Clinical Study Protocol	
Drug Substance	Tezepelumab
Study Code	D5180C00009
Version	4
Date	14 May 2020

A Multicentre, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma (SOURCE)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

IND number: 103031

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VERSION HISTORY

Version 4.0, 14May2020

Changes to the protocol are summarized below.

Section 1.1, SoA, Table 2 – Updated footnote 'o' to clarify that subjects rolling over from this study into the extension study D5180C00018 will continue participation in the follow-up visit(s) (Week 54, Week 60) until the on-site (or alternate site) visit 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 – Study Objectives – Key Secondary objective;
Section 3.0, Objectives and Endpoints – Key Secondary objectives
Revised supportive 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.

CCI [redacted]

Section 1.2, Synopsis – Overall design - added study code "D5180C00018" next to extension study.

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 a clinic visit.

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 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 K" to accommodate the changes made in the protocol.

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

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

Version 3.0, 12Mar2019

Changes to the protocol are summarized below.

Section 1.1, SoA – Table 1 – Study Plan – Enrolment/Run-in period/OCS optimization phase - Footnote a: removed the wording "which can be completed up to 30 days prior to visit 1," to reduce the timeframe between signing of ICF and conducting the remaining Visit 1 assessments. The CSP allows for Visit 1 to be conducted over 3-working days to accommodate signing of ICF prior to withholding asthma medications for required period for Pre-BD spirometry.

Section 1.2, Synopsis – Study Objectives – Key secondary objective – "AERR" was replaced with "AAER." To correct a typographical error.

Section 1.2, Synopsis – Study Objectives – Other Secondary objectives;
Section 3.0, Objectives and Endpoints – 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 – Number of subjects;
Section 1.2, Synopsis – Statistical methods;
Section 4.1 – Overall design;
Section 9.2, Sample Size Determination – Revised approximate number of subjects from 140 to 152. The increase in the randomized subject number will give more than 90% power to reject the null hypothesis for the primary endpoint. The increase in sample size will allow an increase in the proportion of subjects in ≥300 eosinophil/ µl while maintaining the number of subjects in <300 eosinophil/µl. As approximately 35% of subjects will be randomised with ≥300 eosinophils/µL at enrolment, this allows us to better explore the effect of tezepelumab in both the ≥300 eosinophils/µL and <300 eosinophils/µL groups.

Section 1.2, Synopsis – Statistical methods;
Section 1.3, Schema – Figure 1 – Study Design;
Section 9.2, Sample Size Determination – Revised number of subjects per treatment group from 70 to 76. The increase in number of subjects per treatment group is due to the increase in sample size.

Section 4.1, Overall design;
Section 6.3, Measures to minimise bias: randomisation and blinding – Methods for assigning treatment groups – revised percentage of subjects targeted to have ≥ 300 eosinophils/µl at enrolment from at least 30% to approximately 35%. This allows to better explore the effect of tezepelumab in both the ≥ 300 eosinophils/µL and < 300 eosinophils/µL groups.

Section 4.1, Overall design – Added "When the target percentage of subjects for the 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." To describe the approach for subgroup closure per region.

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 the revised 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 # 17 – 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 5.5, Re-Screening – clarified the treatment by adding intravenous in front of antibiotics and systemic in front of antiviral medication. The revised text reads: "Subjects with clinically significant infection, including respiratory infections requiring intravenous antibiotics or systemic antiviral medication during run-in should be screen failed but may be re-screened 2 weeks after completion of the therapy." To clarify the type of treatment for a clinically significant infection that would require the subject to be screen failed.

Section 5.5, Re-Screening – 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 re-screening, 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.

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 – Ensuring blinding – removed "biomarker" from the following laboratory personnel that will have access to the randomization list. The reason for this change is that the laboratory does not require the randomization list for performing biomarker 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 "Study Coordinator(s)" to clarify that the Study Coordinators 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 – replaced "until database lock" with "until primary database lock after last subject completes week 48." To accommodate a planned additional database lock once the last subject completes treatment phase (week 48).

Section 6.5, Table 6 – Restricted Medications - Short-acting beta-agonists (SABA) – Added "Only albuterol/salbutamol is allowed to be used as a rescue medication during the study, except during exacerbations." Since OCS titration criteria and ePRO alerts are based on salbutamol use as rescue medication, the same type of SABA should be used in all subjects.

Section 6.5, Table 7 – Prohibited Medications – Added "Ephedrine (e.g. in antitussives or mucolytics) - Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week

60." The reason for this change is to ensure consistency in standard of care and GINA guidelines.

Section 6.5, Table 7 – Prohibited Medications – Added "Opiates prn (e.g. in antitussives) - Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60." The reason for this change is to ensure consistency with standard of care and GINA guidelines.

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;
Section 8.3.10, Disease under study – Replaced "termination" with "Discontinuation of Investigational Product" to reflect the corresponding eCRF module title. 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 8.1.1.1, OCS Dose Titration – OCS dose titration in the optimization phase – Dosing interval corrected from "10-30 mg" to ">10-30 mg". To ensure consistency with Table 8.

Section 8.1.1.2, Criteria for OCS dose reduction during the optimization and reduction phase – Added "It is at the discretion of the Investigator to continue with the OCS down-titration even if the criteria for OCS reduction have not been met. Such a decision must be justified and documented in the source notes and captured in the eCRF. This decision must be notified to the AstraZeneca study physician within 2 business days." This allows the Investigator the opportunity to continue down titrating OCS, if clinically indicated. This change recognizes that the Investigator will balance their concern about side effects related to OCS use and the patient's clinical status.

Section 8.1.2.3, Exacerbation management – Maintenance phase – Replaced "induction" with "maintenance" to correct the typographical error in the CSP.

Section 8.1.5, Fractional exhaled nitric oxide (FENO) – Removed the wording "which will be recorded as "Yes or No" in the eCRF" from the sentence "Subjects will be asked whether they have had a respiratory infection in the 2 weeks prior to measurement." This change aligns with the eCRF design.

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 8.2.6, Glucocorticoid toxicity index – Revised the text to "Scoring should be performed as per SoA, using the randomisation assessment as the baseline." This is to clarify that the first assessment of GTI is at the randomisation visit.

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 the revised 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 9.4, Statistical Analyses – Added "There will be two DBLs in this study. The primary DBL will be conducted after last subject completes Week 48, and the final DBL will be conducted once all patients have completed the last safety follow-up visit (Week 60). All analyses of the primary and secondary objectives will be performed based on the primary DBL data. Following the primary DBL, data summaries created will be presented as an addendum to the CSR." 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 48). *Section 9.4, Statistical Analyses* – Added "After primary database lock, treatment allocation for subjects 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 9.4.3.1, Analysis of the primary efficacy endpoint* – Added "for subjects who continue to attend monthly visits either at site or by telephone." This is to clarify that post IP discontinuation data, from subjects who discontinued IP and agreed to only telephone contact at Week 48 is not included in the analysis as eDiary data to determine asthma stability will not be available. *Section 9.4.3.3, Analysis of other efficacy endpoints* – Revised the sentence to "Other binary endpoints will be summarized and analysed similarly; these analyses will be adjusted for region and baseline of the corresponding endpoint." The baseline of the corresponding endpoint has been added to the statistical model to adjust for potential baseline imbalance and to harmonise with other analyses. *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.
Version 2.0, 04 April 2018 Changes to the protocol are summarized below.
Section 1.1, SoA – Table 2 – Study Plan – Treatment and follow-up period, Footnote b removed the wording "and additional assessments performed at these visit" and added "At other unscheduled visits assessments may be performed as per investigator's judgement." Section 1.1, SoA – Table 2 – Study Plan – Treatment and follow-up period, Footnote i – Added wording "from the visits after randomization". Section 1.1, SoA – Table 2 – Study Plan – Treatment and follow-up period – Added footnote o with the following wording "Subjects completing the EOT visit may be eligible to enrol in a separate extension study and these subjects will not complete the follow-up visits at Week 54 and Week 60". This is because of the planned extension study.

Section 1.2, Synopsis, Overall design – Added wording "Subjects that complete the 48-week study visit will complete a 12-week post treatment, follow-up period unless the subject is eligible and decides to enrol into a separate extension study."

Section 1.2, Synopsis, Treatments and treatment duration – Added wording "Subjects completing the planned treatment period, may be eligible to enrol in a separate extension study and these subjects will not attend the follow up visit at Week 54 and Week 60".

Section 1.2, Synopsis, Independent Adjudication Committee – Added the following wording in the first paragraph "that occur from randomization until the end of the follow-up period" in relation to MACE and investigator reported malignancies.

Section 1.2, Synopsis, Independent Adjudication Committee – Added the following in the second sentence "that occur from randomization up to the end of treatment period" in relation to cases of ER or urgent care visits and hospitalizations and "that occur from randomization until the end of the follow-up period" in relation to all deaths.

Section 4.1, Overall design – Added the following paragraph "Subjects remaining on IP for entire planned treatment period, may be eligible to enrol in the extension study. These subjects will transition to the extension study, after completing the EOT assessments at week 48 and thus they will not attend the follow-up visits at Week 54 and Week 60."

Section 4.3, Justification for dose – Added the following: "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."

Section 5.1, Inclusion criteria # 5 – Added the wording "as per GINA guideline (GINA 2017)".

Section 5.1, Inclusion criteria # 6 – Added the word "as" and removed the wording "will be based upon GINA guidelines (GINA 2017)". As for this criterion sites should follow equivalent ICS doses mentioned in Appendix F and not GINA guidelines.

Section 5.1, Inclusion criteria # 8 – Added wording "The OCS dose may be administered every other day (or different doses every other day); Average dose over two days = The daily dose." This is to clarify that OCS can be administered every alternate day as well.

Section 5.2, Exclusion criteria # 3 – Added the wording "localized squamous cell carcinoma of the skin".

Section 5.2, Exclusion criteria #12 – Removed "randomization" and added "visit 1".

Section 5.2, Exclusion criteria #13 – Removed wording "randomization or any planned use during course of the study" and added "visit 1".

Section 5.2, Exclusion criteria #24 – Added the word "twice" for upper limit values. This was a typo error thus clarified.

Section 5.2, Exclusion criteria #24 – Removed the wording "Subjects with on-going liver disease or inexplicably elevated liver chemistry values should be excluded from the study". This criterion is covered by exclusion criteria #2.

Section 5.2, Exclusion criteria #32 – Added "or >30mg" for OCS dose as a clarification. This was done to exclude subjects optimized at >30 mg prednisone/prednisolone dose as for such subjects it will not be possible to totally omit OCS during the duration of study.

Section 5.5, Re-screening – Removed the wording "finalized < 2 weeks prior to visit 1 or." Also removed "subject that experiences an exacerbation during the screening period can also be re-screened 4 weeks after their OCS has been stabilized" as these subjects are not to be screen-failed and can continue in the study.

