepoints specified in the SoA.

The Investigator/authorized delegate will check subject's adherence to the paper diary completion to minimize missing data at each study visit. Frequent compliance checks between visits will be necessary to ensure sufficient data is available to meet inclusion criteria 14 and 15.

8.1.18.1 Paper Diary

The paper diary will be completed each day from the evening of V2 to the morning of Visit 14 (V14). The morning diary will include: questions about rescue medication, night-time awakening, and use of maintenance medications. The evening diary will include: questions about rescue medications. Only the occurrence of worsening or new asthma symptoms will be reported on the paper diary.

Please note: During the COVID-19 pandemic, once extra dosing and/or home IP administration is implemented, recording, collection, and dispensation of the subject's paper diaries will continue.

Rescue medication

The number of rescue medication inhalations (puffs) and nebulizer treatments taken will be recorded by the subject in the paper diary twice daily (i.e., in the morning and evening) beginning the evening of V2 until the morning of V14. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and the morning will be recorded in the morning.

Nocturnal awakenings

Nocturnal awakenings due to asthma symptoms will be recorded by the subject in the paper diary each morning, beginning in the morning after V2 until the morning of V14, by answering a question as to whether he/she woke up during the night due to asthma symptoms by a "yes" or "no" response.

Maintenance medication

Maintenance medication administration will be recorded daily in the paper diary in the morning, beginning in the morning after V2 until the morning of V14.

8.1.18.2 Asthma control questionnaire (ACQ-6)

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

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤1.5 indicate partly controlled asthma, and a score >1.5 indicates uncontrolled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful, and a decrease of at least 0.5 is the responder definition for ACQ-6.

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 Table 7, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at center 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 clinical chemistry, hematology and urinalysis will be performed at a central laboratory.

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-Blood	S-CRP
U-Protein	S-Gamma-glutamyl transpeptidase (GGT)
U-Glucose	S-Glucose
	S-Phosphorus
U-Microscopy and culture as required**	S-Potassium
	S-Sodium
	S-Total cholesterol
	S-Uric acid

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

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

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

8.2.1.1 Pregnancy Test

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

- Serum ß-human chorionic gonadotropin (ß-HCG) – the test will be mandatory at enrolment (V1) and at EOT visit, for women of child-bearing potential (WOCBP).

- FSH – the test done at enrolment (V1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months.

- Urine HCG – the test will be performed 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 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 centimeters. Weight and height measurements will be performed in light clothing and with shoes off. Body Mass Index (BMI) will be automatically calculated in the eCRF.

8.2.3 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.

8.2.4 Vital signs

Vital signs (i.e. pulse, blood pressure, respiration rate and body temperature) will be obtained in accordance with SoA.

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

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

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

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

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

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

8.2.5 Electrocardiograms

A 12- or 15-lead ECG will be taken in supine position, prior to blood draw, spirometry, and BD administration.

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

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

ECG evaluation will be recorded in the eCRF.

8.2.6 Other safety assessments

8.2.6.1 Serology

Hepatitis B surface antigen, hepatitis C antibody, HIV-1 and HIV-2 antibodies will be assessed at enrolment (V1) 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.

8.3 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 A.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see section 8.3.3.

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

All AEs, including SAEs will be collected from time of signature of informed consent form throughout the treatment period and the follow-up periods. AEs and SAEs should still be collected after IP discontinuation for subjects that prematurely discontinue from IP and will be encouraged to undergo appropriate study visits/procedures for the full 40-week period.

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 AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs 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 SAEs/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
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

8.3.5 Causality collection

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

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

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

8.3.6 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 CSP mandated laboratory tests, vital signs and ECG will be summarized 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 IP.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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

- The sign or symptom is serious according to definitions, see Appendix B
- The 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 asthma history (defined as within 1 year of V1) as judged by the Investigator.

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

8.3.8 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:

- Anaphylactic reactions
- Immune complex disease (Type III hypersensitivity reactions)
- Malignancy
- Helminth infections
- Severe infections which are defined as:
    - SAEs or
    - Requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infection or
    - Requiring a permanent discontinuation of study drug
- Injection site reactions
- Opportunistic infections
- Guillain Barre Syndrome

8.3.9 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.

8.4 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.

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

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 CRF module.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal 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 abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) 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 paper-based pregnancy outcome report 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 abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP.

