Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00007
Version	5.0
Date	14 May 2020

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number (s):

IND number: 103031

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VERSION HISTORY

Version 5.0, 14 May 2020

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 2 – Updated footnote 'w' to clarify that subjects rolling over from this study into the extension study D5180C00018 will continue participation in the follow-up visit(s) (Week 58, Week 64) until the on-site visit (or alternate site) for extension study randomization and IP administration can be conducted. This is to ensure randomization/first IP administration in the extension study D5180C00018 can be performed at the site (or alternate site) and to increase the chances of subjects transitioning to the extension study.

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

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

Section 1.2, Synopsis – Objectives and Endpoints – Other Secondary Objectives;
Section 3, Objectives and Endpoints – Other Secondary Objectives – Added "at clinic" to fractional exhaled nitric oxide FENO (ppb) to clarify that this is the clinic and not home based FENO.

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Section 1.2, Synopsis – Overall design – Added study code "D5180C00018" next to extension study

Section 1.2, Synopsis - Study Period – updated the estimated date of last subject completed to Q4 2020

Section 1.2, Synopsis – Treatments and treatment duration - Added a note to refer to Appendix I for further guidance if subjects are unable to come to the site during the COVID-19 pandemic.

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

Section 6.5, Table 7, Prohibited medications – For any immunomodulators or immunosuppressives, revised the text "(except for OCS used in the treatment of asthma/asthma exacerbations)" to "(except for

OCS used in the maintenance treatment of asthma, asthma exacerbations in screening/run-in, and protocol defined asthma exacerbations on or after Visit 3)". This is to clarify the wording "except for OCS used in the treatment of asthma" is applicable for subjects on OCS maintenance treatment for asthma and "asthma exacerbation" is applicable if it was a protocol defined exacerbation occurring on or after Visit 3.

Section 6.5, Table 7, Prohibited medications – For other investigational products (including investigational use of an approved drug), revised the text "preferably 4 weeks after the last dose of IP" to "until the follow up visit week 64".

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

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

Section 8.4.7, Independent adjudication committee – Added "in pulmonology, cardiology, neurology and oncology and will operate". The statement now reads "The committee will include specialists in pulmonology, cardiology, neurology and oncology and will operate in accordance to the adjudication committee charter/manual of operations. This change is to align with section 1.2.

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

Section 9.4.5, Other analyses – Added "additional analyses assessing the impact of COVID-19 may be included in the SAP".

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

Appendix H, Table of Abbreviations – Added 1) COVID-19 and 2) HCP

Appendix I – Added Appendix I to describe in more detail the changes made during the COVID-19 pandemic.

Version 4.0, 15 April 2019

Changes to the protocol are summarized below.

Section 1.2, Synopsis – Study Objectives – Other Secondary objectives;
Section 3.0, Objectives and Endpoints – Table 3: Study Objectives – Other Secondary Objectives – Removed neutralizing antibodies (nAb). The reason for this change is that the incidence of ADA is the key outcome measure for the immunogenicity evaluation. Other immunogenicity outcomes, including nAb, are considered supportive and therefore should not be included in this table. They are described in Section 9.4.5 of the protocol.

Section 1.2, Synopsis – Study Objectives – Statistical methods – Added the evaluation of AAER in the subgroup of subjects with baseline eosinophils < 300/μL into the confirmatory hierarchical testing strategy as Level 2, and renumbered subsequent levels accordingly. Added clarification that the nominal significance level of 0.01 is for the primary endpoint in all-comers.

Section 5.1, Inclusion criteria, removed criterion #15 – "Non-sterilized males who are sexually active with a female partner of childbearing potential must use a condom plus spermicide from Day 1 through 16 weeks after receipt of the final dose of IP. In those countries where the above-mentioned method for contraception is not available, a condom can be used alone. Male subjects must not donate or bank sperm during this same time period." To align with version 4.2 of the IB.

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

Section 5.2, Exclusion criteria # 16 – reduced the timeframe for subjects who have been treated with bronchial thermoplasty from 24 to 12 months prior to visit 1. This allows sufficient time for any safety issues related to performing this procedure, (for example asthma exacerbations which occur within 1-2 months after the procedure), to resolve and for efficacy related to the procedure to stabilize.

Section 5.4, Screen Failures – Replaced "Incorrect Enrolment" with "Screen Failure" to align with the proper documentation of the disposition of the screen failed subjects within the eCRF.

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

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

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

Section 6.2, Preparation/handling/storage/accountability – Dose administration – Removed wording "Injection site must be documented on the eCRF and in the source documents at each treatment visit" as it was a repeat sentence.

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

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

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

Section 6.3, Measures to minimise bias: randomisation and blinding – Ensuring blinding – Clarified that no other members of the study team, other than those listed earlier within this section, will have access to the randomization list until after the primary database lock.

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

Section 6.3, Measures to minimise bias: randomisation and blinding – Methods for unblinding – Added "until primary database lock after last subject completes week 52." To accommodate a planned additional database lock once the last subject completes treatment phase (week 52).

Section 6.5.2, Rescue medicine – Added "Regularly scheduled SABA use in the absence of any asthma symptoms is not allowed from enrolment (Visit 1) and throughout the study duration. Prophylactic use of SABA (e.g. prior to planned exercise) or any other use than to curb worsening of asthma symptoms should be documented in medical notes and entered in the eCRF. Any such use of SABA must not be recorded in the Asthma Daily Diary. " This change further clarifies that regularly scheduled SABA use in the absence of any asthma symptoms is not allowed and that the occasional prophylactic use of SABA is not to be recorded in the eDiary.

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

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

Section 7.3.2, Discontinuation or suspension of entire study and site closure – Updated the title of this section and added additional comments about site closure. The rationale for this change is to specify the conditions for closure of sites during and after study completion.

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

Section 8.2.4, Vital Signs – Removed "in degrees Celsius" as the units of body temperature measurement. This is to accommodate the local guidelines as some regions may not be measuring in degrees Celsius.

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

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

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

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

Section 8.8, Biomarkers – Added "The results of exploratory biomarker analyses may be reported outside of the CSR." To clarify the reporting of the exploratory biomarker analyses.

Section 9.1, Statistical hypotheses – Added the evaluation of AAER in the subgroup of subjects with baseline eosinophils < 300/μL into the confirmatory hypotheses, and renumbered subsequent hypotheses accordingly. Added further clarification that the other hypotheses in this section are in all subjects.

Section 9.2, Sample size determination – Added nominal power statement and supporting assumptions for the evaluation of AAER in the subgroup of subjects with baseline eosinophils < 300/μL. Added clarification that the original primary endpoint calculation is based on all subjects.

Section 9.4, Statistical Analyses – Added "There will be two DBLs in this study. The primary DBL will be conducted after the last subject completes Week 52, and the final DBL will be conducted once the last subject has completed the last safety follow-up visit (Week 64). All analyses of the primary and secondary objectives will be performed based on the primary DBL data." This provides clarity around timing of database locks and primary analysis evaluation.

Section 9.4, Statistical Analyses;
Section 9.4.5, Other Analyses – Added "primary" to database lock. To accommodate a planned additional database lock once the last subject completes treatment phase (week 52). Replaced "Clinical Study Protocol deviations identified" with "important Protocol deviations identified" for clarity.

Section 9.4, Statistical Analyses – Added "After primary database lock, treatment allocation for subjects during this study will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the subject." To provide clarity about the blinding approach after the primary database lock.

Section 9.4.1, Multiple testing procedures – Added the evaluation of AAER in the subgroup of subjects with baseline eosinophils < 300/μL into the confirmatory hierarchical testing strategy as Level 2, and renumbered subsequent levels accordingly, following direction from the FDA. Other minor typographical corrections made to this section.

Section 9.4.3.1, Analysis of the primary efficacy endpoint – Added statement that the statistical model

used for categorical subgroup analysis will be used for the AAER analysis of subjects with baseline eosinophils < 300/µL now specified in the multiple testing procedure.

Section 9.4.4, Safety Analyses – Added "each" in front of database lock. To reflect that there will be two database locks.

Appendix B5 – Important medical event or medical treatment – Added "Examples of such events are" to clarify that the examples listed in this section can be considered as an important medical event or medical treatment.

Appendix E – Actions required in cases of increases in liver biochemistry and evaluation of Hy's law – The appendix has been updated including addition of section E6 in conjunction with sponsor's routine pharmacovigilance activities/processes.

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

Version 3.0, 16 March 2018

Changes to the protocol are summarized below.

Version History, Version 2.0, 21 November 2017 – Corrected spelling of "REquieing" in version history, section 8.3.8 to "Requiring."

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

Section 1.1, SoA, Table 1 – Moved SNOT-22 footnote 'i' to corresponding Visit 2 and Visit 2a timepoints on the SoA and updated footnote to state that SNOT-22 at Visit 2 on the handheld device should only be confirmed once both inclusion criteria 8 and inclusion criteria 9 have been met at either Visit 2 or at Visit 2a as per CSP. ePRO assessments (SNOT-22 and practice diary) need only to be collected once, either at Visit 2 or at Visit 2a if applicable. SNOT-22 questionnaire will only be triggered for subjects that have a medical history of current/ongoing nasal polyposis at Visit 2 or Visit 2a as applicable.

Section 1.1, SoA, Table 1 – Updated footnote 'k' to clarify that all total serum IgE, IgA, IgG and IgM results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

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

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

Section 1.1, SoA, Table 2 – Timepoint for Health Care Resource Utilization at Visit 4 was added.

Section 1.1, SoA, Table 2 – Scheduled timepoint for SNOT-22 will be moved from Visit 18 (Week 58) to Visit 17 (Week 52). An additional timepoint for SNOT-22 was added to IPD visit.

Section 1.1, SoA, Table 2 – Updated footnote 'i' to clarify that eosinophils, basophil and monocyte counts will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

Section 1.1, SoA, Table 2 – Updated footnote 'k' to clarify that all total serum IgE, IgA, IgG and IgM results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.

Section 1.1, SoA, Table 2 – Added footnote 'v' to clarify that at unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed in the SoA is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

Section 1.1, SoA, Table 2 - Added footnote 'w' to note that subjects completing the EOT period, may be eligible to enroll in a separate extension study and that these subjects will not complete the follow-up visits at Week 58 and Week 64.

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Section 1.2, Synopsis, Overall design – Added that subjects that complete the 52-week study visit will complete a 12-week post treatment, follow-up period unless the subject is eligible and decides to enroll into a separate extension study.

Section 1.2, Synopsis, Treatment and Treatment Duration – Added that subjects completing the planned treatment period, may be eligible to enroll in a separate extension study and that these subjects will not attend the follow-up visits at Week 58 and Week 64.

Section 1.2, Independent Adjudication Committee – Clarified that the independent adjudication committee will evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of treatment period, as well as all deaths, MACE, and malignancies that occur from randomization until the end of the follow up period.

Section 3, Objectives and Endpoints, Table 3 – Updated the endpoint/variable column that change in sinonasal specific HRQoL in patients with co-morbid nasal polyposis will occur at Week 52.

Section 4.1, Overall design – Added that subjects completing the planned treatment period, may be eligible to enroll in a separate extension study and that these subjects will not attend the follow-up visits at Week 58 and Week 64.

Section 5.1, Inclusion criteria #5 – Added "(GINA 2017)" reference to provide additional details of medium to high ICS doses.

Section 5.1, Inclusion criteria #6 – Removed "as per GINA guidelines (GINA 2017)" and only reference Appendix F.

Section 5.2, Exclusion criteria #12 – Replaced "except stable OCS" with "except for OCS use in the treatment of asthma/asthma exacerbations."

Section 5.2, Exclusion criteria #23 – Clarified that evidence of active liver disease will include

jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase > 2 times the upper limit of normal (ULN) at Visit 1.

Section 5.4, Screen failures – Updated that subjects with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the screening/run-in period may be re-screened.