Section 5.5, Re-Screening – Added wording "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)".

Section 6.1.1, Investigational products, Table 4 – Added "m" and removed "n" as the unit of measure for L-proline.

Section 6.2, Preparation/handling/storage/accountability; Dose preparation – Added the wording "30 minutes to" in step #1 to update the equilibration time of vial.

Section 6.2, Preparation/handling/storage/accountability; 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 6.2, Preparation/handling/storage/accountability – Table 5 – Added superscript "a" to 210 mg in Dose column for clarification.

Section 6.3, Measures to minimize bias: randomization and blinding, Bullet #2 – Added wording: "via the Interactive Web Response System/Interactive Voice Response System (IWRS/IVRS)" in relation to enrolment number.

Section 6.3, Procedures for handling incorrectly enrolled or randomized subject - Added wording "Study treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the subject. In those cases where continuation of the study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. Regardless of what is decided about IP, all randomized subjects should remain in the study and the subjects should continue to be followed up in accordance with defined study procedures."

Section 6.5, paragraph 4, added "asthma" to clarify that no changes are allowed to background asthma medications.

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

Section 6.5, Concomitant therapy – Table 6 - Maintenance treatment with long-acting bronchodilators – Removed "unless there is a medical need as judged by the Investigator".

Section 6.5, Concomitant therapy – Table 6 - Short-acting beta-agonists (SABA) – Removed "unless there is a medical need as judged by the Investigator".

Section 6.5, Concomitant therapy – Table 6 - Additional maintenance controllers - Removed "unless there is a medical need as judged by the Investigator".

Section 6.5, Concomitant therapy – Table 6 - Additional maintenance controllers – Added "However, if theophylline blood concentration is out of therapeutic range after visit 1, dose adjustments are allowed.

Section 6.5, Concomitant therapy – Table 6 - Short-acting anti-cholinergics – Removed "unless there is a medical need as judged by the Investigator".

Section 6.5 – Table 7 – Prohibited medications - Long-acting beta-agonists as a reliever – Removed "unless there is a medical need as judged by the Investigator".

Section 6.5 – Table 7 – Prohibited medications - Suplatast tosilate – Removed "unless there is a medical need as judged by the Investigator".

Section 6.5 – Table 7 – Prohibited medications – Live attenuated vaccines – Removed "the date of randomization" and added "visit 1".

Section 6.5 – Table 7 – Prohibited medications - Live attenuated vaccines –Added the wording "an absolute" within the sentence.

Section 6.5 – Table 7 – Prohibited medications - Any immunomodulators or immunosuppressives – Added the wording "adrenal insufficiency and" within the Medication/class of drug section.

Section 6.5 – Table 7 – Prohibited medications - Any immunomodulators or immunosuppressives – Removed "unless there is a medical need as judged by investigator".

Section 6.5 – Table 7 – Prohibited medications - Blood products or immunoglobulin therapy – Added the wording “an absolute” within the sentence.

Section 6.5, Concomitant therapy - Table 7 – Any marketed or Investigational biologic treatment – Removed “the date of randomization” and added “visit 1”.

Section 6.5, Concomitant therapy – Table 7 – Any marketed or Investigational biologic treatment – Added “benralizumab” to the medication/class of drug section.

Section 6.5, Concomitant therapy – Table 7 - Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases – Removed “unless there is a medical need as judged by investigator”.

Section 6.5, Concomitant therapy – Table 7 - Medications not currently licensed for use in the treatment of asthma – Removed “unless there is a medical need as judged by the Investigator”.

Section 6.7, Treatment after end of study – Added wording “Subjects that are eligible and decide to enrol in a separate extension study will not attend the follow-up visits at week 54 and week 60 and should comply with the requirements of the separate extension study protocol.”

Section 7.1, Discontinuation of study treatment – Added the wording in bullet point 3 related to an adverse event “considered to jeopardize the safety of a subject participating in the study”.

Section 7.1, Discontinuation of study treatment – Added a new bullet point 4 to include “Pregnancy”.

Section 7.1.1, Procedures for discontinuation of study treatment – Removed the wording “do not apply after IPD” and added “can be performed at PI’s discretion and judgement”.
Section 7.1.1, Procedures for discontinuation of study treatment, Option 2 - Added “including the questionnaires that otherwise would have been completed at the site as per SoA” – to emphasize that the subjects will be completing the questionnaires that are marked in SoA as being completed at the site.

Section 8.1.1.1 – Table 9 – Added the following wording below the table “The OCS dose may be administered every other day (or different doses every other day) Average dose over two days = The daily dose”.

Section 8.1.1.2 – Table 10 – Criteria #1 – Added “mean” at the end of the criterion for a consistency.

Section 8.1.1.2 – Table 10 – Added a new footnote c with the following wording for criterion 2: “Number of nights with awakenings due to asthma requiring rescue medication will be counted from the most recent 7 days of available data”.

Section 8.1.1.2 – Table 10 – Criteria #2 – Wording has been changed to "An increase of no more than 2 nights with asthma-related awakenings (requiring rescue medication) over a 7-day period compared with baseline."

Section 8.1.1.2 – Table 10 – Criteria #3 – Removed "any one" and added "all days" as well as "/day", so that the criterion reads: "Mean[a] SABA rescue medication use not more than 4 puffs/day above the baseline [b] mean and <12 puffs/day on all days in the prior 14 days".

Section 8.1.1.2 – Table 10 – Criteria #4 – Added "or hospitalisation" within the wording.

Section 8.1.1.2 – Table 10 – renamed footnotes, previous footnote "c" became "d", previous footnote "d" became "e" and previous footnote "e" became "f".

Section 8.1.1.2, Criteria for OCS dose reduction during the optimization and reduction phase – Added "Steroid" in paragraph that overviews sign and symptoms of AI.

Section 8.1.2 – Table 11 – Criteria # 2 – added "≥" within phrase "12 puffs/day" for the criterion to read: "An increase in rescue medication use of ≥ 4 puffs/day on at least 2 consecutive days compared with the average use during baseline or use of ≥12 puffs/day on any one day".

Section 8.1.2 – Table 11 – Criteria # 4 - Added the wording "or more" within phrase "2 nights with awakenings" for the criterion to read: "An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period [c] compared with the average during baseline, and ≥6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criterion should be met on 2 consecutive days).

Section 8.1.2 – Table 11 – Footnote b - Reworded to "Baseline values for alerts will be calculated from the most recent 7 days of available data prior to visit 2 for the optimization phase and prior to randomization visit 6 for the treatment period".

Section 8.1.2 – Table 11 – Added footnote c with the following wording "Number of nights with awakenings due to asthma requiring rescue medication will be counted from most recent 7 days of available data".

Section 8.1.5, FENO – Removed the wording "The standard single exhalation technique recommended by the ATS will be followed (Dweik et al 2011) and added "The single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017)".

Section 8.1.6.2, ACQ -6 – Removed the wording" decrease of at least 0.5 are considered to be clinically meaningful and is the responder" and added the wording "changes of at least 0.5 are considered to be clinically meaningful and a decrease of at least 0.5 is the responder".

Section 8.1.6.2, ACQ-6 – Added "For IPD subjects ACQ-6 can be completed at home as well".

Section 8.1.6.3, AQLQ(S)+12 – Added "For IPD subjects AQLQ(S)+12 can be completed at home as well".

Section 8.1.6.6, WPAI+CIQ – Added "For IPD subjects WPAI+CIQ can be completed at home as well".

Section 8.2.1 – Table 12 – Removed "S-HbA1C from clinical chemistry and added "B-HbA1C" to Haematology.

Section 8.2.1 – Table 12 – Added a note* under the table "*Urine samples will be first analysed locally using dipsticks and sent to the central laboratory only for analysis when a positive dipstick result for any parameter is observed" referring to U-Microscopy and culture as required.

Section 8.2.5, Electrocardiograms – Removed the wording "post FENO and lung function assessments, after the subject has been resting for at least 15 minutes. The assessment should be performed prior to blood draw and IP administration." Added the wording "after resting for at least 15 minutes, prior to blood draw, FeNO, spirometry, BD administration and IP administration".

Section 8.2.5, Electrocardiograms – Removed "Two copies" and added "A copy".

Section 8.3.7, Adverse events based on examinations and tests – Removed the wording "Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE".

Section 8.3.10, Disease under study – For point # 2 removed "the study" and added "IP".

Section 8.4.6, Independent adjudication committee – Added the following wording in the first sentence "that occur from randomization until the end of the follow-up period" in relation to MACE and investigator reported malignancies. Added the following wording in the second sentence "that occur from randomization up to the end of treatment period" in relation to cases of ER or urgent care visits and hospitalization and "that occur from randomization until the end of the follow-up period" in relation to all deaths.

Section 8.7.1, Optional exploratory genetic sample – Corrected typo "collected form" to "collected from".

Section 9.4.4, Safety Analyses – Removed the word "Study" and added the wording "of IP" in the 2nd paragraph.

Section 10, References – Added "Alving et al 2017" and removed "Dweik et al 2011".

Appendix D – Subject Data Protection - Removed the wording "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". Appendix F – Maintenance therapy equivalence Table, Estimated daily doses for inhaled corticosteroids – Removed the entire Medium dose column. Appendix H – GTI Index Table – Added "2018" below the table. Appendix H – Infection Definitions – Added "2018" below text. Appendix I – Prednisone/Prednisolone doses Table has been revised to reflect updated doses of Prednisone/Prednisolone as well as the title of the first column has been changed from "Desirable daily dose" to "Daily dose." This was done to provide guidance to the sites to decide on 'actual' (and not desirable) daily dose of prednisone/prednisolone made up by using the available tablet strengths in the country. Multiple Sections – Replaced "patient(s)" with "subject(s) in reference to individuals enrolled in this trial.
Version 1.0, 16 October 2017
Initial creation

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

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1. PROTOCOL SUMMARY

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

1.1 SoA

Table 1 Study Plan – Enrolment/Run-in period/OCS optimization phase

Assessment/ activity	Enrolment / Run-in	OCS optimization phase [b]				Refer Section / Appendix
	V1[a]	V2	V3	V4	V5	
	W -10	W -8	W -6	W -4	W -2	
	Visit window (days)					
	N/A	+3[c]	±3	±3	-3[c]	
Informed consent	X					Appendix A 3
Inclusion/exclusion criteria	X	X	X	X	X	Section 5.1 and 5.2
Routine clinical procedures						
Demographics	X					
Medical/Surgical and asthma history	X					
Safety assessments						
Complete physical examination	X					Section 8.2.3
Weight, Height	X					Section 8.2.2
Vital Signs	X					Section 8.2.4
12-lead ECG	X					Section 8.2.5
Assessments of asthma exacerbations	X	X	X	X	X	Section 8.1.2
Adverse events	X	X	X	X	X	Section 8.3
Concomitant medications [d]	X	X	X	X	X	Section 6.5
Laboratory assessments						
Safety laboratory assessments (Clinical chemistry and haematology)	X					Section 8.2.1
Urinalysis (dipstick) [e]	X					Section 8.2.1