8.4.3 Overdose

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

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

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

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

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

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

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

8.4.4 Medication error

If a medication error occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

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

8.4.5 Management of IP-related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions, must be immediately available when IP is being administered. Study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix G .

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

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

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

3. Reduced blood pressure after exposure.

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 3 and 5, 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 Data safety monitoring board

The DSMB is an external independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety data at regular intervals and making appropriate recommendations based on the available data. The DSMB will function independently of all other individuals associated with the conduct of the study, including the study sponsor, AstraZeneca, and operate in accordance with a DSMB Charter.

The DSMB 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 if and as required. 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 DSMB.

8.5 Pharmacokinetics

8.5.1 Collection of samples and drug concentration

Serum and BAL samples for determination of tezepelumab will be collected pre-dose according to the SoA (Section 1.1, Table 1)

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

Samples for determination of tezepelumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca using a validated bioanalytical method. Samples for determination of tezepelumab concentration in BAL will be analyzed by a designated third party on behalf of AstraZeneca using a qualified bioanalytical method.

Samples for determination of urea will be analyzed by a designated third party on behalf of AstraZeneca using qualified bioanalytical methods. Urea concentration will be measured in blood and BAL samples to correct for the dilution factor of the BAL samples. Details of the analytical method used will be described in a bioanalytical report.

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

8.5.2 Collection of samples to measure the presence of ADAs

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

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

ADA sample should be collected in case of any suspected immunologically-related AEs.

8.5.3 Storage and destruction of pharmacokinetic/ADA samples

The PK and ADA samples will be retained for future use at AstraZeneca or designee for a maximum of 15 years following Last Subject Last Visit (LSLV).

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

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

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

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

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

8.7.2 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 LSLV, 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

Mandatory collection of samples for biomarker research is also part of this study. The patient's consent to the use of the donated biological samples is mandatory.
Biological samples will be collected for exploratory analyses to investigate the effect of tezepelumab on biomarkers of inflammation, asthma, pharmacology of tezepleumab and for potential predictors of response.

The following samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA: Blood, plasma, serum, BAL, bronchial brushings, bronchoscopic biopsy and urine samples will be collected according to the SoA in order to evaluate changes in biomarkers related to asthma, inflammation and the TSLP pathway. Biomarkers that may be analyzed include, but are not limited to, cytokines, chemokines and inflammatory mediators associated with asthma and the TSLP pathway.

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

Selected results of this biomarker research may be reported in the CSR (as per section 8.1.6). Biomarkers not reported in the CSR may be reported in an addendum, or separately in a scientific report or publication.

8.8.1 Storage, re-use and destruction of biomarker samples

AstraZeneca or a designee will retain biomarker samples for investigation of research on asthma, the pharmacology of tezepelumab, and potential predictors of response for a maximum of 15 years from the date of the LSLV, after which they will be destroyed.

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 samples may be retained for up to 15 years and used for the purpose of investigating asthma, the pharmacology of tezepelumab, predictors of response or assay validation work. If a subject does not allow samples to be used for future biomarker research they may continue with their samples being used for the main study.

8.8.2 Serum IgE

The levels of serum IgE may be tested by a central laboratory in accordance with the SoA. All total serum IgE results will be redacted from the laboratory reports except for Visit 3. Instructions for sample collection, processing, storage and shipment will be provided in a separate laboratory manual.

8.8.3 Transcriptomics

RNA will be isolated from bronchial brushings. Sample collection will be in accordance with SoA. In addition, other samples including whole blood samples for RNA will be collected in PAX gene blood RNA tubes for ribonucleic acid (RNA), BAL cells and bronchial biopsies will be collected, stored and may be processed for RNA transcriptomics if sufficient material is collected. RNA may be used in the analyses of host gene expression and microbiome research using quantitative methods that may include but are not be limited to RNA microarrays, RNA Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses. Instruction for sample collection, processing, storage and shipment will be provided in a separate laboratory manual. The epithelial three gene mean signature (POSTN, CLCA1, SERPINB2) will be reported in the CSR. Any additional transcriptomics data from bronchoscopic brushings will be reported separately from the CSR in an addendum or in a scientific report or publication. Any exploratory transcriptomics analyses on BAL cells, whole blood and biopsy tissue, will be reported separately from the CSR in an addendum or in a scientific report or publication

8.8.4 Storage, re-use and destruction of transcriptomics samples

Transcriptomics samples are considered biomarker samples so all storage, re-use and destruction instructions defined in section 8.8.1 also applies to any samples collected for transcriptomics.