Section 5.4, Screen failures – Added details pertaining to re-screening of a subject for other reasons.

Section 6.2, Dose Preparation – Updated equilibration time of vial to about 30 minutes to 1 hour at room temperature.

Section 6.2 – Dose Preparation – Added the wording, "If the opened and dispensed vials must be discarded immediately after dose preparation as per site's SOP, the vial labels along with the kit boxes must be retained for IP accountability."

Section 6.3, Procedures for handling incorrectly enrolled or randomized subjects – Added further procedures for handling subjects where continued treatment poses a safety risk.

Section 6.5, Concomitant therapy – Added the word "asthma" to clarify specificity of background medications

Section 6.5, Concomitant therapy – Added description of theophylline testing to note that subjects on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented before Visit 1. If this is not documented before signing the informed consent, it can be obtained after informed consent has been given or as part of the Visit 1 procedures. The sample can be analysed at the central or local lab as applicable. Investigator can use their clinical judgement about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

Section 6.5, Concomitant therapy – Removed bullet point "Dosage information including dose and frequency."

Section 6.5, Table 6, Restricted medications – Removed "(unless there is a medical need as judged by the Investigator)" where applicable.

Section 6.5, Table 6, Restricted medications – For maintenance treatment with ICS/LABA, clarified that patients should be instructed not to take their usual asthma controller medication (i.e., LABA) prior to scheduled ECG assessment. Use of SABA should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at Visit 1.

Section 6.5, Table 7, Prohibited medications – Removed "(unless there is a medical need as judged by the Investigator)" where applicable.

Section 6.5, Table 7, Prohibited medications – For Any immunomodulators or immunosuppressives, replaced "(other than prior, stable OCS for the maintenance treatment of asthma)" with "(except for OCS use in the treatment of asthma/asthma exacerbations)." On the corresponding Usage column, also replaced "prior to Visit 1" with "prior to randomization."

Section 6.5, Table 7, Prohibited medications – For medications not currently licensed for use in the treatment of asthma, updated the Usage column to remove "and for the duration of the study."

Section 6.7, Treatment after the end of the study – Clarified that subjects who complete week 64 should be given standard of care at the discretion of the investigator. Subjects that are eligible and decide to enroll in a separate extension study will not attend the follow-up visits at week 58 and week 64 and should comply with the requirements of the separate extension study protocol.

Section 7.1, Discontinuation of study treatment – Replaced bullet point "An adverse event" with "An adverse event considered to jeopardise the safety of a subject participating in the study."

Section 7.1.1, Procedures for discontinuation of study treatment – For IPD Option 2, added, "In addition to the PRO assessments that are performed at home, the subject may also complete the other clinic specified PRO assessments (as defined in the SoA) at home as well."

Section 8.1.1, Assessment of Asthma Exacerbations – For one of the prespecified worsening threshold, clarified that the alert will trigger if there is an increase of "2 or more nights" with awakenings due to asthma requiring rescue medication over a 7-day period.

Section 8.1.2.1, Spirometry, General Requirements – Clarified that for adult subjects, spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the screening or re-screening period and at randomization visit (Visit 3).

Section 8.2.5, Electrocardiograms – Updated that only a copy of the ECG will be produced and filed.

Section 8.4.7, Independent Adjudication Committee – Clarified that the independent adjudication committee will evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of treatment period, as well as all deaths, MACE, and malignancies that occur from randomization until the end of the follow up period.

Section 9.4.4, Safety analyses – Replaced "AEs leading to study discontinuation" with "AEs leading to discontinuation of IP".

Section Appendix D 2, - Removed "In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition,"

Version 2.0, 21 November 2017

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 1 – Updated footnote 'm' to note that FENO is to be completed at either V2 or V2a.

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

Section 1.1, SoA, Table 2 – Updated to include St. George's Respiratory Questionnaire (SGRQ) at Visits 3, 10, 17 (EOT) and IPD.

Section 1.1, SoA, Table 2, Footnote 'g' – Changed timing of ECG assessment to 'ECG must be performed prior to any blood draws, spirometry, BD administration and IP administration'.

Section 1.1, SoA, Table 2 – Added footnote 't' to indicate that SGRQ must be completed after the

AQLQ(s)+12.

Section 1.1, SoA, Table 2 – Added footnote ‘u’ to indicate that Serum for PK must be collected prior to IP administration.

Section 1.2 – Added clarifications of the outcome measures for other secondary endpoints.

Section 1.2 – Objectives & Endpoints, changed ‘PK: PK parameters’ to ‘PK: Serum trough concentrations’

Section 1.2 – Removed ‘Physical Examinations’ from Safety Endpoints/Variables as specific details from the assessment will not be captured in the case report form.

Section 1.2, Exploratory Objective and Endpoints/Variables - Added St. George’s Respiratory Questionnaire (SGRQ) to the table.

Section 1.3, Figure 1 – Corrected V4 – V16 from ‘Week 0 to 48’ to ‘Week 2 to 48’

Section 3 – Clarifications made of the outcome measures for other secondary endpoints.

Section 3 – Removed ‘Physical Examinations’ from Safety Endpoints/Variables as specific details from the assessment will not be captured in the case report form.

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Section 4.1 – Clarified paragraph describing subgroup closure per region.

Section 4.3, Justification for dose – Added information related to results from PK simulations.

Section 5.1, Inclusion criterion # 2 – Removed ‘Optional’ to clarify consent is a requirement for genetic analysis, added “optional” to sample for genetic analysis and added “applicable for adult subjects only.

Section 5.1, Inclusion criterion # 10 – Separated first bullet point to two points, and added description of an acceptable documented exacerbation.

Section 5.2, Exclusion criterion # 3, Medical conditions – Added “localized squamous cell carcinoma of the skin” to History of Cancer.

Section 5.2, Exclusion criteria # 11 – Replaced ‘prior to randomization’ with ‘prior to Visit 1’

Section 6.2, Dose Preparation – Replaced ‘5 cc’ with ‘5 mL’ for consistency of units.

Section 6.3, Bullet #2 – Added ‘via the Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS)’.

Section 6.3 – Added reference to Section 4.1 and changed ‘maximum’ to ‘approximately’.

Section 6.5, Concomitant therapy – Removed ‘and 7’.

Section 6.5, Table 6, Restricted Medications, Short-acting beta-agonists (SABA) – Added ‘not allowed’ to wording for ‘Usage’ for consistency with other wording for restricted medications in table

and added 'home PEF and domiciliary FENO'.

Section 6.5, Table 6, Additional Maintenance Controllers – Added 'with the exception of any unscheduled visits due to asthma worsening' to wording in 'Usage' for Twice daily LABA or LAMA, LTRA, Twice daily theophyllines and once daily theophyllines.

Section 6.5, Live Attenuated Vaccines – Replaced 'throughout the IP treatment and preferably 4 weeks after the last dose of IP (unless there is a medical need as judged by the Investigator) with 'and during the study including the follow-up period.'

Section 6.5, Table 7, Prohibited medications, Any marketed or to be marketed or investigation biologic treatment – Replaced 'prior to the date of randomization, throughout the IP treatment and preferably 4 weeks after the last dose of IP (unless there is a medical need as judged by the Investigator)' with 'prior to the date of Visit 1, throughout the entire screening run in period, treatment period (even if the subject has discontinued IP) and until the follow up visit week 64.'

Section 6.5.2, Rescue Medication Use – Added 'and domiciliary FENO'

Section 7.1, Discontinuation of study treatment – Added 'pregnancy' to list of reasons for discontinuation

Section 7.1.1, Procedures for discontinuation of study treatment – Added 'However, treatment with marketed or investigational biologics is not allowed until week 64 even if the subject has discontinued IP', to this section.

Section 8.1.1, Assessment of asthma exacerbation – Added description of another acceptable method for documentation of an historic exacerbation.

Section 8.1.1, Assessment of asthma exacerbation – Replaced 'Asthma exacerbations should not be recorded as AEs after randomization. All asthma exacerbations should be recorded in the exacerbation eCRF. In addition, if the asthma exacerbation leads to discontinuation of IP, the investigator must assess whether the asthma deterioration should also be reported as an AE leading to discontinuation of IP (DAE)/AE or withdrawal from study on the AE form' with '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.'

Section 8.1.2.2 – Changed 'and' to 'or' as either salbutamol or albuterol is to be used for the post BD spirometry and reversibility testing. Added, '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'.

Section 8.1.3 – Removed 'The highest of the 3 values will be captured for the morning and for the evening manoeuvres'.

Section 8.1.4.1, FENO at clinic visit – Changed "The standard single exhalation technique recommended by the ATS will be followed" to "A single exhalation technique recommended by the manufacturer will be followed". Reference updated. Added 'the measurement' and removed 'which will be recorded as "Yes or No" in the eCRF'.

Section 8.1.4.2, Domiciliary FENO – Added "given and", "When possible domiciliary FENO assessments should be performed prior to taking their morning inhalers and after the SABA is withheld for at least 6 hours. The subject will perform this measurement daily from Visit 2 or Visit 2a to Visit

17, except on those visits when FENO is scheduled to be performed at clinic/on site as per Table 2. The subject will be asked to blow air out of his/her lungs in one breath every morning, prior to the PEF measurement. Additional breaths may be required to have to achieve an acceptable FENO measurement. Further instructions for use will be described in a separate instruction manual.' Removed 'These instructions for use will be described in a separate instruction manual.' Added 'approximately' 100 subjects.

Section 8.1.4.2 – Section updated to specify number of daily breaths and duration of home FENO testing to be performed by a subject and that it must be collected in the morning prior to the PEF measurement.

Section 8.1.6.1 – Replaced 'study physician' with 'investigator' for consistency and clarification.

Section 8.1.6.2 – Changed 'and is the responder definition for ACQ-6' to 'and a decrease of at least 0.5 is the responder definition for ACQ-6'.

Section 8.1.6.4 – Section was added to describe the collection of the St. George's Respiratory Questionnaire.

Section 8.1.6.6, Health care resource utilization – Section was deleted as this information is duplicated in section 8.9.

Section 8.2.1, Table 8 – 'U-Microscopy and culture as required' was added to the table with footnote to clarify when samples are to be collected and sent to the central laboratory for analysis.

Section 8.2.5, Electrocardiograms – Changed timing of ECG to, 'A 12-lead dECG will be taken in supine position, prior to blood draw, spirometry, BD administration and IP administration'.

Section 8.3.7, Adverse events based on examination and tests – Replaced 'Deterioration of a laboratory value, which is unequivocally due to disease progression, should be reported as an AE/SAE unless unequivocally related to the disease under study' with '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.' Added '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 preexisting asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

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

Section 8.3.8, Adverse Events of Special Interest – Replaced 'Life threatening or Requiring Hospitalization or' with 'SAEs or'.

Section 8.5.1 – Deleted 'Samples from both placebo and treated group will be analyzed.'.

Section 8.7.1 – Corrected typo 'collected form' to 'collected from' and added 'adult' to clarify these samples are to be collected for adult subjects only

Section 10, References - Added 'Jones et al. 1991', 'Jones et al. 2009' and 'Alving et al. 2017'. Removed 'Dweik et al 2011.'