Assessment/ activity	Enrolment / Run-in	OCS optimization phase [b]				Refer Section / Appendix
	V1[a]	V2	V3	V4	V5	
	W -10	W -8	W -6	W -4	W -2	
	Visit window (days)					
	N/A	+3[c]	±3	±3	-3[c]	
Serology (hepatitis B, C; HIV-1; HIV-2)	X					
Serum pregnancy or FSH test [f] (Females only)	X					
Patient reported outcome assessments						
Dispense and train on eDiary [g]	X					Section 8.1.6.1
Daily diary	Completed twice daily at home on eDiary					
Daily diary adherence check [h]		X	X	X	X	
ACQ-6	X	X				Section 8.1.6.2
Lung function assessments						
Pre-BD spirometry [i]	X	X				Section 8.1.3
Post-BD spirometry (Reversibility assessment) [i]	X	X				Section 8.1.3
Home peak-flow monitor (PEF meter) training and distribution	X					Section 8.1.4
Check compliance with home PEF meter		X	X	X	X	
Home assessment of PEF	Measurement every morning and evening					Section 8.1.4
OCS optimization						
OCS switch to prednisone or prednisolone if required	X					
OCS dose reduction		X [j]	X	X		Section 8.1.1.1
OCS dose increase, if indicated [k]					X	Section 8.1.1.1

a Visit 1 can be performed over a period of 3-working days, with the exception of documentation of informed consent. All study assessments including withholding of asthma medications for required period for Pre-BD spirometry at visit 1 to be performed after the documentation of informed consent.

b Visit 2 and 5 will be on-site visits. Visits 3 and 4 can be performed as telephonic visits provided the subject and sites are confident to perform the visit remotely. Depending on clinical judgement, investigator may decide to call the subject on-site for visits 3 and 4 as well. Instructions for OCS dose titrations at visits 3 and 4 can be communicated to the subject on phone. The optimization phase may be extended to account for treatment of an exacerbation to allow for 2-week stable OCS dose prior to randomization.

c At a minimum there should be at least 14 days window (could be extended to 17 days) between visit 1 and 2 and also between visit 5 and 6 (randomization).

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

e Urinalysis analyzed centrally only if dipstick locally is positive.

f Serum pregnancy (β-HCG) test only for WOCBP. FSH test done only in women < 50 years who have been amenorrheic for > 12months to confirm postmenopausal status.

g eDiary should be dispensed after all other assessments have been performed.

h Daily Diary: Asthma symptom diary (ASD), general asthma symptom severity item, rescue medication use, night time awakenings and adherence to maintenance medications.

i If Pre-BD FEV_1 is met and reversibility is not met or vice versa, at visit 1; only the criteria that was not met needs to be verified at visit 2. Post-BD spirometry should be performed 15-30 min after administration of 4 puffs of albuterol/salbutamol. Reversibility can be documented in the previous 12 months prior to or at visit 1 or visit 2. Note: Reversibility (both historical and during screening) is defined as FEV_1 ≥12% and ≥200 mL.

j At visit 2 OCS dose titration will be attempted without referring to the protocol-captured set of baseline eDiary data. At other optimization visits eDiary data preceding the visits, will be compared to the baseline eDiary data derived from the interval between visit 1 and 2 for OCS dose titration decisions. Refer section 8.1.1.2.

k If the subject does not meet the criteria for following OCS dose reduction schedule at visits 3 or 4, the OCS dose should preferentially be returned to one level higher, unless the judgment of the investigator is to maintain the subject on their current dose of OCS, and visit 5 should be activated instead of visit 3 or 4 on the same day. Subject must be maintained on the optimized OCS dose for at least 2 weeks before randomization.

Table 2 Study plan – Treatment and follow-up period

	Induction	Reduction phase									Maintenance phase		EOT[o]	FU	FU	IPD	UNS [b]	Refer Section / Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 54	Wk 60			
	Visit window (days) [a]																	
	0	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	N/A	N/A	
Verifying Inclusion/ exclusion criteria	X																	Section 5.1, 5.2
Weight	X						X						X			X		Section 8.2.2
Randomization	X																	
Health resource utilization (HRU) [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.9
Complete physical examination	X												X			X		Section 8.2.3
Brief physical examination		X	X	X	X	X	X	X	X	X	X	X		X	X			Section 8.2.3
Vital Signs [d]	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	Section 8.3
Assessments of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
12-lead ECG [e]	X						X						X			X		Section 8.2.5

	Induction	Reduction phase										Maintenance phase		EOT[o]	FU	FU	IPD	UNS[b]	Refer Section / Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 54	Wk 60			
	Visit window (days) [a]																	
	0	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	N/A	N/A	
Glucocorticoid toxicity index	X						X						X			X		Section 8.2.6
Safety laboratory assessments (Clinical chemistry and haematology) [f]	X	X		X			X				X		X		X	X		Section 8.2.1
Urinalysis (dipstick) [g]	X	X					X				X		X			X		Section 8.2.1
Urine pregnancy test (dipstick) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
IgE (FEIA)	X																	Section 8.8.2
Total serum IgE, IgA, IgG, IgM [i]	X	X					X				X		X		X	X		Section 8.8.2
PK	X	X		X			X				X		X		X	X		Section 8.5.1
ADA/nAb	X	X		X			X				X		X		X	X		Section 8.5.2
Serum for other biomarker analysis	X	X					X				X		X		X	X		Section 8.8.1
Blood sample for RNA transcriptome profiling	X	X					X				X		X		X	X		Section 8.8.3

	Induction	Reduction phase									Maintenance phase		EOT[o]	FU	FU	IPD	UNS[b]	Refer Section / Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 54	Wk 60			
	Visit window (days) [a]																	
	0	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	N/A	N/A	
Pharmacogenetics assessment [j] (Optional)	X										X		X			X		Section 8.7
Daily diary [k]	Completed twice daily at home on eDiary																	
Daily diary adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X					
ACQ-6	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		Section 8.1.6.3
WPAI+CIQ	X						X						X			X		Section 8.1.6.6
EQ-5D-5L	X	Completed every 2 weeks on the eDiary														X		Section 8.1.6.5
SGRQ	X												X			X		Section 8.1.6.4
FENO [l]	X	X		X			X				X		X		X	X		Section 8.1.5
Pre-BD spirometry	X	X		X			X				X		X		X	X		Section 8.1.3
Post-BD spirometry	X	X					X						X			X		Section 8.1.3
Home assessment of PEF	Measurements every morning and evening throughout treatment period																	
PEF adherence check	X	X	X	X	X	X	X	X	X	X	X	X	X					
Administration of IP [m]	X	X	X	X	X	X	X	X	X	X	X	X						Section 6.2

	Induction	Reduction phase									Maintenance phase		EOT[o]	FU	FU	IPD	UNS[b]	Refer Section / Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20			
	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 54	Wk 60			
	Visit window (days) [a]																	
	0	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±7	±7	N/A	N/A	
OCS dose titration		X	X	X	X	X	X	X	X	X							X[n]	Section 8.1.1.1

EOT – End of treatment; **FU** – Follow-up; **IPD** – Investigational product discontinuation; **UNS** – Unscheduled

a All visits are to be scheduled from the date of randomization; not from the date of previous visit.

b Unscheduled visits may be initiated as needed. At unscheduled visits for assessing an asthma exacerbation, at a minimum, these assessments need to be performed. At other unscheduled visits assessments may be performed as per investigator's judgement.

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

d Vital signs will be taken pre-dose prior to administration of IP. Subjects will be observed 2 hours post treatment for Visits 6 and 7. For all other visits where IP is administered, subjects will be observed for a minimum of 1 hour.

e ECG must be collected prior to any blood draws.

f During treatment period all laboratory samples should be obtained prior to IP administration. Subjects should be fasting for at least 12 hours prior to blood collection. Blood eosinophil, basophils and monocyte numbers from the visits after randomization visit will be redacted from the central laboratory reports.

g Urinalysis analyzed centrally only if dipstick locally is positive.

h For WOCBP urine pregnancy test (dipstick) to be done at site at each treatment visit prior to IP administration. Positive urine pregnancy test must be confirmed by serum β-HCG.

i All immunoglobulin results will be redacted from laboratory reports from the visits after randomization.

j 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

k Daily Diary: ASD, general asthma symptom severity item, rescue medication use, night time awakenings and adherence to maintenance medications.

l FENO test needs to be completed prior to spirometry. FENO results will be redacted.

m IP should be administered after all other assessments have been completed at the visit.

n Up-titration only.

o Subjects completing the EOT visit may be eligible to enrol in a separate extension study D5180C00018 and these subjects will not complete the follow-up visits at Week 54 and Week 60. 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 54, Week 60) until the on-site (or alternate site) visit for extension study randomization and IP administration can be conducted.

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.

- Decision on OCS dose based on remote interview of subject, eDiary data, and if applicable, home visit physical examination and vital signs. The rationale for this change is to ensure optimal OCS dose for asthma control and to reduce the subject risk of exposure to COVID-19.

- Subjects aimed to transition to the extension study D5180C00018 to continue participation in the safety follow-up visit(s) (Week 54, Week 60) 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 (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 due to the COVID-19 pandemic while minimizing the subject risk of exposure to COVID-19.

For further details, please refer to Appendix K.

1.2 Synopsis

International co-ordinating investigator:

Protocol Title:

A Multicentre, Randomized, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Short Title: Tezepelumab OCS Sparing study

Rationale:

The purpose of the present study is to demonstrate the ability of tezepelumab versus placebo in reducing oral corticosteroid (OCS) use in adults with asthma requiring treatment with maintenance OCS in combination with inhaled corticosteroids (ICS) plus long-acting β2 agonist (LABA) with or without other asthma controller therapy, while maintaining asthma control.

OCS are effective agents for controlling airway inflammation in asthma and are indicated for severe persistent asthma, as outlined in Step 5 of the Global Initiative for Asthma (GINA 2017) guidelines. However, when given for extended periods of time, OCS are associated with multiple and potentially debilitating side effects. The odds for developing OCS associated complications are dose dependently associated with long term (≥6 months) OCS use evident at daily doses as low as ≤5 mg prednisone (Dalal et al 2016). As such, a reduction in OCS dose in severe asthma patients requiring chronic maintenance OCS use would be of clinical relevance.