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

Statistical hypotheses: The null hypothesis H0: The ratio (tezepelumab/placebo) of the change, expressed as a ratio, from baseline to EOT for each primary and secondary endpoint between tezepelumab and placebo equals 1 and will be tested versus the alternative hypothesis H1: The ratio (tezepelumab/placebo) of the change, expressed as a ratio, from baseline to EOT for each primary and secondary endpoint between tezepelumab and placebo is not equal to 1. Improvement under treatment is characterized by a reduction in the number of inflammatory cells, so ratios of tezepelumab/placebo less than 1 correspond to beneficial treatment effect of tezepelumab over placebo.

9.1 Sample size determination

The study is sized to explore reductions in airway submucosal inflammation, from baseline to EOT for tezepelumab, versus placebo in the overall study population and across the T2 continuum.

The sample size chosen is based on the change from baseline to EOT in number of airway submucosal eosinophils and in number of airway submucosal neutrophils (ratio of tezepelumab to placebo).

It is estimated that 50 subjects in each treatment arm will provide (using a 2-sided test with a nominal 10% significance level for each endpoint);

- 80% power to observe a reduction in number of airway submucosal eosinophils if the true effect is a 2.7-fold difference versus placebo (assuming standard deviation on log scale of 1.87 and 2.06 for placebo and tezepelumab respectively based on tralokinumab study D2210C00014).

- >90% power to observe a reduction in number of airway submucosal neutrophils if the true effect is a 2.7-fold difference versus placebo (assuming standard deviation

on log scale of 0.71 and 0.97 for placebo and tezepelumab respectively based on tralokinumab study D2210C00014)

This sample size allows exploratory assessment of the effect of tezepelumab on airway inflammation within quartiles across the T2 continuum and within other subgroups of interest. It is assumed that a small proportion of subjects will not have an evaluable primary endpoint value due to failed biopsies. To account for this and subject dropouts, 55 subjects will be randomized in each treatment arm. A 2.7-fold change has been chosen because it is within the range of effect sizes observed with Nucala (Haldar et al 2009) and Fasenra (Laviolette et al 2013)

9.2 Populations for analyses

For purposes of analysis, the following populations are defined:

Table 8 – Population descriptions

Population	Description
Enrolled	All subjects who sign the ICF
Randomized	All subjects randomized to study treatment (irrespective of or whether treatment is subsequently taken)
Full analysis set	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
Evaluable analysis set	All subjects randomized to study treatment who completed at least 20 weeks of study treatment and had an EOT visit date not greater than 8 weeks after date of last dose of IP
Safety analysis set	All subjects who received at least one dose of IP
PK analysis set	All subjects in the full analysis set who received tezepelumab and from whom PK blood and PK BAL samples are assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received).

Efficacy analyses will be based on the evaluable analysis set unless otherwise stated, with patients classified by their randomized treatment, in line with the Intention to Treat (ITT)

principle. Demographic and baseline characteristics will be presented using both the evaluable analysis set and full analysis set.

Safety presentations and anti-drug antibodies (ADA) presentations will be based on the safety analysis set, with subjects assigned according to the treatment they received. A subject who has on one or several occasions received active treatment will be classified as active. Any important deviations from the randomized treatment assignment, and any subjects that have received IP without being randomized, will be listed and considered when interpreting the safety data.

All PK summaries will be based on the PK analysis set.

9.3 Outcome measures for analyses

9.3.1 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 value recorded at the V3 (a or b); if a measurement is not scheduled to be measured at V3 or if the V3 measurement is missing, the last non-missing value before V3 will be used as baseline instead.

The baseline for ACQ-6 will be captured using paper questionnaire at Visit 3b.

For laboratory data and physical examination, baseline will be defined as the latest non-missing assessment prior to first dose (V3b).

Absolute change from baseline outcome variables is computed as (post-randomization value – baseline value).

Percent change from baseline is computed as 100 x 1((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.

The ratio post-randomization value / baseline value will also be computed when stated below.