Appendix E – Removed sections E6 and E7, as this language is from the template and is related to oncology studies only. Appendix H, Table of Abbreviations – Added, 1) 'Annualized' to explain AAER; 2) SGRQ and 3) MCID
Initial Version, 1.0 September 2017

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

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Schedule of Assessments- Screening

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window	**0**	**±4[q]**	**±4[q]**	
Procedures				
Informed consent	X			Section 5.1
Inclusion /exclusion criteria	X	X	X	Section 5.1 and Section 5.2
Demography	X			Section 5.1
FENO[m]		X	X	Section 8.1.4.1
Domiciliary FENO (only for those subjects who have opted in at consent) [n]		Completed at home on domiciliary FENO device		Section 8.1.4.2
Clinical Lung Function Assessments				
Spirometry (pre-BD FEV1, FVC and FEV1/FVC)[c]		X[b]	X	Section 8.1.2
Reversibility (post-BD FEV1, FVC and FEV1/FVC)[d]		X[b]	X	Section 8.1.2.2
Home peak flow monitor training and distribution		X[e]	X[e]	Section 8.1.3
Check Home peak flow compliance and technique		Compliance check throughout screening period		Section 8.1.3
Home assessment every morning and evening PEF		Measurements every morning and evening		Section 8.1.3
Patient Reported Outcome assessments at Visit				
SNOT-22		X[i]	X[i]	Section 8.1.6.9

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window	**0**	**±4[q]**	**±4[q]**	
Distribute ePRO device		X[f]	X[f]	Section 8.1.6
eDiary device training		X	X	Section 8.1.6
ACQ-6[g]	X			Section 8.1.6.2
Check compliance with PRO assessments and follow-up as needed to maintain compliance (every 7 days)		Compliance check throughout screening period		Section 8.1.3
Patient Reported Outcome assessments at home				
Daily Diary[h]		Completed twice daily at home on eDiary		Section 8.1.6.1
Routine safety measurements				
Complete Physical examination	X			Section 8.2.3
Vital signs	X			Section 8.2.4
Weight, Height	X			Section 8.2.2
12-lead ECG[o]	X			Section 8.2.5
Adverse events (AEs/SAEs)	X	X	X	Section 8.3
Medical and asthma history	X			Section 5.1
Assessment of historical asthma exacerbations in the past 12 months	X			Section 8.1.1
Concomitant medication[j]	X	X	X	Section 6.5

	Screening	Run-in		Details in CSP section or Appendix
Visit	**1**	**2[a]**	**2a[b]**	**Details in CSP section or Appendix**
Day	**-42 to -35[a]**	**-28**	**-25**	
Visit window	**0**	**±4[q]**	**±4[q]**	
Laboratory Assessments				
Serum Chemistry	X			Section 8.2.1
Haematology (full)[p]	X			Section 8.2.1
Total immunoglobulin (IgE, IgA, IgG, IgM)[k]	X			Section 8.8.2
Pregnancy or FSH test[l]	X			Section 8.2.1
Serology (Hepatitis B, C; HIV-1; HIV-2)	X			Section 8.2.1
Urinalysis	X			Section 8.2.1

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

[b] Visit 2a is an optional visit. It can be performed if Pre-BD FEV_1 (inclusion criteria 8) and/or reversibility (inclusion criteria 9) is not met at Visit 2. If any one of these inclusion criteria is met at Visit 2, there is no need to repeat the assessment that was met at Visit 2a.

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

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

[e] Home peak flow monitor training and distribution should take place only if the subject has met inclusion criteria 8 and 9. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

[f] The ePRO home device training and distribution should take place only after the inclusion criteria 8 and 9 are both met. If only one of these criteria are met at Visit 2, the distribution of the device should be deferred to Visit 2a, after the other criteria is also met.

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

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

[i] Visit 2 on the handheld device should only be confirmed once both inclusion criteria 8 and inclusion criteria 9 have been met at either Visit 2 or at Visit 2a as per CSP. ePRO assessments (SNOT-22 and practice diary) need only to be collected once, either at Visit 2 or at Visit 2a if applicable. SNOT-22 questionnaire will only be triggered for subjects that have a medical history of current/ongoing nasal polyposis at Visit 2 or Visit 2a as applicable.

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

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

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

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

[n] Domiciliary FENO only for those subjects who have opted in at consent. The home FENO device will be dispensed at V2 once all spirometry criteria are met for this visit. If an optional V2a is required, then the home FENO device will be dispensed at this visit once all spirometry criteria are met.

[o] dECG to be completed prior to any blood draws.

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

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

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

	Random-ization	Treatment													EOT Period[w]	IPD[q]	FU	FU	UNS[v]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Procedures																				
Inclusion /exclusion criteria	X																			Section 5.1 and 5.2
Height[a]															X	X				Section 8.2.2
Weight								X							X	X				Section 8.2.2
Health care resource Utilization[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.9
FENO at clinic[l]	X	X	X	X	X	X		X			X				X	X		X	X	Section 8.1.4.1
Domiciliary FENO[m]	Measurements throughout treatment period																			Section 8.1.4.2
CGI-C			X		X			X			X				X	X				Section 8.1.6.7
Patient Reported Outcome Assessments at Visit[r]																				
Check compliance with PRO assessments and follow-up with subject as needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 8.1.6
ACQ-6[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.6.2
AQLQ(s) +12	X		X		X			X			X				X	X				Section 8.1.6.3
SGRQ[t]	X							X							X	X				Section 8.1.6.4

	Random-ization	Treatment													EOT Period[w]	IPD[q]	FU	FU	UNS[v]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
SNOT-22[d]									X						X	X				Section 8.1.6.9
Patient Reported Outcome Assessments at Home																				
Daily Diary[e]		Completed twice daily at home on the eDiary																		Section 8.1.6.1
PGI-S and PGI-C[f]	X	X	X	X	X										X	X				Section 8.1.6.8 8.1.6.7
EQ-5D-5L	X	Completed every 2 weeks at home on the eDiary														X				Section 8.1.6.6
WPAI and CIQ	X							X							X	X				Section 8.1.6.5
Routine safety measurements																				
Complete Physical examination	X														X	X			X	Section 8.2.3
Brief physical examination			X	X	X	X	X	X	X	X	X	X	X	X			X	X		Section 8.2.3
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Assessment of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
12-lead ECG[g]	X							X							X	X		X		Section 8.2.5
Laboratory Assessments[h]																				

	Random-ization	Treatment													EOT Period[w]	IPD[q]	FU	FU	UNS[v]	Details in CSP section or Appendix
Visit	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		**18**	**19**		**Details in CSP section or Appendix**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**		**58**	**64**		
Day (visit window)	**0**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**		**±7**	**±7**		
Serum Chemistry	X				X			X			X				X	X		X	X	Section 8.2.1
Haematology (full)[i]	X	X	X		X			X			X				X	X		X	X	Section 8.2.1
Urinalysis	X				X			X			X				X	X		X		Section 8.2.1
Urine pregnancy test, dipstick[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Section 8.2.1.1
Serum for ADA and nAb	X		X		X			X			X				X	X		X		Section 8.5
Serum for PK[u]	X		X		X			X			X				X	X		X		Section 8.6
IgE (FEIA)	X																			Section 8.8.2
Total immunoglobulin (IgE, IgA, IgG, IgM)[k]	X	X	X		X			X			X				X	X		X	X	Section 8.8.2
Serum for biomarker analysis	X	X	X		X			X			X				X	X		X	X	Section 8.8
Blood sample for DNA (optional)[n]	X							X							X			X		Section 8.7.1
Blood samples for RNA transcriptome profiling	X	X	X		X			X							X			X	X	Section 8.8.3
Flow Cytometry[s]	X							X							X					Section 8.8.4
Lung Function Assessments																				
Spirometry (pre-BD FEV1, FVC and FEV1/FVC)[o]	X	X	X	X	X	X		X			X				X	X	X	X	X	Section 8.1.2
Post-BD FEV1, FVC and FEV1/FVC)	X							X							X	X			X	Section 8.1.2.2
Home peak flow compliance and technique check	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				Section 8.1.3

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

[a] Only to be measured for the adolescent subject.
[b] Asthma specific resource utilization (eg unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).
[c] ACQ-6 to be completed before AQLQ(s)+12.
[d] SNOT-22 questionnaire will only be completed during the treatment period for those subjects who have completed SNOT-22 at Visit 2.
[e] Daily Diary: Asthma Symptom Diary (ASD), and items related to: Rescue medication use, Global asthma severity, Night time awakenings, Adherence to maintenance medication.
[f] PGI-C will not be collected at Visit 3.
[g] ECG must be collected prior to any blood draws, spirometry, BD administration and IP administration.
[h] All blood sampling should be done prior to IP administration.
[i] Eosinophils, basophil and monocyte counts will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.
[j] For WOCBP and adolescent females, urine pregnancy test (dipstick) will only be performed at treatment visits, prior to IP administration.
[k] All total serum IgE, IgA, IgG and IgM results will be redacted from the central laboratory reports except Visit 1, at Visit 3 prior to IP administration and any repeat testing that is performed during the screening/run-in period.
[l] At clinic, FENO must be performed prior to spirometry assessments. All FENO measurements will be blinded for sites and subjects throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the FENO values post randomization.
[m] Domiciliary FENO assessment must be performed after appropriate restrictions are met as per section 8.1.4.2 and prior to performing PEF assessment at home. All FENO measurements will be blinded for sites and subjects throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the FENO values post randomization.
[n] Blood sample for DNA is optional and will be collected from subjects who have consented to participate in the genetic analysis component of the study.
[o] Visit 3 spirometry must be performed on the day of randomization prior to IP administration after appropriate restriction are met as per section 8.1.2.1. For every other visit, pre-BD spirometry assessments must be performed only after appropriate restrictions are met as per section 8.1.2.1, if not this should be rescheduled to the earliest opportunity within the allowed visit window.
[p] IP should be administered after all other assessments have been completed to a scheduled visit.

[q] Refer to section 7.1.

[r] The ePRO questionnaires should be completed prior to FENO and spirometry assessments at clinic.

[s] Flow cytometry will be performed in a subset of subjects that have provided consent.

[t] SGRQ to be completed after AQLQ(s)+12

[u] Serum for PK must be collected, prior to IP administration.

[v] At unscheduled visits for assessing an asthma exacerbation, the assessment/activity listed above is only the minimum needed to be performed. Other unscheduled visits may be initiated as needed, and assessments performed as per investigator's judgement.

[w] Subjects completing the EOT period, may be eligible to enroll in a separate extension study D5180C00018 and that these subjects will not complete the follow-up visits at Week 58 and Week 64. During the Corona Virus Disease 2019 (COVID-19) pandemic, subjects enrolling in the separate extension study D5180C00018 will continue participation in the follow-up visit(s) (Week 58, Week 64) until the on-site visit (or alternate site) for extension study randomization and IP administration can be conducted.

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

CHANGES REQUIRED DURING THE COVID-19 PANDEMIC

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

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

- The option of home visits including home administration of Investigational Product (IP) performed by a qualified Health Care Professional (HCP). Additional information related to the visit can be obtained remotely by phone call and/or video conference. The rationale for this change is to minimize the risk of subjects missing scheduled IP administration and visit assessments due to inability/unwillingness to visit the site during the COVID-19 pandemic.

- Remote visits (phone call and/or video conference) to replace on-site visits, if subjects cannot attend the visits at the study site,

at an alternate site or have home visits. The rationale for this change is to ensure that assessments and collection of information continue for visits that cannot be done at the site, at an alternate site or at the subject's home. This will reduce the risk of subject exposure to COVID-19

- Subjects aimed to transition to the extension study D5180C00018 to continue participation in the safety follow-up visit(s) (Week 58, Week 64) until the on-site (or alternate site) extension study randomization and IP administration can be conducted. The rationale for this change is to ensure randomization/first IP administration in the extension study D5180C00018 can be performed at the site (or alternate site) and to increase the chances of subjects transitioning to the extension study.

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

For further details, please refer to Appendix I.

1.2 Synopsis

International co-ordinating investigator

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SW3 6NP

Protocol Title:

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

Short Title:

Tezepelumab Exacerbation study

Rationale:

The purpose of this global study is to confirm the efficacy and safety of 210 mg dose of tezepelumab administered subcutaneously (SC) every 4 weeks (Q4W) in adults and adolescents (12 years of age and older) with a history of asthma exacerbations and severe, uncontrolled asthma receiving medium or high dose inhaled corticosteroid (ICS) plus at least one additional asthma controller medication with or without oral corticosteroids (OCS). The study will evaluate the incidence of asthma exacerbations and other efficacy parameters such as lung function, asthma control and quality of life as well as a safety evaluation to further characterize the benefit-risk profile of the drug.