Both mepolizumab and benralizumab have been shown to effectively reduce asthma exacerbations in severe asthma patients and to enable reduction in the maintenance OCS dose in OCS-dependent severe asthma patients.

Thymic stromal lymphopoietin (TSLP) is an upstream and pleiotropic cytokine, the blockade of which is anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

Tezepelumab is a TSLP monoclonal antibody. Given that TSLP has been implicated as a mediator of steroid resistance (Liu et al 2017), the inhibition of TSLP by tezepelumab may be effective in reducing the need for steroids in OCS dependent asthma patients.

The phase 2b tezepelumab efficacy study (CD-RI-MEDI9929-1146) conducted in patients with inadequately controlled severe asthma demonstrated a considerable reduction in the annualized asthma exacerbation rate (AAER) in subjects using OCS maintenance treatment.

Thus, it would be valuable to evaluate the ability of tezepelumab in reducing OCS use in severe asthma population.

Study objectives:

Primary objective:	**Endpoint/variable:**
To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in subjects with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	**Primary outcome variable:** Categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control The categories for percent change from baseline in daily OCS dose are defined as: 1. ≥90% to ≤100% reduction 2. ≥75% to <90% reduction 3. ≥50% to <75% reduction 4. >0% to <50% reduction 5. no change or any increase **Primary outcome measure:** Cumulative odds ratio vs placebo at Week 48
Key Secondary objective:	**Endpoint/variable:**

To evaluate the effect of tezepelumab compared with placebo on asthma exacerbations	**Key secondary outcome variable**: Annualised asthma exacerbation rate (AAER) **Outcome measure:** AAER ratio vs placebo over 48 weeks **Supportive outcome variable**: Time to first asthma exacerbation **Outcome measure:** Asthma exacerbation hazard ratio vs placebo over 48 weeks **Supportive outcome variable**: Rate of asthma exacerbation associated with ER visit, urgent care visit or hospitalisation **Outcome measure:** AAER ratio vs placebo over 48 weeks **Supportive outcome variable**: Proportion of subjects who did not experience an asthma exacerbation **Outcome measure:** Difference in proportions vs placebo at Week 48
Other Secondary objectives:	**Endpoint/variable:**
To evaluate the effect of tezepelumab compared with placebo on the prescribed OCS daily maintenance dose	**Outcome variables:** • Proportion of subjects with 100% reduction from baseline in daily OCS dose at Week 48 • Proportion of subjects with daily OCS dose ≤5 mg at Week 48 • Proportion of subjects with ≥50% reduction from baseline in daily OCS dose at Week 48 **Outcome measure:** Odds ratio vs placebo at Week 48
To evaluate the effect of tezepelumab compared with placebo on pre-bronchodilator (BD) lung function	**Outcome variables:** Change from baseline in pre-BD forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference vs placebo at Week 48

To assess the effect of tezepelumab compared with placebo with regards to asthma symptoms and other asthma control metrics	**Outcome variables:** Change from baseline in: • Weekly mean daily Asthma Symptom Score as captured in the daily Asthma Symptom Diary (ASD) • Weekly mean rescue medication use • Weekly mean home peak expiratory flow (PEF) (morning and evening) • Weekly mean number of night-time awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6) score **Outcome measure:** Mean difference vs placebo at Week 48
To assess the effect of tezepelumab compared with placebo with regards to asthma related and general health-related quality of life	**Outcome variables:** Change from baseline in: • Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score • European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score **Outcome measure:** Mean difference vs placebo at Week 48
To evaluate the efficacy of tezepelumab compared with placebo on health resource utilization and productivity loss due to asthma	**Outcome variables:** • Number of asthma specific resource utilizations (e.g. 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 48 weeks • Difference in WPAI+CIQ score vs placebo at Week 48
To assess the effect of tezepelumab on biomarkers	**Outcome variable:** Change from baseline in FENO, peripheral blood eosinophils and total IgE **Outcome measure:** Mean difference vs placebo at Week 48

To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	• PK: Serum trough concentrations • Immunogenicity: Incidence of anti-drug antibodies (ADA)
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
To evaluate the effect of tezepelumab on corticosteroid toxicity	Glucocorticoid toxicity index
Exploratory objectives	**Endpoint/variable:**
CCI	

Overall design:

This is a multicentre, randomized, double-blind, parallel group, placebo-controlled Phase 3 study designed to demonstrate the efficacy and safety of 210 mg tezepelumab administered subcutaneously (SC) every 4 weeks (Q4W) versus placebo in reducing OCS use in subjects with asthma requiring treatment with maintenance OCS in combination with high-dose ICS plus LABA with or without other asthma controller therapy, while maintaining asthma control.

The study will consist of a screening/run in period for 2 weeks, an OCS optimization phase for up to 8 weeks, a treatment period of 48 weeks and a post-treatment follow-up period of 12 weeks. The treatment period will consist of an induction phase for 4 weeks, an OCS reduction phase for 36 weeks and a maintenance phase for 8 weeks.

Subjects that complete the 48-week study visit will complete a 12-week post treatment, follow-up period unless the subject is eligible and decides to enrol into a separate extension study D5180C00018.

Study period:

Estimated date of first subject enrolled: Q1 2018

Estimated date of last subject completed: Q4 2020

Number of Subjects:

Approximately 152 subjects will be randomized to tezepelumab or placebo (1:1) globally from about 65-75 study sites. Randomization will be stratified by region.

Treatments and treatment duration:

After the initial enrolment and confirmation of entry criteria all subjects will enter a 2-week run-in period plus an up to 8-week optimization phase to establish a minimum effective dose of the prescribed OCS. The optimization phase may be extended to account for treatment of an exacerbation to allow for 2-weeks of a stable OCS dose prior to randomization.

After the OCS optimization phase, subjects who fulfil the eligibility criteria will be randomized to a 48-week treatment period.

There are 3 phases in the 48-week treatment period following randomization where subjects will be administered study drug.

- Induction phase – from week 0 to week 4 when subjects should remain on their optimized OCS dose.
- OCS reduction phase – from week 4 to week 40 when OCS dose reduction should be started at week 4 with the possibility of dose titration every 4 weeks. No down-titration after week 36.

- Maintenance phase – from week 40 to week 48 when subjects should remain on the OCS dose reached at week 40 (or earlier if OCS dose reduction failed because of clinical deterioration) or remain on complete oral corticosteroid elimination if possible.

Post treatment safety follow-up visits will be performed at week 54 and at week 60.

Subjects completing the planned treatment period may be eligible to enrol in a separate extension study and these subjects will not attend the follow up visit at Week 54 and Week 60

Subjects should preferably be maintained on their currently prescribed ICS plus LABA with or without other asthma controller therapy, without change, from 3 months before screening until end of study.

Subjects who prematurely discontinue investigational product (IP) during the study will be encouraged to undergo scheduled study visits/procedures for the full 48-week period. Further information is provided in section 7.1.

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 major adverse cardiac events (MACE) (to be defined in the charter) and 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, that occur 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 operate in accordance with the dedicated adjudication committee charter/manual of operations.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals.

DSMB will operate in accordance with a DSMB charter and periodically review unblinded safety summary tables and listings, evaluate for subject safety and make appropriate recommendations. The committee will function independently of all other individuals associated with the conduct of the studies, including the study sponsor AstraZeneca.

Statistical methods:

Approximately 152 subjects (76 per treatment group) are needed for this study based on the primary objective (with primary endpoint as defined above).

With 76 subjects per treatment group it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint will be at least 90%, assuming:

- An odds ratio of 2.75 and the proportional odds assumption
- The proportion of subjects in the 5 different dose reduction categories for placebo is as follows:
  - Category 1 (90% - 100% reduction): 10% of subjects
  - Category 2 (75% - <90% reduction): 10% of subjects
  - Category 3 (50% - <75% reduction): 15% of subjects
  - Category 4 (>0% - <50% reduction): 15% of subjects
  - Category 5 (no reduction or an increase): 50% of subjects

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 48 (for which every attempt will be made to collect data after discontinuation of IP up until week 48). No need is envisaged to adjust the planned number of randomized subjects in order to obtain an appropriate number of evaluable subjects.

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

- Percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (primary endpoint)
- AAER over 48 weeks (key secondary endpoint)

The primary endpoint in the tezepelumab group will be compared to that in the placebo group using a proportional odds (ordinal logistic regression) model. The response variable in the model will be the ordered category number (1-5) at Week 48 as defined above. Treatment and region will be included as factors in this model. Baseline OCS dose will be included in the model as a continuous (linear) covariate.

Analysis of the key secondary endpoint will compare the AAER over 48 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, and history of exacerbations (≤2, or >2 in previous 12 months) will be included as factors in the model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable.

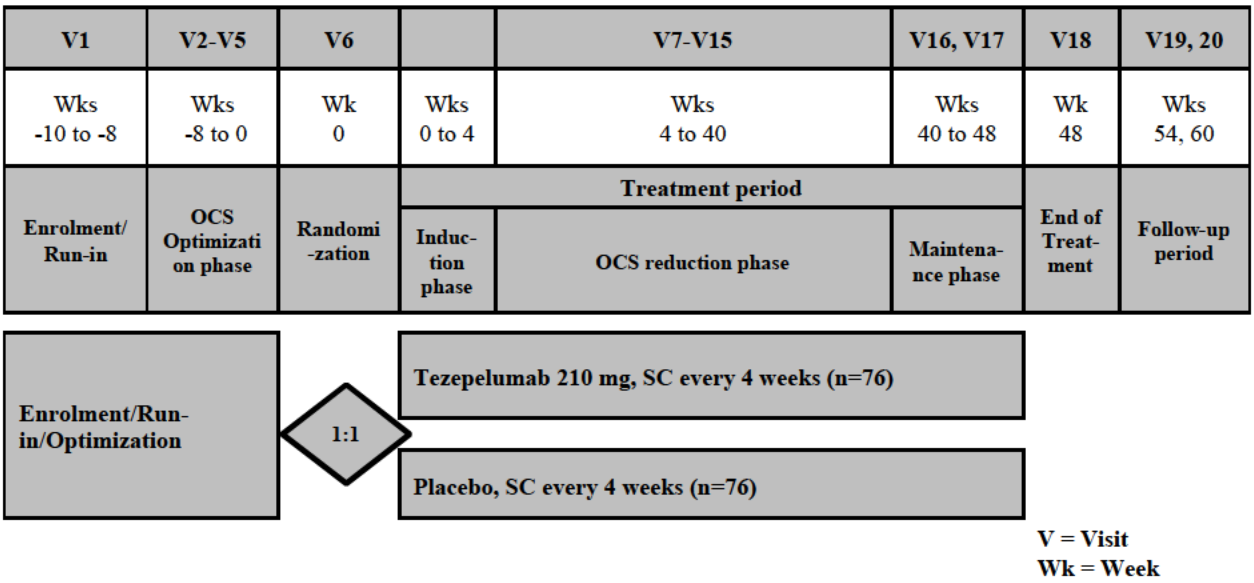
Additional sensitivity analyses will be performed on the primary and key secondary endpoints, including analyses to explore the impact of missing data and early discontinuation from IP.