9.3.2 Primary outcome measure

The change, expressed as a ratio, in number of airway inflammatory cells per mm^2 determined by microscopic evaluation of bronchoscopic biopsies from baseline (V3b) to EOT/V3b will be compared between treatments. This will be done separately for eosinophils, neutrophils, T cells, and mast cells.

An absolute change variable is considered as a supportive variable to the primary variable.

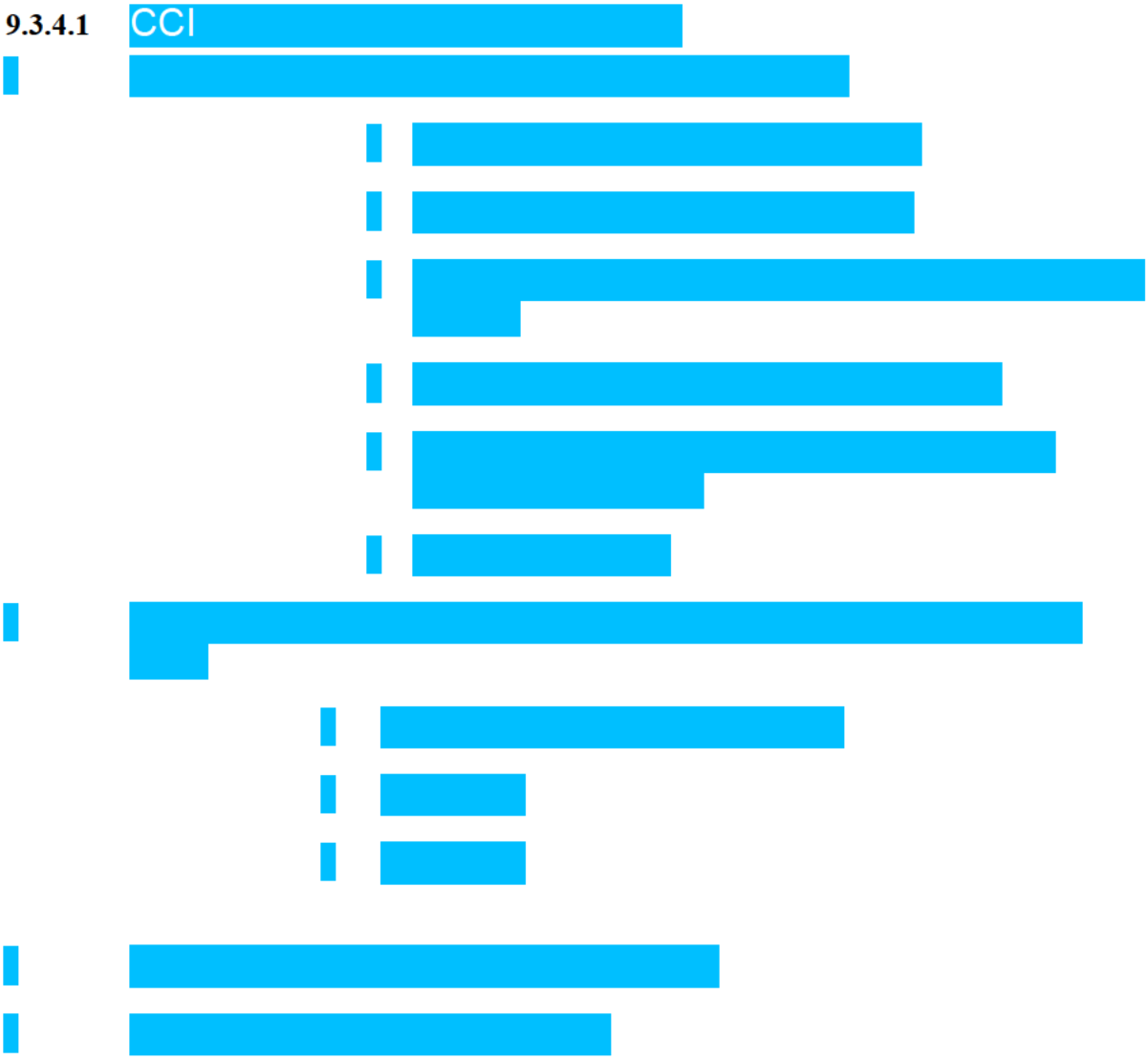
9.3.3 Secondary outcome measures

- The change, expressed as ratio, in RBM thickness from baseline to EOT.
- The change, expressed as a ratio, in % airway epithelial integrity from baseline to EOT.
- The change, expressed as a ratio, in airway inflammatory cells/mm^2 from baseline to EOT across the spectrum of T2 status.