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo	Primary endpoint: Annualized asthma exacerbation rate (AAER) Primary outcome measure: AAER ratio vs placebo over 52 weeks
Key secondary objectives:	**Endpoint/variable:**
To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo	Key Secondary: change from baseline in pre-dose/pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV_1) Key outcome measure: Mean difference vs placebo at Week 52

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

To assess the effect of 210 mg of tezepelumab SC Q4W on other asthma control metrics	Outcome variables: Change from baseline in • weekly mean rescue medication use • weekly mean morning and evening peak expiratory flow (PEF) • weekly mean number of night time awakenings Outcome measure: Mean difference vs placebo at Week 52
To evaluate the effect of 210 mg tezepelumab SC Q4W compared with placebo on health resource utilization and productivity loss due to asthma	Outcome variables: • Asthma specific resource utilization (eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • Work Productivity and Activity Impairment (WPAI+CIQ) Questionnaire and Classroom Impairment Questionnaire score Outcome measures: • Difference in number of asthma specific resource utilizations vs placebo over 52 weeks • Difference in WPAI+CIQ score vs placebo at Week 52
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentrations Immunogenicity: Incidence of anti-drug antibodies
To assess the effect of 210 mg of tezepelumab SC Q4W on general health-related quality of life	Outcome variable: European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score Outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on patient (PGI-C and PGI-S) and clinician impression of overall asthma severity (CGI-C)	Outcome variable: Patient Global Impression of Change/Severity (PGI-C, PGI-S) and Clinician Global Impression of Change (CGI-C) Outcome measure: Proportion of responses at Week 52

Safety objective:	**Endpoint/variable:**
To evaluate the safety and tolerability of tezepelumab	Adverse events/serious adverse events Vital signs Clinical chemistry/haematology/urinalysis parameters Digital electrocardiograms
Exploratory objectives	**Endpoint/variable:**
CCI	

CCI	

Overall design:

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

The study will consist of a screening/run in period between 5-6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. Subjects who discontinue investigational product (IP) during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period. Further information is provided in section 7.1.1.

Subjects who complete the 52-week study visit will complete a 12-week post treatment, follow-up period unless the subject is eligible and decides to enroll into a separate extension study D5180C00018.

Study Period:

Estimated date of first subject enrolled Q4 2017

Estimated date of last subject completed Q4 2020

Number of Subjects:

Approximately 1060 subjects will be randomized to either tezepelumab or placebo (1:1) globally from about 400 sites. The subjects will be stratified by region and age (adult/adolescents). Since the primary analysis of the primary endpoint will include all available data, including after treatment discontinuation, no need is envisaged to adjust the number of subjects planned to be randomized in order to obtain a number of evaluable subjects.

Treatments and treatment duration:

The study will consist of a screening/run in period between 5-6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. Subjects will be randomized in a 1:1 ratio to either 210 mg of tezepelumab or matching placebo both administered Q4W SC. During the treatment period, IP will be administered from Day 0 until week 48. No IP will be administered at week 52. Subjects that complete the 52-week study visit will complete a 12 week off-treatment follow-up period for assessments including safety and anti-drug antibodies. Subjects who complete the planned treatment period may be eligible to enroll in a separate extension study (these patients will not attend the Follow-up visits at Week 58 and Week 64). Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period (see section 7.1.1).

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

Independent Adjudication Committee

An independent adjudication committee will be constituted to provide an external independent assessment of blinded data during the Phase 3 trials to confirm the diagnosis of: 1) MACE (Major Adverse Cardiac Events) (will be defined in the charter) and 2) investigator reported malignancies that occur from randomization until the end of the follow up period.

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

Data Safety Monitoring Board:

A Data Safety Monitoring Board (DSMB) will be responsible for assessing safety aspects of adolescent involvement in the study. The DSMB will also review safety data for adults to provide context for the adolescent review. The DSMB will periodically review unblinded safety summary tables and listings and evaluate for subject safety and make appropriate recommendations. The committee will operate in accordance with a DSMB Charter.

Statistical methods

Approximately 1060 subjects (530 per treatment group) are needed for this study to achieve greater than 90% overall power based on the primary and secondary objectives (for which primary and key secondary endpoints are defined in section 3).

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

until Week 52). No need is envisaged to adjust the number of subjects planned to be randomized in order to obtain a number of evaluable subjects.

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

- Level 1: AAER over 52 weeks (primary endpoint)
- Level 2: AAER over 52 weeks in subjects with baseline eosinophils < 300/μL
- Level 3: Change in pre-bronchodilator FEV1 from baseline at Week 52 (key secondary endpoint)
- Level 4: Change in AQLQ(S)+12 total score from baseline at Week 52 and change in ACQ-6 score from baseline at Week 52 (simultaneous testing of these 2 key secondary endpoints)
- Level 5: Change in weekly mean Asthma Symptom Diary score at Week 52 from baseline (key secondary endpoint)

The primary endpoint in all-comers will be tested at a 2-sided significance level of 0.01 to further ensure statistically persuasive evidence.

The primary analysis of the primary endpoint will compare AAER over 52 weeks between treatment groups using a negative binomial model. The response variable will be the number of asthma exacerbations experienced by the subject over the study period. Treatment, region, age and history of exacerbations will be included as factors in the model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable.

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

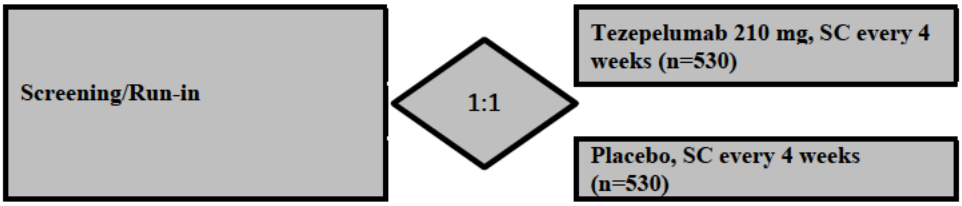
Sensitivity analyses will be performed on the primary and key secondary endpoints, including analyses to explore the impact of missing data and early discontinuation from IP. Further analyses will also be performed to explore the consistency of treatment effects across demographic and baseline subgroups.

All safety variables will be summarized descriptively. The safety analysis will be performed using the safety analysis set.

1.3 Schema

Figure 1 Study design

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



V: Visits

2. INTRODUCTION

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

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

The etiology of asthma is thought to be multi-factorial, influenced by both genetic and environmental mechanisms. The majority of cases arise when a person becomes hypersensitive to allergens. Despite the availability of multiple therapeutic options, asthma continues to be a major health problem. Worldwide, asthma currently affects approximately 300 million people; by 2020, asthma is expected to affect 400 million people (Partridge 2007). Each year in the US, asthma accounts for an estimated 8.9 million outpatient visits, 1.9 million emergency room visits, 479,000 hospitalizations (DeFrances et al 2008), and 3400 deaths (Centers for Disease Control and Prevention 2017).

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

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

2.2 Background

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

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that is produced in responses to proinflammatory stimuli (e.g., infectious, allergic and environmental stimuli) and trauma. TSLP has an upstream and central role in the initiation of immune responses, and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells and basophils (Watson and Gauvreau, 2014). Classically, TSLP may be a critical component in the initiation and perpetuation of the T helper 2 (Th2) response and the resulting cascade of cytokines associated with Th2 driven asthma (Kaur and Brightling, 2012). Asthma is recognized as a heterogeneous disease. There are subsets of patients that do not exhibit Th2-associated disease (Wenzel 2012), and there are emerging data that TSLP may also mediate non-allergic (non-T helper cell 2) inflammation (Tanaka et al, 2009, Ziegler et al, 2013).

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

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with TSLP receptor (TSLPR). Owing to the central role of TSLP in initiating and maintaining a Th2 response, anti-TSLP therapy may provide an opportunity to treat the upstream underlying mechanisms of asthma by reversing the established inflammatory responses to asthma triggers.

Results of a completed inhaled allergen challenge study in 31 adult subjects with mild atopic asthma (Study 20101183) demonstrated that tezepelumab attenuated the LAR and EAR to allergen challenge, as measured by the AUC (Area Under the Curve) for the percent fall in FEV1 and the maximum percent fall in FEV1. Tezepelumab also attenuated the increase in FENO value on the post-allergen day compared with the pre-allergen day. Multiple doses of 700 mg IV tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. No subjects developed anti-drug antibodies (ADA) after receiving tezepelumab. Based upon these

data, MedImmune/AZ have conducted a randomized, double-blind, placebo-controlled, dose range finding study in asthmatics who were inadequately controlled with medium or high dose ICS/long-acting β2 agonist (LABA) with or without other controller medications.

Study CD-RI-MEDI9929-1146 was a Phase 2b multicenter, multinational, dose-ranging, double-blind, randomized, parallel-arm, placebo-controlled study to evaluate the effect of 3 dose levels of tezepelumab on the AAER in adult 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. An AAER reduction of 61%, 71%, and 66% for the 70 mg Q4W, 210 mg Q4W, and 280 mg Q2W tezepelumab groups, respectively, compared with placebo were observed in the intent-to-treat (ITT) population ($p<0.001$). After repeated SC administration, mean serum trough concentration increased over time and achieved steady-state by week 12. Tezepelumab exhibited linear pharmacokinetics (PK) across 3 doses. A total of 5 (4.1%) placebo subjects and 8 (1.8%) tezepelumab subjects who had no detectable ADA at baseline had detectable ADA post-treatment; no subjects developed neutralizing ADA in the study. The results of this study did not identify safety signals associated with tezepelumab for any dosing regimen. The frequencies of treatment emergent adverse events (TEAEs) were similar between the placebo (62.2%) and the total tezepelumab (64.2%) dose groups and a majority of subjects had TEAEs that were mild or moderate in severity and not related to investigational product (IP). Few subjects had TEAEs that resulted in permanent discontinuation of IP. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no safety signals were identified.

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, improvement in lung function and asthma control metrics.

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

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

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

3. OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Objectives and Endpoints

Primary objective:	**Endpoint/variable:**
To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo	Primary endpoint: AAER Primary outcome measure: AAER ratio vs placebo over 52 weeks
Key secondary objectives:	**Endpoint/variable:**
To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo	Key Secondary: change from baseline in pre-dose/pre-bronchodilator (Pre-BD) forced expiratory volume in 1 second (FEV_1) Key outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on health status/health related quality of life compared with placebo	Key Secondary: Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score Key outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on asthma control compared with placebo	Key secondary: Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) Score Key outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on asthma symptoms compared with placebo	Key secondary: Change from baseline in weekly mean daily Asthma Symptom Diary score Key outcome measure: Mean difference vs placebo at Week 52

Other Secondary Objectives	**Endpoint/variable:**
To assess the effect of 210 mg of tezepelumab SC Q4W on other endpoints associated with asthma exacerbations	Outcome variable: Time to first asthma exacerbation Outcome measure: Asthma exacerbation hazard ratio vs placebo over 52 weeks Outcome variable: Proportion of subjects who did not experience an asthma exacerbation Outcome measure: Difference in proportions vs placebo at Week 52 Outcome variable: Annualized rate of exacerbations associated with emergency room visit, urgent care visit, or hospitalization Outcome measure: AAER ratio vs placebo over 52 weeks
To assess the effect of 210 mg of tezepelumab SC Q4W on biomarkers	Outcome variables: Change from baseline in • fractional exhaled nitric oxide FENO (ppb) at clinic • peripheral blood eosinophils • total serum IgE Outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on other asthma control metrics	Outcome variables: Change from baseline in • weekly mean rescue medication use • weekly mean morning and evening peak expiratory flow (PEF) • weekly mean number of night time awakenings Outcome measure: Mean difference vs placebo at Week 52

To evaluate the effect of 210 mg tezepelumab SC Q4W compared with placebo on health resource utilization and productivity loss due to asthma	Outcome variables: • Asthma specific resource utilization (eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire (WPAI+CIQ) score Outcome measures: • Difference in number of asthma specific resource utilizations vs placebo over 52 weeks • Difference in WPAI+CIQ score vs placebo at Week 52
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentrations Immunogenicity: Incidence of anti-drug antibodies
To assess the effect of 210 mg of tezepelumab SC Q4W on general health-related quality of life	Outcome variable: European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score Outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on patient (PGI-C and PGI-S) and clinician impression of overall asthma severity (CGI-C)	Outcome variables: Patient Global Impression of Change/Severity (PGI-C, PGI-S) and Clinician Global Impression of Change (CGI-C) Outcome measure: Proportion of responses at Week 52
Safety objective:	**Endpoint/variable:**
To evaluate the safety and tolerability of tezepelumab	Adverse events/serious adverse events Vital signs Clinical chemistry/haematology/urinalysis parameters Digital electrocardiograms
Exploratory objectives	**Endpoint/variable:**
CCI [redacted]	[redacted]

CCI	

4. STUDY DESIGN

4.1 Overall design

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

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

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

The study will randomize approximately 1060 subjects globally in a 1:1 ratio to either tezepelumab or placebo. Approximately 80 adolescents aged 12 to 17 years, will be included as subjects. The subjects will be stratified by region and age (adult/adolescents).