All safety variables will be summarized descriptively. The safety analysis will be performed using the safety analysis set, which consists of all subjects receiving any IP.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



2. INTRODUCTION

2.1 Study rationale

OCS are effective agents for controlling airway inflammation in asthma and are indicated for severe persistent asthma, as outlined in Step 5 of the Global Initiative for Asthma (GINA 2017) guidelines. However, when given for extended periods of time, OCS are associated with multiple and potentially debilitating adverse outcomes. These include but are not limited to metabolic disorders, such as glucose intolerance and dyslipidemia (Gounarides et al 2008, Oliveira et al 2011), osteoporosis (Sambrook et at 1990), adrenal axis insufficiency, and excessive and abnormal fat deposition (Gounarides et al 2008). The odds for developing OCS associated side effects are dose dependently associated with long term (≥6 months) OCS use starting at doses as low as ≤5 mg per day of prednisone (Dalal et al 2016). A way to reduce daily OCS dose in severe asthma patients who require maintenance therapy with OCS would be clinically valuable.

The results by Liu et al 2017 from human blood and lung type 2 innate lymphoid cells from asthmatic patients suggest that TSLP is a mediator of steroid resistance. In the phase 2b study CD-RI-MEDI9929-1146, tezepelumab treatment reduced the AAER in severe asthma patients on

maintenance OCS treatment (Data on file). Other biologics (mepolizumab and benralizumab) have been shown to effectively reduce the AAER and have also been demonstrated to enable reduction in daily OCS dose in severe asthma patients requiring maintenance therapy with OCS (Bel et al 2014, Nair et al 2017). Thus, there is reason to believe that tezepelumab should be effective in reducing the daily OCS dose in severe asthma patients on maintenance OCS treatment.

The purpose of the present study is to demonstrate the ability of tezepelumab versus placebo to enable reductions of the daily maintenance OCS use in adults with asthma also using high-dose ICS plus LABA with or without other asthma controller therapy, while maintaining asthma control.

2.2 Background

Asthma is a chronic inflammatory airway disease characterized by bronchial hyperreactivity and reversible airflow limitation that causes wheezing, shortness of breath, cough, and chest tightness. Although several treatments are available (e.g. ICS, LABA and LAMA), there is a clear unmet medical need among patients with severe asthma.

Biologic therapies can provide additional asthma control for such patients. Omalizumab may be suitable 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 (NUCALA US PI 2015, 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 LABA/ICS 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, independent 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 response to proinflammatory stimuli (e.g., infectious, allergic and environmental stimuli) and trauma. TSLP has an upstream and central role in the initiation of inflammatory 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 (Tedeschi SK et al 2017, 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 now recognized as a heterogenous disease with subsets of patients that do not exhibit Th2-associated disease (Wenzel 2012). 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 human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with TSLP receptor (TSLPR).

Results of a completed study in 31 adult subjects with mild atopic asthma (Study 20101183) demonstrated that administration of tezepelumab attenuated both the early and late phase allergic response and suppressed the expected increase in FENO following inhalation allergen challenge (Gauvreau et al 2014). Multiple doses of 700 mg IV tezepelumab demonstrated an acceptable safety profile in subjects with mild atopic asthma. 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/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 (Corren et al 2017). Subjects were randomized in a 1:1:1:1 ratio to 1 of 3 dose levels of SC tezepelumab (280 mg every 2 weeks [Q2W], 210 mg Q4W, or 70 mg Q4W) or placebo (Q2W) for 52 weeks. A total of 584 subjects received at least 1 dose of IP (tezepelumab or placebo). Statistically significant AAERR of 61%, 72%, 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 ($p<0.001$). Moreover, clinically significant benefits in lung function, ACQ-6 and AQLQ+12 were observed. In addition, blood eosinophil numbers and FENO were significantly suppressed.

After repeated SC administration, mean serum tezepelumab trough concentration increased over time and achieved steady-state by week 12. Tezepelumab exhibited linear PK across the 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. Few subjects had TEAEs that resulted in permanent discontinuation of investigational product. Overall, tezepelumab was well-tolerated with an acceptable safety profile and no safety signals were identified.

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

2.3 Benefit/risk assessment

In order to evaluate the clinical benefit-risk balance, preclinical and clinical data, 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, have been considered. Benefits for tezepelumab over placebo include a clinically meaningful AAERR, an increased FEV_1 and an improvement in 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. Potential risks with tezepelumab will be mitigated by the selected inclusion/exclusion criteria and continuous monitoring of safety data during the study. In the present study, measures are taken to mitigate the risk for embryonal, fetal and child exposure to tezepelumab.

The benefit/risk assessment for tezepelumab in severe asthma based on the development through Phase 2 is favourable. 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 AEs of tezepelumab may be found in the Investigator's Brochure.

See Section 8.4.7 for information regarding the DSMB.

3. OBJECTIVES AND ENDPOINTS

Table 3 **Study objectives**

Primary objective:	**Endpoint/variable:**
To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in subjects with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	**Primary outcome variable:** Categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control The categories for percent change from baseline in daily OCS dose are defined as: 1. ≥90% to ≤100% reduction 2. ≥75% to <90% reduction 3. ≥50% to <75% reduction 4. >0% to <50% reduction 5. no change or any increase **Primary outcome measure:** Cumulative odds ratio vs placebo at Week 48
Key Secondary objective:	**Endpoint/variable:**

To evaluate the effect of tezepelumab compared with placebo on asthma exacerbations	**Key secondary outcome variable**: AAER **Outcome measure:** AAER ratio vs placebo over 48 weeks **Supportive outcome variable**: Time to first asthma exacerbation **Outcome measure:** Asthma exacerbation hazard ratio vs placebo over 48 weeks **Supportive outcome variable**: Rate of asthma exacerbation associated with ER visit, urgent care visit or hospitalisation **Outcome measure:** Asthma exacerbation rate ratio vs placebo over 48 weeks **Supportive outcome variable**: Proportion of subjects who did not experience an asthma exacerbation **Outcome measure:** Difference in proportions vs placebo at Week 48
Other Secondary objectives:	**Endpoint/variable:**
To evaluate the effect of tezepelumab compared with placebo on the prescribed, OCS daily maintenance dose	**Outcome variables:** • Proportion of subjects with 100% reduction from baseline in daily OCS dose at Week 48 • Proportion of subjects with daily OCS dose ≤5 mg at Week 48 • Proportion of subjects with ≥50% reduction from baseline in daily OCS dose at Week 48 **Outcome measure:** Odds ratios vs placebo at Week 48
To evaluate the effect of tezepelumab compared with placebo on Pre-BD lung function	**Outcome variables:** Change from baseline in Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference vs placebo at Week 48

To assess the effect of tezepelumab compared with placebo with regards to asthma symptoms and other asthma control metrics	**Outcome variables:** Change from baseline in: • Weekly mean daily Asthma Symptom Score as captured in the daily Asthma Symptom Diary (ASD) • Weekly mean rescue medication use • Weekly mean home peak expiratory flow (morning and evening) • Weekly mean number of night-time awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6) score **Outcome measure:** Mean difference vs placebo at Week 48
To assess the effect of tezepelumab compared with placebo with regards to asthma related and general health-related quality of life	**Outcome variables:** Change from baseline in: • Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score • European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score **Outcome measure:** Mean difference vs placebo at Week 48
To evaluate the efficacy of tezepelumab compared with placebo on health resource utilization and productivity loss due to asthma	**Outcome variables:** • Number of asthma specific resource utilizations (e.g. 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 48 weeks • Difference in WPAI+CIQ score vs placebo at Week 48
To assess the effect of tezepelumab on biomarkers	**Outcome variable:** Change from baseline in FENO, peripheral blood eosinophils and total IgE **Outcome measure:** Mean difference vs placebo at Week 48

To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	• PK: Serum trough concentrations • Immunogenicity: Incidence of ADA
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
To evaluate the effect of tezepelumab on glucocorticoid toxicity	Glucocorticoid toxicity index
Exploratory objectives	**Endpoint/variable:**
CCI	

4. STUDY DESIGN

4.1 Overall design

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

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

This is a Phase 3, multi-centre, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effect of 210 mg Q4W SC of tezepelumab on OCS dose reduction in adult subjects with OCS dependent asthma.

The study will randomize approximately 152 subjects globally in a 1:1 ratio to either tezepelumab or placebo. The subjects will be stratified by region.

All subjects must have received OCS for the treatment of asthma for at least 6 months prior to visit 1 and must have been on a stable dose of between ≥ 7.5 to ≤ 30mg (prednisone or prednisolone) daily or daily equivalent for at least 1 month prior to visit 1. Subjects must have been on a medium- to high- dose ICS for the past 12 months and LABA with high dose ICS for at least 3 months prior to visit 1. Additional maintenance asthma controller medications are allowed according to standard practice of care. Their use must be documented for at least 3 months prior to visit 1. See inclusion criteria 4-7.

Subjects in the study will be required to have had at least one asthma exacerbation in the past 12 months. Details on acceptable historical documentation is specified in section 5.1.

Eosinophils will be assessed using central lab analyses. Approximately 35% of the subjects will be targeted to have ≥ 300 eosinophils/µl at enrolment. When the target percentage of subjects for the 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 of 2 weeks, an OCS optimization phase for up to 8 weeks and a treatment period of 48 weeks consisting of a 4-week induction phase, a 36-week OCS reduction phase and an 8-week maintenance phase. The duration of the post-treatment follow-up period is 12 weeks (week 48-60). During the treatment period, IP will be administered SC starting at randomization and continue until week 44. IP will not be administered on week 48. There are up to 18 visits from screening to scheduled end of treatment, followed by two 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. Further details are specified in section 5.5.

Subjects who are administered IP week 44 and complete the 48-week study visit will complete a 12-week post-treatment follow-up period.

Subjects who prematurely discontinue IP during the study will be encouraged to undergo appropriate study visits/procedures for the full 48-week period. Subjects should have an IPD visit at 4 weeks from the final dose of IP. A follow-up visit should then be scheduled 16 weeks after last IP administration. Further information is provided in section 7.1.1. Any new treatments that are initiated will be recorded in the electronic case report form (eCRF).

Subjects remaining on IP for entire planned treatment period, may be eligible to enroll in the extension study. These subjects will transition to the extension study, after completing the EOT assessments at week 48 and thus they will not attend the follow-up visits at Week 54 and Week 60.