Absolute change variables are considered as supportive variables.

9.3.4 Exploratory outcome measures

9.3.4.1 CCI



9.3.4.2 CCI

9.3.4.6 CCI

9.3.4.8 Calculation or derivation of pharmacokinetics and immunogenicity variables

Blood samples (processed to serum) for pharmacokinetic and immunogenicity assessments will be collected from all subjects in accordance with schedule in Table 1. ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer). Details of the method will be provided in validation reports as well as in bioanalytical reports.

Samples with confirmed positive ADAs will be archived for possible testing for nAb.

Pharmacokinetics and immunogenicity of tezepelumab

Tezepelumab serum concentrations will be tabulated by time along with descriptive statistics. Tezepelumab concentrations in BAL will also be evaluated.

ADA status(positive vs. negative) and titers at specified visits will be summarized by treatment group. Descriptive statistics including number of subjects, mean, standard deviation, median, and range of the actual ADA titers by treatment group and visit, where possible, will be provided. The prevalence and incidence of ADA over the course of the study will be calculated and tabulated by treatment group. The association of ADA status across the study (positive vs. negative) with AEs/SAEs may be evaluated.

9.3.5 Calculation or derivation of safety variables

The following safety data will be collected: vital signs, physical examination, 12- or 15-lead ECG, hematology, clinical chemistry, urinalysis, and reported AEs.

Change from baseline to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

9.3.5.1 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 run-in (onset date ≥ V1 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.

9.3.5.2 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 (OSAEs) 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.

9.3.5.3 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 hematology and clinical chemistry variables between baseline and each subsequent on treatment assessment will be calculated as described in Section 9.3.1. 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

9.3.5.4 ECGs

Twelve-lead ECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as V1.

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.

9.3.5.5 Physical Examination

Complete and brief physical examinations will be performed at time points specified in Table 1.

What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 8.2.3. 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 (i.e., V3a) 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.

9.3.5.6 Vital signs

Pre-dose 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.

Changes in vital sign variables between baseline and each subsequent scheduled assessment will be calculated as described in 9.3.1. 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.

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

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.

EOT assessments done at either week 28 or later will be discussed in the Statistical Analysis Plan (SAP).

9.4.1 Efficacy analyses

Efficacy analyses will be based on the evaluable analysis set, and subjects will be classified according to their randomized treatment.

The analysis of study endpoints will include all data captured during the double-blind treatment period. This includes data regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the subject withdraws consent to study participation.

Summary data will be presented in tabular format by treatment. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, standard deviation (SD), geometric mean, SD of log values, median, and range. All data will be listed and data listings will be sorted by treatment and subject number.

The primary and secondary variables will be analyzed using geometric means. Geometric mean is often used to evaluate data covering several orders of magnitude, and for evaluating ratios, percentages, or other data sets bounded by zero. A geometric mean, unlike an arithmetic mean, tends to dampen the effect of very high values, which might bias the mean if an arithmetic mean was calculated. The geometric mean is also a log-transformation of data to enable meaningful statistical evaluations; it accounts for some of the expected skewness in the data, but with the possibility to use a parametric analysis with a p-value directly linked to the confidence interval for the treatment effect. Both the difference in number of cells and the ratio will be reported, but the statistical analysis will only be based on the ratio. Nonparametric analyses will be applied as sensitivity analyses.

All hypothesis testing will be reported using 2-sided tests with a nominal 10% significance level and 90% confidence intervals (CIs). For the primary endpoints only, 2-sided 95% CIs will also be reported. The direction of interest for each of the primary endpoints is that the ratio tezepelumab/placebo is lower than 1. Nominal p-values will be reported for primary and secondary variables i.e., no adjustment of multiplicity will be performed. P-values will be rounded to 3 decimal places.

9.4.2 Analysis of the primary variable(s)

The primary efficacy objective will be evaluated through statistical testing of the within subject change from baseline to (EOT), expressed as a ratio, in number of airway submucosal inflammatory cells (separately eosinophils, neutrophils, T cells, and Mast cells).