All subjects must have been on a medium to high dose ICS for at least 3 months prior to screening (see Appendix F for definitions of medium to high dose ICS) and have been on at least one asthma controller medication with or without OCS in the 3 months prior to date of informed consent as per inclusion criteria 6 and 7.

The total study population will be monitored to ensure a broad subject distribution across 3 different key clinical factors. Approximately 20% of the total study population will be subjects who are treated with a total daily dose of medium dose ICS as well as on at least one additional maintenance asthma controller medication with or without OCS in the previous 3 months prior to date of informed consent.

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

The study will also aim to randomize a similar percentage of subjects with <300 eosinophils/µl and ≥ 300 eosinophils/µl. In addition, a reasonable number of subjects is expected to be randomized with < 150 eosinophils/µl and > 450 eosinophils/µl.

The anticipated percentages for the factors above may be applied to the adult population instead of the overall population to avoid difficulties with adolescent recruitment, if necessary. When the target percentage of subjects for the ICS, exacerbations or eosinophil subgroup in a region is reached, consideration will be given to closing the IWRS/IVRS randomization for that subgroup, which may be done either overall or within a specific 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 6 and Table 7) provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial.

The study will consist of a screening/run in period between 5-6 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks. During the treatment period, IP will be administered starting at Day 0 until week 48. IP will not be administered on week 52. Subjects who discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 52-week period. Further information is provided in section 7.1.1. Any new treatments that are initiated will be recorded in the eCRF.

Subjects who complete the 52-week study visit will complete a 12-week post treatment - follow-up period for the assessment of safety and anti-drug antibodies. Subjects that complete the planned treatment period as defined in the protocol (see Section 1.2) may be eligible to enroll in a separate extension study (these patients will not attend the Follow-up visits at Week 58 and Week 64). All other patients will attend the follow up visits.

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

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

4.2 Scientific rationale for study design

The purpose of this global study is to provide evidence of the efficacy and safety of 210 mg dose of tezepelumab administered Q4W SC in adults and adolescents (12 years of age and older) with a history of asthma exacerbations and severe uncontrolled asthma receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS.

The primary (AAER) and key secondary endpoints (lung function and asthma control) are well accepted measures for a study in severe asthma. These endpoints have been shown in the Phase 2b study to clearly differentiate the tezepelumab benefit from placebo. In order to avoid bias the study will be randomized and double blinded. Subject entry will be stratified by region and age (adolescents and adults) to ensure equitable distribution for analysis.

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

4.3 Justification for dose

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

To ensure that the dose of 210 mg Q4W is an appropriate dose across adolescents from the age of 12 to 17 years old, PK simulations were conducted to compare exposures between adults and adolescents based on the adult body weight distribution from the phase 2b study and the adolescent body weight distribution from the Centers for Disease Control and Prevention growth charts (US).

The mean exposure in the adolescent population as a whole was found to be 1.67-fold higher in adolescents than in adults at the 210 mg Q4W dose. Compared to the overall variability in the PK of tezepelumab (coefficient of variation [CV] approximately 45% to 50%), and the fact that tezepelumab has been shown to be well-tolerated at the 280 mg Q2W dose (which resulted in approximately 2.7-fold higher exposure than at the 210 mg Q4W dose in adults), the adolescent exposures at the 210 mg SC dose are considered unlikely to pose a safety risk.

The dose of 210 mg SC Q4W has been selected for evaluation in both the adult and adolescent populations with a body weight of ≥40 kg.

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

4.4 End of study definition

The end of study is defined as when the last subject has completed his/her last scheduled contact.

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

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

5. STUDY POPULATION

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

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to 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.

5.1 Inclusion criteria

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

Informed consent

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

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

The ICF process is described in Appendix A 3.

Age

3. Subjects must be 12 to 80 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.

5. Subjects who have received a physician-prescribed asthma controller medication with medium or high dose ICS as per GINA guideline (GINA 2017) for at least 12 months prior to Visit 1.

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

   – Equivalent ICS doses as detailed in Appendix F.

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

8. Morning pre-BD FEV1 <80% predicted normal (<90% for subjects 12-17 years of age) at either Visit 2 or Visit 2a.

9. Evidence of asthma as documented by either:

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

   OR

   Post-BD (albuterol/salbutamol) reversibility of FEV1 ≥12% and ≥200 mL during screening (15-30 min after administration of 4 puffs of albuterol/salbutamol) at either Visit 2 or at Visit 2a.

10. Documented history of at least 2 asthma exacerbation events within 12 months prior to Visit 1. These can be as follows:

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

OR

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

OR

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

NOTE: For 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.

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

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a 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.
- Subjects can provide evidence of prescriptions for systemic steroids used during an exacerbation.

- A documented conversation that is recorded in a timely manner between the investigator/nurse or nurse practitioner and a 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.

11. ACQ-6 score ≥1.5 at screening.

Weight

12. Weight ≥40 kg at Visit 1.

Reproduction

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

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

    - Adolescent specific recommendations: If subject is female and has reached menarche, or has reached Tanner stage 3 breast development (even if not having reached menarche), the subject will be considered a female of child bearing potential.

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

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

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

15. Inclusion Criterion# 15 removed with version 4.0 of Clinical Study Protocol.

Inclusion criteria at randomization:

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

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

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

18. Minimum compliance with daily eDiary during the run-in period (having a minimum of 18 fully compliant days in the 21 days up to and including the day of randomization - Day 0).

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

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

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

20. Minimum compliance with background asthma medication(s) as captured in the eDiary during the run-in period (having a minimum of 18 fully compliant dosing days in the 21 days up to and including the day of randomization - Day 0).

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

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

5.2 Exclusion criteria

Medical conditions

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

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

   – Affect the safety of the subject throughout the study

   – Influence the findings of the study or the interpretation

   – Impede the subject's ability to complete the entire duration of study

3. History of cancer:

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

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

4. History of a clinically significant infection, including upper (URTI) or lower respiratory tract infection (LRTI), requiring treatment with antibiotics or antiviral medications finalized < 2 weeks before Visit 1 or during the run-in period.

5. A helminth parasitic infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.

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

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

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

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

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

Prior/concomitant therapy

11. Receipt of any marketed or investigational biologic agent within 4 months or 5 half-lives (whichever is longer) prior to Visit 1 or receipt of any investigational non-biologic agent within 30 days or 5 half-lives (whichever is longest) prior to Visit 1.

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

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

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

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

15. Receipt of live attenuated vaccines 30 days prior to the date of randomization and during the study including the follow-up period.

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

Prior/concurrent clinical study experience

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

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

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

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

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

Diagnostic assessments

22. Any clinically meaningful abnormal finding in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the 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.

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

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

Other exclusions

25. Pregnant, breastfeeding, or lactating women.

    A serum β-HCG pregnancy test must be drawn for women of childbearing potential (including adolescent females) at the screening visit. If the results of the serum β-HCG cannot be obtained prior to dosing of the IP, a subject may be enrolled on the basis of a negative urine pregnancy test, though serum β-HCG must still be obtained. If either test 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.

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

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.

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 Visit 1 and throughout the conduct of the study.

Current smokers or subjects with smoking history ≥ 10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of <10 pack years must have stopped for at least 6 months 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 serious adverse event (SAE).

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

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

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

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

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

HIV2, hepatitis B and C, and FSH). If the timeframe between Screening and re-screening is more than 30 days, then all Visit 1 assessments should be repeated.

Subjects who experience an asthma exacerbation during the screening/run-in period may remain in screening and proceed with study visits 14 days after they have completed their course of oral steroids or returned to their maintenance dose of oral steroids

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

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

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

6. STUDY 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 4 Study Treatments

	Treatment 1	**Treatment 2**
Study treatment name:	Tezepelumab	Placebo
Dosage formulation:	CCI	
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

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 may be performed at the subject's home by a qualified HCP. Please refer to Appendix I for further details.

Dose Preparation

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

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

To prepare the 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 2mL or 3mL sterile syringe.
4. Withdraw 1.9 mL of the IP from the vial.
5. Remove and discard the 21G 1½-inch sterile disposable needle from the syringe.
6. Attach a new 27G ½-inch sterile disposable needle to the same syringe in step 5.
7. Apply the appropriate label to the syringe.

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

The IP will be administered by one SC injection (see Table 5) and must be prepared using disposable plastic syringes and aseptic technique.

Table 5 Investigational Product Dose Preparation

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

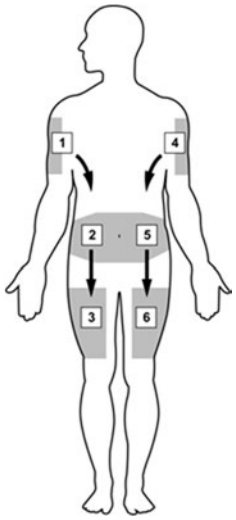
[a] Due to the gradations available on 2 mL or 3 mL disposable plastic syringe, dose based on 1.9 mL administered volume is 209 mg.

Dose Administration

IP will be administered by a qualified healthcare professional (e.g., pharmacist or study nurse) at the site. The injection site must be recorded in the source documents at each treatment visit and in the eCRF. The person administering the dose will wipe the skin surface of the upper arm, anterior thigh or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be inserted at a 90 degree angle approximately

halfway into the SC tissue. The IP will be slowly injected (at least 5 second duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. In cases when rotation of the injection site is not feasible and/or the subject prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents. The suggested injection site rotation sequence is presented below in Figure 2.

Figure 2 Suggested schema of Rotation of Injection Sites



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 a subject skips 2 consecutive IP administrations, the AZ 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 page with questions about the injection site reaction.

6.3 Measures to minimize bias: randomization and blinding

Subject enrolment and randomization

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 the Interactive Web Response System/ Interactive Voice Response System (IWRS/IVRS).

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

Specific information concerning the use of the IWRS/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.

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

In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented.

Methods for assigning treatment groups

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

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

In order to achieve the assumed exacerbation rates used to determine sample size, it is expected that approximately 40% of subjects will have ≥3 exacerbations in the 12 months prior to Visit 1. Therefore, enrolment of subjects with only 2 exacerbations in the 12 months prior to Visit 1 may be halted if this subgroup within a region reaches approximately 60% of randomized subjects. (Refer to section 4.1)

The distribution of subjects across the range of baseline eosinophil levels will be operationally controlled by ensuring that a similar percentage of subjects with eos levels < 300 and ≥ 300 are randomized and a reasonable number of subjects is expected to be randomized with eos levels <150 and > 450.