4.2 Scientific rationale for study design

This is a global study designed to evaluate the efficacy and safety of a fixed 210 mg dose of tezepelumab administered Q4W SC in severe asthma subjects who are on maintenance OCS and ICS/LABA therapy, with or without additional asthma controller(s). The primary efficacy measure will be based on the percentage change from baseline in the prescribed, daily, average OCS dose at week 48 post randomization while not losing asthma control.

This study is double blind to reduce the risk of bias. Tezepelumab is compared to placebo on top of standard of care to better assess the effect in the appropriate clinical context. This study is a randomized, parallel group, double-blinded study in which subjects are stratified by region. The asthma study population has been chosen as one in need of reduction of the daily OCS dose. Subjects should be on maintenance OCS, high dose ICS and LABA to ensure that a severe asthmatic population is included in the trial.

In the optimization phase, the lowest OCS dose is defined as the OCS dose at which asthma control is maintained. The duration of the induction phase is defined by the time to reach effect in the phase 2b study. In the reduction phase, strict criteria will be followed for down titration of the OCS dose. The maintenance phase is to assess the effectiveness to maintain asthma control without exacerbations. This study has a similar design and endpoints as previous studies with mepolizumab (Bel et al 2014) and benralizumab (Nair et al 2017). A difference in this study design from previous OCS sparing studies is that the duration of the present study is longer; 48 weeks compared to 24 - 28 weeks in previous trials. The reduction phase in the present study has a longer duration to allow more subjects to reduce daily OCS dose to 0 mg. In addition, the maintenance phase is of longer duration as compared to the previous studies to better evaluate the sustainability of the treatment effect.

This phase 3 study will evaluate the OCS reduction capacity of tezepelumab and the effect on the AAER and other aspects of lung function, asthma control, and safety to further characterize the benefit-risk profile of the drug and understand how best to position it in the treatment pathway.

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 pharmaco-dynamic endpoint 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 AAERR 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 the AAER. Therefore, the dose of 210 mg Q4W has been selected for evaluation in this study. 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.

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

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

For procedures for withdrawal of incorrectly enrolled subjects see Section 6.3.

5.1 Inclusion criteria

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

Informed consent

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

2. Provision of signed and dated written optional Genetic informed consent prior to collection of sample for genetic analysis (refer to 0 for specific requirements for genetic sampling).

The ICF process is described in Appendix A 3.

Age

3. Subject must be 18 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 must have received a physician-prescribed medium- or high-dose ICS as per GINA guideline (GINA 2017) for at least 12 months prior to visit 1.

6. Subjects must have received physician prescribed LABA and high dose ICS (total daily dose >500µg fluticasone propionate dry powder formulation equivalent) for at least 3 months prior to visit 1. The ICS and LABA can be parts of a combination product, or given by separate inhalers.

   – Equivalent ICS doses as detailed in 0.

7. Additional maintenance asthma controller medications are allowed according to standard practice of care i.e., leukotriene receptor antagonists (LTRAs), theophylline, long-acting muscarinic antagonists (LAMAs), secondary ICS and cromones. The use of these medications must be documented for at least 3 months prior to visit 1.

8. Subjects must have received OCS for the treatment of asthma for at least 6 months prior to visit 1 and on a stable dose of between ≥ 7.5 to ≤ 30mg (prednisone or prednisolone) daily or daily equivalent for at least 1 month prior to visit 1. The OCS dose may be administered every other day (or different doses every other day); Average dose over two days = The daily dose.

9. Morning pre-bronchodilator (BD) FEV_1 must be < 80% predicted normal at visit 1 or visit 2.

10. Subjects must have evidence of asthma as documented by post-BD (albuterol/salbutatomol) reversibility of FEV_1 ≥12% and ≥200 mL (15-30 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 12 months prior to or at visit 1 or at visit 2.

11. Subjects must have a history of at least 1 asthma exacerbation event within 12 months prior to visit 1. For the purpose of this study an asthma exacerbation is defined as a worsening of asthma that either:

- required treatment with a burst of systemic corticosteroids for at least 3 days or a single depot- injectable corticosteroid dose OR
- resulted in an emergency department visit (defined as evaluation and treatment for <24 hours in an ER or urgent care center) which required systemic corticosteroids (as per above) OR
- An inpatient 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 acceptable documentation of an exacerbation:

- 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 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.

Weight

12. Body weight ≥ 40 kg at visit 1.

Reproduction

13. Negative pregnancy test (urine or serum) for female subjects of childbearing potential.

14. Females of childbearing potential who are sexually active with a non-sterilized 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 investigational product. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

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

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

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

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

15. Inclusion Criterion # 15 removed with version 3.0 of Clinical Study Protocol

Inclusion criteria at randomization

16. Subject must have received the optimized OCS dose for at least 2 weeks prior to randomization.

17. Minimum 10 days compliance with the morning and evening eDiary completion during the 14 days prior to randomization.
    A compliant day requires completion of evening eDiary and subsequent morning eDiary such that an ASD daily score can be calculated.

    – The period for this criterion is the duration from the evening of the final OCS dose adjustment (defining the optimized dose) during the optimization phase until the morning of the randomization visit.

18. Minimum 10 days compliance with OCS, ICS, LABA and other asthma controller medications as captured in the eDiary during the 14 days prior to randomization.

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

19. Acceptable inhaler, peak flow meter, and spirometry techniques as judged by the investigator.

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 ever diagnosed with pulmonary or systemic disease, 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 or lower respiratory tract infection (URTI and LRTI, respectively), requiring treatment with antibiotics or antiviral medications finalized < 2 weeks before screening 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 any known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.

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

11. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of systemic corticosteroids or increase in the maintenance dose of OCS finalized within 30 days prior to visit 1.

Prior/concomitant therapy

12. 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.

13. Treatment with the following medications within the last 12 weeks prior to visit 1 : systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine, oral/parenteral/intra-articular corticosteroids for other use than treatment of asthma).

14. Receipt of immunoglobulin or blood products within 30 days prior to visit 1.

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

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

17. Subjects who have been treated with bronchial thermoplasty in 12 months prior to visit 1.

Prior/concurrent clinical study experience

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

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

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

21. Subject randomized in the current study or previous tezepelumab studies.

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

Diagnostic assessments

23. Any clinically meaningful abnormal findings 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 entire duration of the study.

24. Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase beyond twice the upper limit of normal.

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

26. A positive human immunodeficiency virus (HIV) test at screening or subject taking antiretroviral medications, as determined by medical history and/or subject's verbal report.

Other exclusions

27. Pregnant, breastfeeding, or lactating women.

    A serum β-human chorionic gonadotropin (HCG) pregnancy test must be drawn for women of childbearing potential at the screening visit. If the results of the serum β-HCG cannot be obtained prior to dosing of the investigational product, 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.

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

29. 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

30. Previous allogeneic bone marrow transplant.

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

Exclusion criteria at randomization

32. During the optimization period, asthma control reached at an OCS dose of <7.5 mg or >30mg and/or 3 consecutive dose reductions after which asthma control was still obtained.

33. Evidence of clinically significant infection or subject receiving treatment with antibiotics or antiviral medications.

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 study site. Subjects should not eat or drink 1 hour prior to having FENO assessment.

5.3.2 Alcohol, tobacco and other

Chronic alcohol or drug abuse within 12 months prior to visit 1 and throughout the conduct of the study is not allowed.

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 study site.

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 randomly assigned to Study treatment. 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.

5.5 Re-screening

Subjects with clinically significant infection, including respiratory infections requiring intravenous antibiotics or systemic antiviral medication during run-in should be screen failed but may be re-screened 2 weeks after 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 visits prior to randomization), subjects may potentially be re-screened. These cases should be discussed with the AstraZeneca Study Physician and documented approval for re-screening should be filed in the Investigator Study File (ISF).

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).

Any re-screened subject will be re-enrolled and reassigned their originally assigned enrolment number after signing a new Informed Consent Form (ICF). All visit 1 assessments as listed in the SoA should be re-performed 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.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to tezepelumab 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	0.7% (w/v) sodium carboxy methyl cellulose in 10 mM acetate, 250 mM L-proline, 0.01% (w/v) polysorbate 80, pH 5.0
Route of administration	Subcutaneous	Subcutaneous
Dosing instructions:	Refer section 6.2	Refer 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 authorised 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 authorised 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 K 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 5 cc single use glass vials to be stored at 2°C to 8°C until used. If there are any defects 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 study nurse) at the site.

The IP product 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 manager will select IP 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 the IP for administration, remove the tab portion of the vial cap and clean the stopper with 70% ethyl alcohol or equivalent.

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

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

5. Apply the appropriate label to the syringe.

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

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

Assigned vial should be used at one time to prepare the dose required at each visit. Unused product in opened and dispensed vial 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 below) and must be prepared using disposable plastic syringes and aseptic technique.

Table 5 Investigational product dose preparation

Dose	Number of vials required	Syringe size required	Total volume administered
210 mg [a]	1	3 mL	1.9 mL
Placebo	1	3 mL	1.9 mL

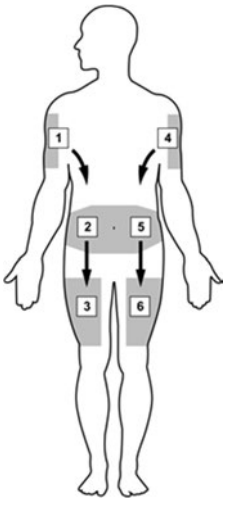
[a] Due to gradations available on 3 mL disposable plastic syringe, dose based on 1.9 mL administered volume is 209 mg.

Dose administration

IP will be administered by a qualified healthcare professional (e.g., pharmacist or study nurse) at the site. The 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 seconds duration is recommended) into the SC tissue using gentle pressure. The area should not be massaged after injection. It is advised that the site of injection of IP be rotated such that the subject receives IP at a different anatomical site at each treatment visit. Injection site must be documented on the eCRF and in the source documents at each treatment visit. In cases when rotation of the injection site is not feasible and/or the subject prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents.

The suggested injection site rotation sequence is presented below in Figure 2.

Figure 2 Rotation of injection sites



Subjects should be observed for a minimum of 2 hours after 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 minimise bias: randomisation and blinding

Subject enrolment and randomization

The Investigator(s) should keep a subject screening log listing of those who have entered pre-study screening. The Investigator(s) will:

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

2. Assign the potential subject a unique enrolment number (which begins with an 'E') via 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 stratified by region. Randomization numbers will be grouped in blocks. If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects will not be replaced

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

Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study medication. There can be no exceptions to this rule. Subjects who

are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

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

Approximately 35% of the subjects will be targeted to have ≥ 300 eosinophils/µl at enrolment. Therefore, further enrolment of subjects with < 300 eosinophils/µl may be halted to achieve the required percentage.