The primary variable of within subject change from baseline to EOT (expressed as a ratio) in numbers of each of the airway submucosal inflammatory cells will be analyzed using an analysis of covariance (ANCOVA) including at least screening blood eosinophil strata (screening blood eosinophil count <150 cells/μL, 150 - <300 cells/μL, and ≥ 300 cells/μL at Visit 1), baseline value, and treatment as covariates. The analysis will be performed by using log-transformed data and estimated geometric means and the ratio of geometric means with both 95% and 90% two-sided confidence intervals will be presented.

If the change from baseline for a subject, expressed as a ratio, is zero, the value will be replaced by half the smallest observed value among the subjects with non-zero values, before doing the logarithmic transformation. If the baseline value for a subject is zero, the baseline value will be replaced by half the smallest observed value among subjects with non-zero values, before calculating the change from baseline. If both baseline and on-treatment for a subject is zero, the value for the ratio is defined to be 1.

Available values at both baseline and (EOT) are required for a subject to be included in the analysis and it is unlikely that a subject with a missing baseline value will undergo a second biopsy.

9.4.3 Analysis of the secondary variable(s)

The secondary variables of within subject change, expressed as a ratio, from baseline up to EOT in RBM thickness and % airway epithelial integrity will be analysed using the same ANCOVA model described for the primary variable. The secondary analysis of inflammatory cells across the spectrum of T2 status will be assessed by using the same ANCOVA model described for the primary variable with the addition of elements in the ANCOVA model for T2 quartile (categorical) and interactions between T2 quartile and treatment as well as visual data displays.

The analyses of inflammatory cells will be performed by using log-transformed data. The scale (i.e. ratio, percent change, or absolute change) and possible log transformation for the other secondary endpoints will be determined using blinded data prior to database lock.

9.4.4 Supportive analysis

For the primary and secondary variables, alternative transformations or non-parametric analysis methods may be applied as supportive analyses if substantial deviations from the parametric assumptions are observed. This will be assessed and documented prior to unblinding.

For the primary variables, the analysis may be repeated using the full analysis set, hence including assessments in subjects who complete at least 16 weeks of study treatment and had an EOT visit date not greater than 12 weeks after date of last dose of IP as a supportive analysis.

It is likely that some biopsy specimens will not be evaluable. Also, due to the invasive procedures performed, it is likely that some subjects will withdraw from the study. We cannot rule out that there is a relationship between unobserved values and the likelihood of data being missing and therefore the effect of missing data may be assessed using multiple imputations and a range of assumptions for the missing data.

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

Full details of the supportive analyses will be pre-specified in SAP and documented prior to database lock of the study.

9.4.5 Exploratory analysis

Exploratory variables will be summarized using descriptive statistics and graphical displays. How changes in biomarkers correlate with changes in airway inflammation and remodeling will be explored graphically.

9.4.6 Safety analyses

Safety analyses will be based on the Safety Analysis Set, and subjects will be classified according to the treatment they received. A subject who has on one or several occasions received active treatment will be classified as active.

9.4.7 Other analyses

PK, immunogenicity, pharmacodynamic analyses will be described in the statistical analysis plan finalized before database lock. Details of the biomarker 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.

Three gene mean from epithelial brushings transcriptomics will be used to determine T2 activity. Analysis for any other transcriptomic data, if generated, will be described in the exploratory analysis plan (EAP), which will be finalized before the database lock. The results from the EAP will be reported outside the CSR.

9.5 Interim analyses

- No interim analyses are planned in this trial.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

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

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

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

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

The Investigator will be responsible for the following:

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

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

A 2 Financial disclosure

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

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

A 3 Informed consent process

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

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

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

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

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

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

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or 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.

During the COVID-19 pandemic, re-consenting remotely may be obtained if local/regional guidelines allow.

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 CSP and letters to Investigators.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

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

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

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

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

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

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

A 8 Source documents

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

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

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

A 9 Site and Study Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the Investigator

- Discontinuation of further study intervention development

A 10 Publication policy

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter 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 unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

B 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize 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 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g. bronchospasm, laryngeal edema). 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, hospitalization, 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 anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- 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 etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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

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

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

B 8 Medication error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

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

The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the center 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. 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 (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- 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.