In addition, the proportion of subjects on medium dose ICS will be operationally controlled to comprise approximately 20% of the subjects.

Ensuring blinding

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

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

The following personnel will have access to the randomization list:

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

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 until after the primary database lock.

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.

Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) and delegate(s) at the study sites from the 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 until primary database lock after last subject completes week 52 has been documented.

6.4 Treatment compliance

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

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

6.5 Concomitant therapy

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

To satisfy inclusion criteria 6, a history of continuous treatment with medium or high dose ICS plus a second controller medication for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF prior to the date of randomization.

In order to satisfy inclusion criterion 7, a history of all asthma controller medications for the 3 months prior to Visit 1 until the end of the study should be documented in source and recorded in the eCRF. No changes are allowed to background asthma medications throughout the duration of the study except during the treatment of an asthma exacerbation.

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

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

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

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

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

Table 6 Restricted medications

Medication/class of drug:	Usage
Maintenance treatment with ICS and long-acting bronchodilators (including ICS/LABA combinations)	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. The 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 should be avoided within 6 hours before ECG assessments. The medication restrictions are waived for the screening ECG at Visit 1. Twice daily bronchodilators should be withheld for at least 12 hours prior to the scheduled FENO and spirometry at site. Once daily bronchodilators should be withheld for at least 24 hours prior to the scheduled FENO and spirometry at site. 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 throughout the IP treatment and preferably 4 weeks after the last dose of IP, PRN use is allowed if needed, however attention should be paid to the following restrictions. SABA should be withheld for at least 6 hours prior to scheduled spirometry, FENO, ECG at site with the exception of any unscheduled visits due to asthma worsening. When possible, home PEF and domiciliary FENO assessments should be taken after the SABA is withheld for at least 6 hours.

Table 6 Restricted medications

Medication/class of drug:	Usage
Additional Maintenance Controllers	No changes in either dose or regimen are allowed from V1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. Once daily LABA 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 throughout the IP treatment and preferably 4 weeks after the last dose of IP . They may be used for managing an asthma exacerbation event.

Table 6 Restricted medications

Medication/class of drug:	Usage
Inactive/killed vaccinations (e.g. inactive influenza)	Allowed provided they are not administered within 5 days before or after any study visit.
Allergen Immunotherapy	Allowed, if on stable therapy for at least 2 months prior to date of Visit 1 with no anticipated change during the treatment period. These should not be administered on the same day as IP administration.

Table 7 Prohibited medications

Prohibited medication/class of drug:	Usage
Long-acting beta-agonists as a reliever (e.g. Symbicort Maintenance and Reliever Treatment)	Not allowed 15 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed within 15 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Live Attenuated Vaccines	Not allowed 30 days prior to the date of randomization, and during the study including the follow-up period.
Any immunomodulators or immunosuppressives (except for OCS used in the maintenance treatment of asthma, asthma exacerbations in screening/run-in, and protocol defined asthma exacerbations on or after Visit 3)	Not allowed 12 weeks prior to randomization, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Immunoglobulin or blood products	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Any marketed (e.g. omalizumab, mepolizumab, reslizumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of Visit 1, throughout the entire, screening run in period, treatment period (even if the subject has discontinued IP) and until the follow up visit week 64.
Other investigational products (including investigational use of an approved drug)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to Visit 1, during screening/run-in and throughout the IP treatment and until the follow up visit week 64.

Table 7 Prohibited medications

Prohibited medication/class of drug:	Usage
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.

6.5.1 Other concomitant treatment

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

6.5.2 Rescue Medication Use

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

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

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

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

6.5.3 Bronchial Thermoplasty

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

6.6 Dose modification

N/A

6.7 Treatment after the end of the study

Subjects who complete week 64 should be given standard of care at the discretion of the investigator. Subjects that are eligible and decide to enroll in a separate extension study will not attend the follow-up visits at week 58 and week 64 and should comply with the requirements of the separate extension study protocol.

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 jeopardise the safety of a subject participating in the study
- Pregnancy
- Severe non-compliance with the Clinical Study Protocol
- Development of any study specific criteria for discontinuation, including:
  - An anaphylactic reaction to the IP requiring administration of epinephrine
  - A helminth parasitic infestation requiring hospitalization
  - An asthma-related event requiring intubation
  - Any malignancy except subjects who develop basal cell carcinoma or localized squamous cell carcinoma of the skin, provided that the malignancy is excised and determined to have clean margins
- 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 in section 7.3. 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 64 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 (+/-5 days) post last IP administration. Subjects who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments.

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

1. The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks treatment period.

2. The subject will be offered follow-up on a monthly basis via telephone calls while continuing ediary and ePEF completion (no further procedures will be performed), until the subject completes 52 weeks in the study. In addition to the PRO assessments that are performed at home, the subject may also complete the other clinic specified PRO assessments (as defined in the SoA) at home as well. The subject should return for a follow-up visit 16 weeks (+/- 5 days) (refer to SoA, V19 – Week 64) post last IP administration and for the EOT visit at Week 52 (+/-5 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 ediary and ePEF), they will complete a follow-up visit at 16 weeks (+/-5 days) (refer to SoA, Visit 19 – week 64) post last IP administration. After this visit the Investigator

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

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

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

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 adverse events (AE). The Investigator will follow-up subjects as medically indicated. A withdrawal visit is essential to collect as much data as possible for the subject as per EOT visit described in SoA, Table 2. The subject will return all study supplied equipment including Home PEF meter and eDiary.

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

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

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

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

7.3.1 Withdrawal due to recruitment completion

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

7.3.2 Discontinuation or suspension of entire study and Site Closure

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

The sponsor designee also reserves the right to close the study site at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site

is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

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, 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 Assessment of asthma exacerbation

Subjects enrolled in the study should have had at least 2 or more exacerbations in the prior 12 months before Visit 1. The list below defines what is acceptable documentation for historical exacerbations:

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a 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 consecutive 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
- An emergency room 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.

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

- Decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline, and/or
- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or
- An additional nebulized β2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criteria should be met on 2 consecutive days), and/or
- An increase in total asthma symptom score (the sum single-item global assessment of daytime symptoms [evening assessment] and single-item global assessment of night time [morning assessment] of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

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

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

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

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

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

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

8.1.2 Spirometry

8.1.2.1 General Requirements

Lung function (FEV1 and $FEF_{25-75\%}$) will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

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

Important!

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

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

Time of day for scheduled center visit spirometry

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

screening period and at randomization visit (Visit 3). Spirometry testing can be initiated during the whole day for adolescent subjects.

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

Spirometry technique

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

Spirometry references

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

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

FEV_1% of PNV = (FEV_1 measured/FEV_{1PNV}) x 100

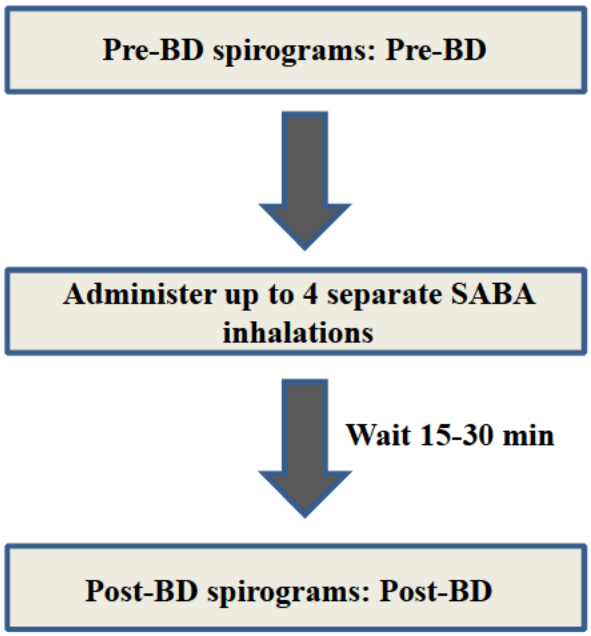
8.1.2.2 Post-BD spirometry and FEV_1 reversibility assessment

All subjects must meet inclusion criteria 9 either by having documented historical reversibility or by demonstrating reversibility either at Visit 2 or Visit 2a.

If documented historical reversibility is available, the post-BD spirometry procedures must be performed at Visit 2 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.

Visit 2a is an optional visit at which the reversibility testing/ post BD spirometry can be repeated, if the inclusion criteria were not met or the 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 centre for source data verification. The printout must be marked with the study code, enrollment code, date

and time of measurement, visit number. If a printout cannot be printed, the mean value of the measurements will be recorded in the subject's charts.

8.1.3 Home PEF testing

An electronic, hand-held spirometer (AM3G+™ to measure PEF) will be provided to the subject after inclusion criteria 8 and 9 has been met. This can be either at Visit 2 or at Visit 2a

Home PEF testing will be performed by the subject in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home PEF should start from the evening of Visit 2 or Visit 2a until the morning of Visit 17 (Week 52) using an ePEF meter device (AM3G+™) supplied by the vendor (eResearch Technology Inc.). When possible, ambulatory lung function measurements should be taken at least 6 hours after the last dose of SABA rescue medication.

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

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

8.1.4 FENO

8.1.4.1 FENO at clinic visit

Airway inflammation will be evaluated using a standardized single-breath FENO test in accordance with the SoA. A single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017).

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) 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 FENO measurements will be blinded for sites and subjects throughout. The sponsor will be unblinded to the FENO values prior to randomization and blinded to the FENO values post randomization.

8.1.4.2 Domiciliary FENO

A home FENO sub-study will be performed as part of this protocol in adult subjects. Subjects will be given and trained on the usage of collecting home based FENO measurements using the device NIOX VERO® (CIRCASSIA). When possible domiciliary FENO assessments should be performed prior to taking their morning inhalers and after the SABA is withheld for at least 6 hours. The subject will perform this measurement daily from Visit 2 or Visit 2a to Visit 17, except on those visits when FENO is scheduled to be performed at clinic/on site as per Table 2. The subject will be asked to blow air out of his/her lungs in one breath every morning, prior to the PEF measurement. Additional breaths may be required to have to achieve an acceptable FENO measurement. Further instructions for use will be described in a separate instruction manual.

This sub-study will include approximately 100 subjects and be exploratory in nature.

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

8.1.5 CompEx

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

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

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

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

AND at least one of the following:

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

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

8.1.6 Patient reported outcomes

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

At home PRO assessment will start the evening of Visit 2, if the subject meets inclusion criteria 8 and 9 at this visit. If only one of these criteria are met at Visit 2, the at home ePRO assessment should be deferred to the evening of Visit 2a, after the other criteria is also met. Subjects will complete assessments twice daily and at other timepoints specified in the SOA.

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

8.1.6.1 Daily Diary

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

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

ASD

Asthma symptoms will be recorded using the ASD (Globe et al 2015), which comprises 10 items (5 items in the morning; 5 items in the evening). The morning items assess nighttime symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and the frequency of nighttime awakening. The evening items assess symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and activity limitation since waking. Items are scored from “0” (no symptom, no nighttime awakening, or no activity limitation) to “4” (very severe symptom, unable to sleep, or extreme activity limitation). A daily ASD score is

the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. Calculation of a daily ASD score requires data from the evening diary assessment and the subsequent morning diary assessment. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4.

Global asthma symptom items

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

Rescue medication

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

Nocturnal awakenings

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

Maintenance medication

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

8.1.6.2 Asthma Control Questionnaire (ACQ-6)

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

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

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

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced

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

8.1.6.4 St. George's Respiratory Questionnaire (SGRQ)

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

8.1.6.5 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ consists of questions about how asthma and asthma related issues impact a subject's ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the subject's experience over the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss.

The WPAI+CIQ will be completed using the eDiary in accordance with the SoA.