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.

To further prevent unblinding, blood eosinophil, basophils and monocyte numbers from the visits after randomization visit will be redacted from the central laboratory reports. In addition, FENO results will also be blinded throughout the study.

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

The following personnel will have access to the randomization list:

- those carrying out the packaging and labelling of IP
- those generating the randomization list
- personnel at the IWRS/IVRS company
- supply chain management department
- patient safety department at AstraZeneca
- bioanalytical lab performing the PK, ADA, and nab sample analysis
- those involved in the reporting and reviewing the DSMB presentations

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

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

Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) and Study Coordinator(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 documents and reports 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 48 has been documented.

6.4 Treatment compliance

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

Information about any asthma treatment in the 12 months prior to and all other concomitant treatments 3 months prior to the date of the visit 1 and given during the study, with reason for the treatment, will be collected by the Investigator/authorized delegate at each visit and recorded in the eCRF.

To satisfy inclusion criteria 5 to 8, there should be a documented history of treatment with medium- or high-dose ICS for at least 12 months and LABA with high dose ICS for at least 3 months prior to visit 1. Use of OCS for at least 6 months, with a dose stable for at least 1 month prior to visit 1, should also be documented in source.

Medium dose ICS corresponds to 500 µg and high dose ICS corresponds to >500 µg fluticasone propionate dry powder formulation equivalents as outlined in 0. Subjects may also receive other physician prescribed asthma controller medications.

No changes are allowed to background asthma medications (except OCS) throughout the duration of the study except during the treatment of an asthma exacerbation.

However, subjects prematurely discontinuing IP administration should be given locally available standard of care therapy, allowing changes to background medications at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until week 60 even if the subject has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. Thus, the effects and side effects of concomitant treatment of tezepelumab and other biologics have not been evaluated. The time for elimination of tezepelumab (5 half-lives) is approximately 16 weeks. However, the duration of downstream pharmacodynamics effects of tezepelumab is unknown. For additional information regarding pharmacokinetic and phamacodynamic effects of tezepelumab, reference should be made to the investigator brochure.

OCS medication as well as maintenance asthma medications 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 analyzed at the central or local lab as applicable. Investigator can use their clinical judgement about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Table 6 **Restricted medications**

Medication/class of drug:	**Usage**
Maintenance treatment with long-acting bronchodilators (including ICS/LABA combinations)	No changes, in dose and regimen, are allowed from visit 1, during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP. ICS/LABA should not be taken prior to scheduled spirometry, FENO, ECG and home lung function assessments (to be administered once assessments are completed): • Twice daily bronchodilator 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 to washout of their asthma medications for unscheduled visits due to asthma worsening.
Short-acting beta-agonists (SABA)	Regular scheduled use not allowed from visit 1, during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP. PRN use is allowed; however, attention should be paid to the following restrictions: If possible, SABA should be withheld for at least 6 hours prior to scheduled spirometry, FENO, ECG at site and home lung function assessments. Only albuterol/salbutamol is allowed to be used as a rescue medication during the study, except during exacerbations.

Medication/class of drug:	Usage
Additional maintenance controllers	No changes, in dose and regimen, are allowed from visit 1, during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP. Once daily LABA and LAMA should be withheld for at least 24 hours prior to the scheduled spirometry and FeNO. Twice daily LABA- or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry and FENO at site. LTRA should be restricted for at least 24 hours prior to scheduled spirometry and FENO at site. Subjects on theophylline should have blood concentration levels within therapeutic range documented before proceeding in the study. However, if theophylline blood concentration is out of therapeutic range after visit 1, dose adjustments are allowed. Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry and FENO at site. Once daily theophyllines should be withheld for at least 24 hours prior to scheduled spirometry and FENO at site.
Short-acting anti-cholinergics (e.g. ipratropium)	Not allowed as a rescue treatment for worsening of asthma symptoms from visit 1, during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP. May be used for managing an asthma exacerbation event.
Inactive/killed vaccinations (e.g. inactive influenza)	Allowed provided they are not administered within 5 days before or after any study visit.
Allergen immunotherapy	Allowed if on stable therapy for at least 30 days prior to visit 1; no anticipated changed during treatment period. Should not be administered on the same day as IP administration.

Table 7 Prohibited medications

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 run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP.

Medication/class of drug:	Usage
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed 15 days prior to visit 1, during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP.
Live attenuated vaccines	Not allowed 30 days prior to visit 1; throughout IP treatment and preferably 4 weeks after last dose of IP (unless there is an absolute medical need as judged by the Investigator) and follow-up period.
Any immunomodulators or immunosuppressives (corticosteroids with systemic effects such as oral, parenteral, or intra-articular administration for reasons other than asthma are not allowed. However, corticosteroid treatment of adrenal insufficiency and acute anaphylaxis is allowed.)	Not allowed 3 Months or 5 Half Lives (whichever is longer) prior to visit 1; during run-in and optimization phase, throughout IP treatment and preferably 16 weeks after last dose of IP.
Blood products or immunoglobulin therapy	Not allowed 30 days prior to visit 1; during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP (unless there is an absolute medical need as judged by the Investigator).
Any marketed (e.g. benralizumab, omalizumab, mepolizumab, reslizumab) or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to visit 1 ; throughout the entire treatment period (even if the subject has discontinued IP) and until the follow up visit week 60.
Other IP (including investigational use of an approved drug)	Not allowed 30 Days or 5 Half Lives (whichever is longer) prior to visit 1; during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60.
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to visit 1; during run-in and optimization phase, throughout IP treatment and preferably 4 weeks after 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 run-in and optimization phase, throughout IP treatment and preferably 4 weeks after last dose of IP.
Spironolactone	Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60.
Eplerenon	Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60.

Medication/class of drug:	Usage
Ephedrine (e.g. in antitussives or mucolytics)	Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60.
Opiates prn (e.g. in antitussives)	Not allowed from visit 1, during run-in and optimization phase, throughout the entire treatment period (even if the subject has discontinued IP) until the follow up visit week 60.

6.5.1 Other concomitant treatment

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

6.5.2 Rescue medicine

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

The study site will supply albuterol /salbutamol rescue medication that will be provided by the sponsor/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 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

After the end of the study at week 60, subjects should be given standard of care at the discretion of the investigator. Subjects that are eligible and decide to enrol in a separate extension study will not attend the follow-up visits at week 54 and week 60 and should comply with the requirements of the separate extension study protocol.

NB There is a potential risk that spironolactone and eplerenon may aggravate adrenal insufficiency in this population

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from IP in the following circumstances. Note that discontinuation from study treatment is NOT the same as a complete withdrawal from the study.

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

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 prematurely discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for premature 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 60 even if the subject has discontinued IP.

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 and a follow-up visit at 16 weeks (+/-5 days) (refer to SoA, V20 – Week 60).

Subjects who discontinue treatment should be encouraged to return for all regularly scheduled visits as per SoA. Protocol specified OCS dose reductions according to schedule can be performed at PI's discretion and judgement .

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

Option 1: Ideally the subject should continue all regular clinic visits and perform all assessments as per SoA until scheduled EOT visit at Week 48 (+/-5 days).

Option 2: (If the subject cannot comply or does not wish to comply with option 1 above) To be followed up on a monthly basis via telephone calls while continuing at-home eDiary and ePEF completion including the questionnaires that otherwise would have been completed at the site as per SoA. Followed by an **on-site** EOT visit at Week 48 (+/-5 days).

Option 3: (If the subject cannot comply with option 1 or 2 above) To be only contacted on phone at the scheduled EOT visit at Week 48 weeks (+/-5 days).

The EOT visit will be completed immediately in the case of subsequent early withdrawal. 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 (and at IPD visit for subjects choosing option 3 above).

If the subject chooses option 2 or 3, the key information to be collected during the telephone calls are AEs/SAEs, changes in concomitant medication, health care utilization, and 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 withdrawal' on the Discontinuation of Investigation 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 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 ICF.

7.3.1 Withdrawal due to recruitment completion

When the required number of subjects are randomized in the study, ongoing subjects in run-in period or optimization phase may 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 subjects 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 summarised in the SoA.

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

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 eCRF. A copy of the completed eCRFs 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.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study (excluding optional blood samples) will not exceed 220 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The total amount of blood collected over the duration of study will not exceed 450 mL.

8.1 Efficacy assessments

8.1.1 Overview of OCS dose management

During the OCS optimization phase, the minimum OCS dose while maintaining asthma control (optimized dose) will be reached for all subjects. Asthma control and the criteria for OCS dose reduction are described in section 8.1.1.2. The optimized OCS dose will be kept stable for 2 weeks prior to randomization and will be considered the baseline OCS dose.

The baseline OCS dose should be maintained at the same level from visit 5 (two weeks prior to randomization) to visit 7 (end of induction phase).

OCS dose reduction will commence at visit 7 and continue at 4-week intervals until visit 15 in accordance with the OCS dose titration schedule described in section 8.1.1.1 (reduction phase). During the reduction phase a minimum stable OCS dose, or complete elimination of requirement for OCS, while maintaining asthma control, will be reached for each subject.

If possible, no adjustments should be made to the OCS dose at visit 16 and 17 (maintenance period) and until visit 18 (End of treatment).

8.1.1.1 OCS dose titration

At visit 1 subjects will continue with or be switched to prednisone/prednisolone. For subjects not previously receiving prednisone/prednisolone as OCS, the conversion table shown in 0 will be used to calculate the equivalent prednisone/prednisolone dose for dose titrations.

The OCS dose titration will follow the same approach for both the optimization and the reduction phase. The dose of OCS should be reduced if the subject meets the protocol defined criteria indicating that it is acceptable for the subject to reduce OCS, as described in section 8.1.1.2. When a subject does not meet these criteria defining asthma control, the investigator should preferentially increase up one step unless the judgment of the investigator is to maintain the subject on their current dose of OCS, depending on the rationale for not reducing per schedule. The OCS dose changes and their reasons must be documented in the source documentation and recorded in the appropriate eCRF form.

OCS dose titration in the optimization phase

In the OCS dose optimization phase, dose titration should begin at visit 2.

Baseline readings to be used for dose titrations in the optimization period will be the mean of measures (morning PEFs, SABA use and night time awakenings) collected between visit 1 and visit 2. Dose reduction at visit 2 is the only titration visit during the optimization phase that will not be based upon a protocol-captured set of baseline data because determining a change from baseline will not be possible.

Visits 3 and 4 can be performed as telephonic visits provided the subject and sites are confident to perform the visit remotely. Depending on clinical judgement, investigator may instead decide to call the subject on-site for visits 3 and 4. OCS dose reductions can occur at 2-week intervals according to the titration schedule (Table 8). In the dosing interval >10-30 mg prednisone or prednisolone per day, the change in daily dose is 5 mg, whereas in the interval 7.5-10 mg, the corresponding reduction is 2.5 mg.