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the CSP 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 any time after the consent is signed. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE), such subjects would be important to include in any genetic analysis. 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 LSLV, 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 study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study center. 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) 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 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 AE 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 AE and SAE 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) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

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

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

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

Central laboratories being used:

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

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

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

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

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

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

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 CSP.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up 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 tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP to ensure timely analysis and reporting to health authorities within calendar days from the 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 PHL 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:

- Provide 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.

Hy's Law lab kit for central laboratories

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

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

References

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

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

Appendix F Maintenance therapy equivalence table

Estimated daily doses for inhaled corticosteroids

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid[a]	**Medium**	**High**
Beclomethasone dipropionate (CFC)[b]	>500–1000	>1000
Beclomethasone dipropionate (HFA)[c]	>200–400	>400
Budesonide	>400–800	>800
Ciclesonide	>160–320	>320
Fluticasone furoate (e.g. Arnuity® Ellipta® Breo®)	n.a.	200
Fluticasone propionate	>250–500	>500
Fluticasone propionate HFA	>250–500	>500
Mometasone furoate	>220–440	>440
Triamcinolone acetonide	>1000–2000	>2000
Inhaled Corticosteroid in ICS/LABA combination[a]	**Medium**	**High**
Beclomethasone dipropionate (e.g. Fostair®)	>200–400	>400
Fluticasone propionate HFA (e.g. Seretide®, Advair®)	>250–500	>500
Fluticasone furoate (e.g. Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (e.g. Symbicort®)	>400–640	>640
Mometasone Furoate (e.g. Dulera®)	>220–400	>400

[a] The ICS doses were derived from GINA 2018 and the ICS/LABA combinations were derived from GINA 2017 and 2018 and using prescribing information

[b] CFC: Chlorofluorocarbon propellant

[c] HFA: hydrofluoroalkane propellant

Appendix G Anaphylaxis: signs and symptoms, management

G 1 Introduction

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

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

G 2 Clinical criteria for defining anaphylaxis and immune complex disease

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune complex disease

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

G 3 Signs and symptoms and management of acute anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles

- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Lightheadedness
- Headache
- Uterine cramps
- Generalized warmth

G 4 Management of acute anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

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

(g) Consider atropine for symptomatic bradycardia.

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

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

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

Appendix H Abbreviations

The following abbreviations and special terms are used in this study CSP.

Abbreviation or special term	Explanation
AAER	Annualized Asthma Exacerbation Rate
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHR	Airway Hyperresponsiveness
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
AntiLKM	Anti-Liver/Kidney Microsomal Antibody
AO	Airwave Oscillometry
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AX	Area under the reactance curve
BAL	Bronchoalveolar Lavage
BD	Bronchodilator
β-HCG	Beta-Human Chorionic Gonadotropin
BUN	Blood Urea Nitrogen
BV5	Blood Vessels less than $5mm^2$ in Cross-Sectional Area
BV10	Blood Vessels less than $10mm^2$ in Cross-Sectional Area
CLCA1	Chloride Channel Accessory 1
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form (paper)
CSA	Clinical Study Agreement

Abbreviation or special term	**Explanation**
CSR	Clinical Study Report
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E/I	Expiratory-to-Inspiratory
EDN	Eosinophil-derived Deurotoxin
ER	Emergency Room
EOT	End of Treatment
PRO	Patient Reported Outcome
EU	European Union
FAS	Full Analysis Set
FEIA	Fluorescent Enzyme Immunoassay
$FEF_{25\%-75\%}$	Forced Expiratory Flow over 25-75% of the Vital Capacity
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FRI	Functional Respiratory Imaging
fSAD	Functional Small Airway Disease
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

Abbreviation or special term	Explanation
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonization
ICI	International Co-ordinating Investigator (If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally).
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ISH	In-Situ Hybridization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IXRS	Interactive Voice/Web Response System
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LAR	Late Asthmatic Response
LIMS	Laboratory Information Management System
LRTI	Low Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit