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

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

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

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

8.1.6.7 Clinician and Patient Global Impression of Change assessment (CGI-C/PGI-C)

The Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) instruments are used to evaluate the overall response to treatment. For the CGI-C the investigator (clinician) will be asked to rate the degree to which the overall asthma status may have changed when compared to baseline (i.e. randomization visit/initiation of study drug). The assessment uses a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; and 7 = Very Much Worse. The PGI-C asks subjects to report change from baseline using the same scale as the CGI-C. The CGI-C will be completed at the site by the investigator. The PGI-S will be completed by the subject at home per the SoA

The CGI-C will be completed at the site visits as indicated in Table 2. It is recommended that the same clinician completes the CGI-C at all applicable visits for an individual subject. Before making the assessment, the clinician will need to access and review the results from all relevant assessments including lung function measurements (FEV_1 and PEF) and subject reported outcomes (Asthma Symptom Diary, ACQ-6 and AQLQ(S) +12) performed before the visit, Adherence to the subject reported outcomes should be closely monitored.

8.1.6.8 Patient Global Impression of Severity assessments (PGI-S)

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the subject's perception of overall symptom severity at the time of completion using a 6-point categorical response scale (no symptoms to very severe symptoms). The PGI-S will be completed at home using the eDiary per the SoA

8.1.6.9 Sino-nasal Outcome Test (SNOT-22)

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

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

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 8 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, must be conducted in accordance with the laboratory manual and the SoA.

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

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

Table 8 Laboratory safety variables

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

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

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

8.2.1.1 Pregnancy Test

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

- Serum ß-human chorionic gonadotropin (ß-HCG) – the test done at enrolment (Visit 1) only, for WOCBP and adolescent females (analysed at central laboratory).
- FSH – the test done at enrolment (Visit 1) only, for female subjects to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months.
- Urine HCG – the test will be performed at the study site for WOCBP and adolescent females 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.

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, if the manual measurement 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 prior to IP administration, in accordance with local standards.

8.2.5 Electrocardiograms

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

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

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

ECG data and 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 (Visit 1) only. All testing for these will be performed at a central laboratory. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual provided to the sites.

8.3 Collection of adverse events

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

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

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

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

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

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

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest, 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 collect 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 hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

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 investigational product?'

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

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

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff**: Have you/the child had any health problems since the previous visit/you were last asked?** or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms

that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

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

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

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

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. 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 preexisting asthma history (defined as within 1 year of Visit 1) as judged by the Investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfills 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 systemic 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 4 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.

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.

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

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital 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 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

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

8.4.3 Overdose

A dose in excess of 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 in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) 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 manifest as 1 of 3 clinical scenarios:

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

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

3. Reduced blood pressure after exposure.

Subjects will have had a pre-assessment (i.e., vital signs and lung function) prior to IP administration. At Visits 3 and 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 Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of assessing safety aspects of adolescent involvement in the study. The DSMB will also review safety data for adults to provide context for the adolescent review. The DSMB will evaluate cumulative safety and other clinical trial 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 studies, including the study sponsor, AstraZeneca. The committee will 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.

8.4.7 Independent Adjudication Committee

An independent adjudication committee will be constituted to provide an external independent assessment of blinded data during the Phase 3 trials to confirm the diagnosis of MACE events and investigator reported malignancies that occur from randomization until the end of follow up period.

This independent adjudication committee, will also evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of treatment period, as well as all deaths from randomization until the end of follow up period to evaluate whether any such event is due to a worsening of asthma. The committee will include specialists in pulmonology, cardiology, neurology and oncology and will operate in accordance with the Adjudication Committee Charter/Manual of Operations.

8.5 Pharmacokinetics

8.5.1 Collection of samples and drug concentration

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

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

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

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

8.5.2 Collection of samples to measure for the presence of ADAs

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

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies 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 analyzed for the presence of ADA-neutralizing antibodies.

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's Last Visit.

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

8.6 Pharmacodynamics

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

8.7 Genetics

8.7.1 Optional exploratory genetic sample

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

Approximately 34 mL blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study as per Table 2 in the SoA.

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

The blood sample for genetic research should be obtained from the subjects at Visit 3, 10, 17 and 19, as outlined in the SoA.

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

Please refer to Appendix D for further details.

8.7.2 Storage and destruction of genetic samples

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

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

8.8 Biomarkers

8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will not be reported in the CSR but in an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.8.2 Serum Immunoglobulins

The levels of total IgE, IgA, IgG and IgM (nephelometry/chemiluminescence) and seasonal and perennial allergen specific IgE (ImmunoCAP; FEIA) will be tested by a central laboratory in accordance with the SoA. Instructions for sample collection, processing, storage and shipment will be provided in a separate laboratory manual.

8.8.3 Transcriptomics

Whole blood samples will be collected in PAXgene blood RNA tubes for ribonucleic acid (RNA) sample preparation in accordance with SoA. RNA may be used in the analyses of host gene expression and microbiome research using quantitative methods that may include but not be limited to RNA microarrays, RNA Seq and quantitative reverse-transcriptase polymerase chain reaction technologies and stored for future analyses. Instruction for sample collection, processing, storage and shipment will be provided in a separate laboratory manual.

8.8.4 Flow Cytometry

Flow cytometry will be performed in approximately 100 adult subjects. The goals of analyzing the subsets of immune cells present in peripheral blood are to investigate the association of immune cell numbers and activation status in the blood to the clinical status of asthma and to evaluate the effects of tezepelumab on the immune cell repertoire in asthma. These immune cells include but are not limited to CD4+ T helper type I (Th1) cells, Th2, Th17 cells and basophils.

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 Clinical Study Report (CSR).

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

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

Primary endpoint – all subjects

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

versus

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

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

AAER – subjects with baseline eosinophils < 300/µL

H02: AAER ratio over 52 weeks (tezepelumab/placebo) = 1

versus

H12: AAER ratio over 52 weeks (tezepelumab/placebo) ≠ 1

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

Key secondary endpoints – all subjects

H03: Difference in mean change from baseline in pre-bronchodilator FEV1 at 52 weeks (tezepelumab minus placebo) = 0

versus

H13: Difference in mean change from baseline in pre-bronchodilator FEV1 at 52 weeks (tezepelumab minus placebo) ≠ 0

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

H04a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) ≠ 0

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

H04b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) ≠ 0

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

H05: Difference in mean change from baseline in weekly mean Asthma Symptom Diary score at 52 weeks (tezepelumab minus placebo) = 0

versus

H15: Difference in mean change from baseline in weekly mean Asthma Symptom Diary score at 52 weeks (tezepelumab minus placebo) ≠ 0

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

9.2 Sample size determination

Approximately 1060 subjects will be randomly assigned to study treatment using 1:1 allocation between the two treatments. Since the primary analysis of the primary endpoint will include all available data, including after treatment discontinuation, no need is envisaged to adjust the number of subjects planned to be randomized in order to obtain a number of evaluable subjects.

With 530 subjects per treatment group it is estimated that, using the multiple testing procedure described in Section 9.4 with an overall Type 1 error control at α=0.05 and a Type 1 error control for the primary endpoint at α=0.01, the power for the primary and the key secondary endpoints will be at least 90%. The Type 1 error control at α=0.01 for the primary endpoint is chosen to further ensure statistically persuasive evidence.

For the primary endpoint (in all subjects), assuming a placebo rate of 0.9, a shape parameter of 2.4 (over-dispersion) and a dropout rate of 10% (uniform over the study), there will be >99% power to detect a rate reduction of 50% at a 2-sided significance level of 1%. The methodology used is described in Keene et al, 2007 and Zhu and Lakkis 2014. The minimum detectable rate reduction with the above assumptions is 27%.

For AAER in subjects with baseline eosinophils < 300/μL, assuming a placebo rate of 0.6 and assuming that half of subjects will be in this subgroup (i.e. 265 subjects per treatment group), there will be 94% power to detect a rate reduction of 50% at a 2-sided significance of 5%, with the same shape parameter and dropout assumptions as above.

For each of the key secondary endpoints, change from baseline in pre-bronchodilator FEV1, change from baseline in AQLQ(S)+12 total score, change from baseline in ACQ-6, and change from baseline in weekly mean Asthma Symptom Diary score, the nominal power is 95% or higher, assuming standard deviations of 400 mL and 1.3, 1.3, and 1.3 units respectively, and true differences of 100 mL and 0.3, 0.3, and 0.3 units respectively. The minimum detectable differences being significant, under the above assumptions are 50 mL for FEV1, 0.16 for AQLQ(S)+12 total score, and -0.16 for each of Asthma Symptom Diary score and ACQ-6 score.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Randomly Assigned to Study treatment	All subjects randomized to study treatment (irrespective of whether treatment is subsequently taken)
Full Analysis Set	All subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.
Safety Analysis Set	All subjects who received at least one dose of IP.

Pharmacokinetic analysis set (PK)	All subjects in the full analysis set who received tezepelumab; including PK blood samples that are assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received).

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

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

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

9.4 Statistical analyses

There will be two DBLs in this study. The primary DBL will be conducted after the last subject completes Week 52, and the final DBL will be conducted once the last subject has completed the last safety follow-up visit (Week 64). All analyses of the primary and secondary objectives will be performed based on the primary DBL data.

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

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

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

Frequency and percentages of subject disposition and reasons for discontinuation of IP will be presented. Subjects who prematurely discontinue the IP will be listed along with the reason for discontinuation. In addition, frequency and percentages of withdrawal from the study together with reasons will be presented.

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

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

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

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

9.4.1 Multiple testing procedures

The overall Type 1 error rate will be strongly controlled at the 0.05 level across the primary and key secondary endpoints. The primary endpoint (in all subjects) will be tested at the 0.01 level to further ensure statistically persuasive evidence. In order to assess the primary objective of effect across the all-comer population, the subgroup of subjects with baseline eosinophils < 300/µL has been added into the multiple testing procedure following direction from the FDA. The following hierarchical testing strategy will be applied, ordered by clinical relevance, with the hypotheses to be tested as defined in Section 9.1:

Level 1

The null hypothesis H01 will be tested at a 2-sided 1% significance level with regard to the primary endpoint (AAER) in all subjects.

Level 2

If H01 is rejected at the 2-sided 1% significance level, then the null hypothesis H02 will be tested at a 2-sided 5% significance level with regard to the AAER in subjects with baseline eosinophils < 300/µL.

Level 3

If H02 is rejected at the 2-sided 5% significance level, then the null hypothesis H03 will be tested at a 2-sided 5% significance level with regard to change from baseline in pre-bronchodilator FEV1.

Level 4

If H03 is rejected at the 2-sided 5% significance level, then the null hypotheses H04a and H04b will be simultaneously tested at an overall 2-sided 5% significance level with regard to:

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

using a truncated Hochberg approach. In general under this approach, the higher of the two ordered p-values within Level 4 will be evaluated at a $\gamma\alpha + (1-\gamma)\alpha/2$ significance level (2-sided), and the lower of the 2 ordered p-values within Level 4 will be evaluated at a $\gamma\alpha/2 + (1-\gamma)\alpha/2$ significance level (2-sided), where $\alpha = 0.05$, and where γ is the truncation parameter ($0 \leq \gamma \leq 1$)

It is noted an intermediate choice $0 < \gamma < 1$ of the truncation parameter represents a choice between these extremes of regular Hochberg (corresponding to $\gamma = 1$) and Bonferroni approaches ($\gamma = 0$), balancing considerations of how stringent hypothesis testing should be in Level 4 in order to claim significance, versus the ability to subsequently claim significance from formal hypothesis testing in Level 5. In this trial γ will be set to 0.5.

Using this choice of truncation parameter, the higher of the two Level 4 p-values will be evaluated at a 3.75% significance level (2-sided). If it is significant at the 3.75% level, then both hypotheses H04a and H04b will be rejected, and testing will proceed to Level 5. If it is not significant at the 3.75% level, then the lower of the 2 Level 4 p-values will be evaluated at a 2.5% significance level (2-sided). If it is significant, then the relevant null hypothesis (either H04a or H04b) will be rejected, and testing will proceed to Level 5. If it is (also) not significant, then formal testing will stop at Level 4. The significance levels for subsequent evaluation in Level 5 for each of these scenarios are given below.