Abbreviation or special term	**Explanation**
MAb	Monoclonal Antibody
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimum Clinically Important Difference
MCT	Mannitol Challenge Testing
MNAR	Missing-Not-at-Random
nAB	Neutralizing Antibodies
OCS	Oral Corticosteroids
OSAE	Other Significant Adverse Event
PD	Pharmacodynamic
PGx	Genetic research
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
POSTN	Periostin
PT	Preferred Term
Q4W	Every 4 Weeks
R5-R20	Peripheral airway resistance defined as the difference in resistance between 5 Hz (R5, total respiratory system resistance) and 20 Hz (R20, central resistance)
RBM	Reticular Basement Membrane
RNA	Ribonucleic Acid
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation or special term	**Explanation**
SERPINB2	Serpin Family B Member 2
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
SOC	System Organ Class
SDV	Source Data Verification
TLC	Total Lung Capacity
TPV	Third Party Vendor
TSLP	Thymic Stromal Lymphopoietin
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential

Appendix I Medication washout periods for airway hyper-responsiveness

Medication	Time to Withhold
INHALED NON-STEROIDAL ANTI-INFLAMMATORY AGENTS (e.g. sodium cromoglycate, nedocromil sodium)	6-8 hours
SHORT-ACTING BETA$_2$ AGONISTS (e.g. salbutamol, terbutaline)	8 hours
INHALED CORTICOSTEROIDS (e.g. beclomethasone dipropionate, budesonide, fluticasone propionate)	12 hours
IPRATROPIUM BROMIDE	12 hours
LONG-ACTING BETA$_2$ AGONISTS (e.g. salmeterol, formoterol)	24 hours
INHALED CORTICOSTEROIDS PLUS LONG-ACTING BETA$_2$ AGONISTS (e.g. fluticasone and salmeterol, budesonide and formoterol)	24 hours
THEOPHYLLINE	24 hours
TIOTROPIUM BROMIDE	72 hours
ANTIHISTAMINES (e.g. cetirizine, fexofenadine and loratadine)	72 hours
LEUKOTRIENE-RECEPTOR ANTAGONISTS (e.g. montelukast sodium)	4 days

Food: Ingestion of significant quantities of coffee, tea, cola drinks, chocolate or other food containing caffeine may decrease bronchial responsiveness and should be totally avoided on the day of the test.

Appendix J Changes related to COVID 19 Pandemic

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

J 1 Home IP Administration Instructions

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 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. Minimum requirements for collection are listed below under the extra dose(s) instruction (J.3)

Please refer to the Transportation, Preparation, Administration by the Health Care Professional and Handling of Investigational Product (IP) for Home Administration (or alternative site) of the IP working instructions for more information.

J 2 Phone Call visit to replace On-site visit (where applicable)

The last follow up visit is an on-site visit where safety assessments are performed including vital signs, blood and urine samples and physical examination. There are several currently enrolled subjects who are expected to have their last follow up visit on site. During the COVID-19 pandemic, on-site follow up visit may be replaced by a phone call and/or a virtual visit if allowed by local/regional guidelines.

Having a phone call and/or a virtual visit with the subject will allow:

- Adverse Events
- Concomitant Medication
- Exacerbation history to be reported and documented for safety

J 3 Extra Dose(s)

During the COVID-19 pandemic, sites may administer 1-6 additional IP doses at weeks 28, 32, 36, 40, 44 and 48 (as needed) until the sites may be able to resume performing the end of treatment (EOT) study assessments, mainly bronchoscopies, in accordance to local regulations/guidelines during COVID-19 pandemic. Once the bronchoscopy can be performed, the site should schedule the patient to have the EOT study assessments 4 weeks after the last dose. If the subjects have extra IP doses administered, at minimum, the following is expected:

- Vital Signs
- Urine pregnancy test (dipstick) prior to IP administration
- Any worsening of underlying asthma symptoms/Asthma exacerbations since last contact with the subject
- Adverse events reported since last contact with the subject
- Collection of healthcare utilization data
- New concomitant medications since last contact with the subject
- Collection of paper diaries from previous visit and distribution of new paper diaries
- Complete the appropriate eCRF pages related to COVID-19
- Optional Safety lab samples and/or visit specific lab samples, as per the PI discretion

J 4 Reconsenting of subjects during the COVID-19 pandemic

It is critical that where a subject is unable to travel to the site, obtaining re-consent remotely necessary for the implementation of the new urgent changes in the Cascade study during the COVID-19 pandemic. Please ensure that applicable local guidelines and regulations are followed on re-consenting process.

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