Level 5

The null hypothesis H05 will be tested at the significance level retained from Level 4, which depends on the outcomes in Level 4 as follows:

- Case 1: If both comparisons in Level 4 exhibit statistical significance, then H05 will be tested at a 2-sided 5% significance level with regard to change from baseline in weekly mean ASD score.
- Case 2: If only one of the comparisons in Level 4 exhibits statistical significance, then H05 will be tested at the 2-sided significance level $\alpha - [\gamma\alpha + (1-\gamma)\alpha/2]$ retained from Level 4, where $\alpha = 0.05$.

Using the proposed choice of $\gamma = 0.5$, if both H04a and H04b were rejected in Level 4, then H05 in Level 5 will be tested at a 2-sided 5% significance level (Case 1). If only one of H04a and H04b was rejected in Level 4, then H05 in Level 5 will be tested at a 2-sided 1.25% significance level (Case 2).

9.4.2 Definition of baseline

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.

For weekly means derived from subject diaries, baseline is defined as the mean of the available data in the most recent week prior to the first dose of study treatment. If more than 3 days are missing, then the baseline weekly mean will be set to missing.

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

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

9.4.3 Efficacy analysis

9.4.3.1 Analysis of the primary efficacy endpoint

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

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to perform the statistical test specified in Section 9.1, and to estimate the treatment effect and both its 99% and 95% confidence intervals. The response variable in the model will be the number of asthma exacerbations experienced by a subject over the 52-week study period (or shorter duration if not followed up for the full 52 weeks). Treatment, region, age (adolescents or adults) and history of exacerbations (2 or >2 in previous 12 months) will be included as factors in this model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occur. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, will not be included in the calculation of time at risk for exacerbation.

Descriptive summaries of the asthma exacerbations will also be presented.

Annualized rates for the individual exacerbation criteria (emergency room or urgent care visits due to asthma that required systemic corticosteroids, hospitalization due to asthma, or use of

systemic corticosteroids) will be summarized descriptively and analyzed using a similar model as for the primary endpoint.

For the purpose of showing consistency of treatment effect across continuous baseline biomarkers (including, but not necessarily limited to, baseline eosinophils, FENO and total IgE), the AAER will be modelled across the continuous biomarker using methods such as moving average or smoothing splines.

For the purpose of showing consistency of treatment effect across categorical baseline or demographic variables (including, but not necessarily limited to, high and low eosinophil categories, high and low FENO categories, specific IgE status, age categories, gender, race, history of exacerbations, asthma controller therapy at randomization, and medium/high ICS dose), a similar model will be fitted as for the primary analysis with additional factors for the relevant subgroup variable and its interaction with treatment. This includes the analysis of AAER in subjects with baseline eosinophils < 300/μL specified in Section 9.4.1.

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

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

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

9.4.3.2 Analysis of key secondary efficacy endpoints

The main analysis of the key secondary endpoints (changes from baseline to Week 52 for each of pre-bronchodilator FEV1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean ASD score) will quantify the effect of the initially randomized treatment at Week 52, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications, including for subjects who discontinued study treatment prior to Week 52. This analysis will therefore include all available data after treatment discontinuation. Missing data from study discontinuation will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

Change from baseline for the key secondary endpoints in the tezepelumab group will be compared to that seen in the placebo group using a mixed model for repeated measures (MMRM) model. This model will be used to perform the statistical tests specified in Section 9.1,

and to estimate the treatment effect at Week 52 and its 95% confidence interval for each endpoint. The response variable in the model will be change from baseline at each scheduled post-randomization visit up to and including Week 52, and irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region, age (adolescents or adults) and treatment by visit interaction will be included as factors in this model. Baseline of the corresponding endpoint will also be included in the model as a continuous linear covariate. Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same subject. If the MMRM model fails to converge with unstructured covariance, the SAP will pre-specify the approach for selecting a simpler covariance structure. The Kenward-Roger approximation to estimating the degrees of freedom will be used for tests of fixed effects derived from the MMRM model.

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

The consistency of treatment effects across continuous and categorical demographic/baseline variables will be investigated in a similar manner to the primary endpoint. In the case of categorical variables, appropriate terms will be added to the MMRM model, including a treatment by visit by subgroup interaction term, to enable the treatment effects within each subgroup category at Week 52 to be estimated. Any further subgroup analyses, and exact definition of all relevant categories where needed, will be pre-specified in the SAP.

Sensitivity analyses on the key secondary endpoints will be performed, and will be fully specified in the SAP. These may include, but not necessarily be limited to, the same items considered for the primary endpoint in Section 9.4.3.1.

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

As further supportive analyses to the analyses of change from baseline in ACQ-6 and AQLQ(S)+12, responders/non-responders (as defined in Sections 8.1.6.2 and 8.1.6.3) will be summarized descriptively and analyzed using a logistic regression model with factors which will include treatment, region and age (adolescents or adults). Baseline of the corresponding endpoint will also be included in the model as a continuous linear covariate. Further details of the logistic regression models and how missing responses at Week 52 will be handled will be specified in the SAP.

9.4.3.3 Analysis of other efficacy endpoints

Annual rates for other relevant endpoints will be summarized descriptively and analyzed using a similar model as for the primary endpoint (Section 9.4.3.1).

Other binary endpoints will be summarized descriptively and analyzed using a logistic regression model with factors which will include treatment, region and age (adolescents or adults). Baseline

of the corresponding endpoint will also be included in the model (where relevant) as a continuous linear covariate.

Other continuous endpoints will be summarized descriptively and analyzed using an MMRM model analogous to that specified for key secondary endpoints (Section 9.4.3.2). Log transformation of endpoints prior to implementing the MMRM will be considered for continuous endpoints which do not meet the distributional assumptions, and this will be pre-specified in the SAP where possible.

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

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

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

9.4.4 Safety analyses

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

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

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

AEs of Special Interest (AESIs), as defined in Section 8.3.8 will also be summarized descriptively by treatment group.

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

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

9.4.5 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical an alysis plan finalized before primary database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

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

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

9.5 Interim analyses

No interim analyses are planned in this trial.

9.5.1 Data Safety Monitoring Board (DSMB)

Details regarding DSMB are provided in Section 8.4.6.

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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 centre.

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-consent may be obtained remotely and/or verbally if local/regional guidelines allow in order to reduce the risk of subjects of COVID-19 exposure during clinic visits. For further details please refer to Appendix I.

A 4 Data protection

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

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

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

A 5 Committees structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, 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 Publication policy

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

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

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

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

B 3 Life threatening

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

B 4 Hospitalisation

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

B 5 Important medical event or medical treatment

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

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

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

B 6 Intensity rating scale:

1. mild (awareness of sign or symptom, but easily tolerated)

4. moderate (discomfort sufficient to cause interference with normal activities)

5. severe (incapacitating, with inability to perform normal activities)

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

B 7 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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

B 8 Medication Error

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 centre until shipment or disposal (where appropriate).

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

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

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

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

C 2 Withdrawal of Informed Consent for donated biological samples

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

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

The Investigator:

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

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

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(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 aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting subjects.

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

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

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

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

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

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

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

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

Exclusion criteria

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

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

Withdrawal of consent for genetic research:

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

Collection of samples for genetic research

Blood samples for genetic research will be obtained from subjects at Visit 3, 10, 17 and 19. 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. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

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

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations 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 organisations. 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 centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdraw from the genetic aspect of the study at any time.

Subject data protection

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

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

Data management

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

AstraZeneca and its designated organisations 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 organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

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

Statistical methods and determination of sample size

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

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

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.

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

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

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

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

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 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 timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

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

- ALT $\geq 3 \times$ ULN
- AST $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ 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 (and also 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
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

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

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

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

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

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

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

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

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

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

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

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

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

- Provide any further update to the previously submitted SAE SAE of Potential Hy's Law, (report term now ' Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E6 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. For studies using a local laboratory, the list may be modified based on clinical judgement. 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 IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

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

REFERENCES

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

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

Appendix F Maintenance Therapy Equivalence Table

Estimated daily doses for inhaled corticosteroids[a]

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

[a] The Japanese asthma pediatric guidelines will be followed for the Japanese adolescent subject (the medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥ 200 µg/day of FP or other ICSs of equivalent dose).
[b] The ICS doses for the ICS/LABA combinations were derived from GINA 2017 and using prescribing information.

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 (eg, IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in section 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in section 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 (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

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

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

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

   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

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

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

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

Immune Complex Disease

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

G 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

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

- Headache
- Uterine cramps
- Generalized warmth

G 4 Management of Acute Anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

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

(b) Establish and maintain airway.

(c) Administer oxygen.

(d) Establish venous access.

(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

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

(g) Consider atropine for symptomatic bradycardia.

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

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

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

Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. A revised nomenclature for allergy for global use: report of the nomenclature review committee of world allergy organization. J Allergy Clin Immunol. 2004;113:832–6.

Appendix H Abbreviations

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

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

Abbreviation or special term	Explanation
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ER	Emergency Room
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions 5 Level
EU	European Union
FEIA	Fluorescent Enzyme Immunoassay
$FEF_{25\%-75\%}$	Forced expiratory flow over 25-75% of the vital capacity
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FU	Follow-Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin

Abbreviation or special term	Explanation
IL-13	Interleukin-13
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IUO	Investigational Use Only
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IXRS	Interactive Voice/Web Response System
LABA	Long-Acting β2-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LAR	Late Asthmatic Response
LIMS	Laboratory Information Management System
LRTI	Low Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonists
LSLV	Last Subject Last Visit
MAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MCID	Minimum Clinically Important Difference
MNAR	Missing-Not-at-Random
nAb	Neutralizing Antibodies
OCS	Oral Corticosteroids
OAE	Other Significant Adverse Event
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PEO	Performance Evaluation Only
PGx	Genetic research
PGI-C	Patient Global Impression of Change

Abbreviation or special term	Explanation
PGI-S	Patient Global Impression of Severity
PI	Principal Investigator
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
PRO	Patient Reported Outcome
PT	Preferred Term
Q4W	Every 4 Weeks
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SOA	Schedule of Assessment
SOC	System Organ Class
SDV	Source Data Verification
Th2	T Helper 2 Cells
TLC	Total Lung Capacity
TSLP	Thymic Stromal Lymphopoietin
TSLPR	Thymic Stromal Derived Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of Childbearing Potential
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

Appendix I 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.

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

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

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

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

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

I 2 Visits at an Alternate Location (where applicable)

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

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

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

During the COVID-19 pandemic, on-site visits may be replaced by a remote visit (phone call and/or video conference) if subjects cannot attend the visits at the study site, at an alternate site or have home visits and if allowed by local/regional guidelines.
Having a phone call and/or a video conference with the subject will allow conduct of study procedures including reporting of adverse events, concomitant medication, information on asthma exacerbation and healthcare resource utilization while minimizing the risk to subjects of COVID-19 exposure.

I 4 End of Treatment Visit / Transition to the Extension Study D5180C00018

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

Subjects aimed to transition to the extension study D5180C00018 will continue participation in the safety follow-up visit(s) (Week 58, Week 64) until the on-site (or alternate site) extension study randomization and IP administration can be conducted.

If on-site (or alternate site) randomisation / IP administration into the extension study D5180C00018 is not possible by the end of study safety follow-up (Week 64), a subject will not transition to the extension study. These cases should be discussed with the AstraZeneca study physician.

I 5 Re-consenting of Subjects During the COVID-19 Pandemic

If a subject is unable to travel to the site due to the COVID-19 pandemic, it is necessary to obtain re-consent remotely and/or verbally for the implementation of the new urgent changes in the study during the COVID-19 pandemic. This will minimize the risk to the subject of COVID-19 exposure with clinic visits. Applicable local guidelines and regulations on re-consenting process should be followed.

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