Table 8 OCS dose titration schedule during the optimization phase

Regimen	Starting dose of OCS (mg/day) at each visit of optimization period	Change by (mg/day) [a]
Daily regimen	>10-30	5.0
	7.5-10	2.5

[a] During the Optimization phase the reductions should occur at 2-week intervals.

The optimized dose of OCS will be decided by using the criteria for the OCS dose reduction schedule, described in section 8.1.1.2, Table 9. In cases when the subject is optimized on their OCS dose at visit 3 or 4, visit 5 should be activated, instead of visit 3 or 4, on the same day and he/she should be maintained at the optimized dose of OCS for at least 2 weeks before being randomized. Conversely, the optimization phase may be extended to account for treatment of an exacerbation to allow for 2-week stable OCS dose prior to randomization. The optimized dose

reached during the OCS optimization phase becomes the subject's baseline OCS dose for analysis purposes.

Subjects who are considered by Investigators not to be candidates for starting OCS dose reduction in the optimization phase, based upon asthma symptoms or other clinical reasons, should be screen-failed. Similarly, if the subject is non-compliant to eDiary completion and OCS, ICS/LABA or other asthma controller use and due to which the OCS dose cannot be optimized, then the subjects should be screen-failed.

If a subject reaches asthma control at an OCS dose of <7.5 mg during this phase, or asthma control is still obtained after 3 consecutive OCS dose reductions, then the subject will be a screen failure and will not be randomized.

OCS dose titration in the treatment period

No OCS titration should occur during the induction phase (visit 6-7).
Dose titration during the treatment period will begin at visit 7 and end no later than at visit 15 (reduction phase). It is performed at 4-week intervals according to the titration schedule in Table 9.

Table 9 OCS dose titration schedule during the reduction phase (V7-V15) [a]

Optimized dose at V-6 Wk0	V-7 Wk4	V-8 Wk8	V-9 Wk12	V-10 Wk16	V-11 Wk20	V-12 Wk24	V-13 Wk28	V-14 Wk32	V-15 Wk36
30	25	20	15	10	7.5	5	2.5	0	0
25	20	15	10	7.5	5	2.5	0	0	0
20	15	10	7.5	5	2.5	0	0	0	0
15	10	7.5	5	2.5	0	0	0	0	0
12.5	7.5	5	2.5	0	0	0	0	0	0
10	7.5	5	2.5	0	0	0	0	0	0
7.5	5	2.5	0	0	0	0	0	0	0

The OCS dose may be administered every other day (or different doses every other day) Average dose over two days = The daily dose
[a] All doses expressed in mg/day of Prednisone/Prednisolone.

Unlike the optimization phase, for all subjects entering the dose reduction phase, the baseline values for titration will be the mean of measures (morning PEFs, SABA use and night time awakenings) collected daily two weeks prior to randomization (visit 6). Similar to optimization phase, though, is that dose reduction at visit 7 is the only titration visit during the reduction phase that will not be based upon a protocol-captured set of baseline data (because the OCS dose is the same as during baseline). At a minimum 10 days of completed morning and evening eDiary assessments should be available prior to randomization to consider the mean as baseline for the OCS reduction phase.

All subjects will enter the OCS dose maintenance phase at visit 16 (week 40). No further dose reductions should be attempted after visit 15 (week 36).

8.1.1.2 Criteria for OCS dose reduction during the optimization and reduction phase

OCS dose titration (reduction) should be attempted at each visit as per the SoA. Subject should meet all of the criteria listed in Table 10 to follow the dose titration schedule. For OCS dose titrations at each visit subjects should have a minimum compliance of 10 of the last 14 days before the visit with morning and evening eDiary completion, OCS, ICS/LABA and other asthma controller use. Compliance is calculated from the data available from eDiary completion between visits. In the event of a lower eDiary compliance, using the visit window period the planned visit could be delayed to allow for 10 of the last 14 days compliance or study physician should be consulted to decide if the OCS dose reduction should follow as per schedule.

Table 10 Criteria for following OCS dose reduction schedule

Criteria	Definition of asthma control
1	Morning PEF ≥80% of mean [a] morning measures as compared with baseline [b] mean
2[c]	An increase of no more than 2 nights with asthma-related awakenings (requiring rescue medication) over a 7-day period compared with baseline [b]
3	Mean [a] SABA rescue medication use not more than 4 puffs/day above the baseline [b] mean and <12 puffs/day on all days in the prior 14 days [d]
4	No asthma exacerbation requiring increased systemic corticosteroids or hospitalization since the previous visit
5	Investigator judges subject's asthma control to be sufficient to allow OCS dose reduction [e]
6	No signs/symptoms of adrenal insufficiency (at OCS dose reductions below 5 mg) [f]

[a] Mean values to be considered for each titration visit will be from completed eDiary records 14 days prior to the visit.
[b] Baseline values for optimization phase are calculated from completed eDiary records of a minimum of 10 out of 14 days before visit 2. Similarly baseline values for the reduction phase will be calculated from a minimum of 10 out of 14 days before randomization visit.
[c] Number of nights with awakenings due to asthma requiring rescue medication will be counted from the most recent 7 days of available data.
[d] Each nebulization used will be counted as 2 puffs.
[e] Investigator will provide detailed rationale in eCRF for not reducing the OCS dose.
[f] Investigator will provide detailed description, in the eCRF, of the signs/symptoms of AI for not reducing the OCS dose according to schedule.

It is at the discretion of the Investigator to continue with the OCS down-titration even if the criteria for OCS reduction have not been met. Such a decision must be justified and documented in the source notes and captured in the eCRF. This decision must be notified to the AstraZeneca study physician within 2 business days.

When a decision is made to not reduce the OCS dose according to the reduction algorithm, the reason(s) for not reducing OCS must be documented in the source notes and captured in the eCRF. Depending on the rationale for not reducing per schedule, the investigator should preferentially increase up one step unless the judgment of the investigator is to maintain the

subject on their current dose of OCS. This will be defined as the optimized OCS dose for the optimization phase and the visit must be combined with Visit 5.**Once the optimized OCS dose is reached, no further OCS dose reductions should be performed during the optimization phase.** The subject should be maintained on that OCS dose until randomization (Visit 6). Subjects who do not meet all of the criteria for continuing OCS down titration specified in Table 10during the reduction phase, should preferentially be returned to the previous effective OCS dose (i.e. the higher dose level prior to not meeting the down-titration criteria) after they have returned to their baseline level of asthma control established prior to the randomization visit. However, depending on the rationale for not reducing per schedule, the investigator may decide to maintain the subject on the OCS dose at which the down-titration criteria were not met. **Further dose reductions, during the reduction phase, can be considered in the opinion of the Investigator** (further reductions will follow the scheduled titration, see Table 9). The decision and reason must be captured in the eCRF.

Throughout the reduction phase, subjects should be monitored for the signs and symptoms of adrenal insufficiency (AI). When subjects reach a prednisone/prednisolone dose of 5 mg/day the investigator should inform them of the signs and symptoms of AI and provide them a **steroid card** informing health care providers that the subject may need additional corticosteroids in case of medical emergencies. In evaluating subjects for OCS dose reductions to below 5 mg/day the investigator should be vigilant for signs and symptoms of AI. The recommended initial dose reduction from 5 mg/day should be to 2.5 mg/day. After 4 weeks at this OCS dose another reduction to 0 mg/day should be considered. However, if, in the judgment of the investigator, OCS dose reduction should be more gradually tapered, dose reductions of 1 to 1.25 mg/day every 1-4 weeks may be considered.

For doses below 5 mg if the exact dose strength is not available in the country the daily dose to be administered could be achieved by dosing every other day. Daily dose will be the average of 2 days. See 0 for help dosing < 5 mg in relation to tablet strength. Subjects with a final daily OCS dose >0 and ≤5 mg who are unable to reduce their OCS dose further due to AI, should be specified in eCRF.

8.1.2 Asthma exacerbations – Assessment and management

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

- A temporary bolus/burst of systemic corticosteroids (at a dose at least 1 level higher than the current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids. **Note:** Per protocol up titration of OCS dose to 1 level higher (as described in Table 9) is not considered an exacerbation event per se.
- 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.

For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs identified by physical examination/subject interview or by the subject asthma e-Diary.

The ePRO device will be programmed to alert both the subject and study site when any of the pre-specified worsening thresholds as mentioned in Table 11 are crossed.

Table 11 eDiary alert criteria

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

When 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.

[a] An alert in itself will not qualify as a clinically significant exacerbation and the site should follow up with the subject as appropriate.

[b] Baseline values for alerts will be calculated from the most recent 7 days of available data prior to visit 2 for the optimization phase and prior to randomization visit 6 for the treatment period.

c Number of nights with awakenings due to asthma requiring rescue medication will be counted from most recent 7 days of available data.

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.

For the protocol, the start of an exacerbation is defined as the start date of additional systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER or urgent care visits requiring additional 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 additional systemic corticosteroids (a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course 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 and both should be counted as one and the same exacerbation.

Reasonable attempts should be made by the Investigator to bring the subject into the study site for evaluation of a diary alert or subject initiated contact due to asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled (UNS) visit or as part of an ordinary site visit if the worsening happens to be coincident with a scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (e.g., by the primary care HCP or at an ER/hospital) and details entered into the specific eCRF (EXACATE) module in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

8.1.2.1 Exacerbation management during the run-in period

Subjects who experience an asthma exacerbation during the run-in period may remain in the study. After the treatment of exacerbation, the subject should preferentially be placed on an OCS dose one step (or more if considered necessary by the investigator) higher than the dose they were on when the exacerbation occurred, unless the judgment of the investigator is to maintain the subject on their current dose of OCS. They should be on a stable OCS dose for a period of 2-weeks before beginning the optimization phase.

8.1.2.2 Exacerbation management during the optimization phase

If a subject experiences an asthma exacerbation during optimization phase, OCS dose reduction should stop. After the treatment of exacerbation, the subject should preferentially be placed on an OCS dose one step (or more if considered necessary by the investigator) higher than the dose they were on when the exacerbation occurred, unless the judgment of the investigator is to maintain the subject on their current dose of OCS. The optimization phase could be extended to allow for the subject to be on a stable OCS dose for 2 weeks prior to randomization.

8.1.2.3 Exacerbation management during the treatment period

Those who experience an exacerbation after randomization may remain on the IP at the Investigator's discretion.

Induction phase
If a subject experiences an exacerbation during the induction phase, start of OCS dose reductions may be delayed. After the OCS bolus/burst to treat an exacerbation is complete, the subject may be returned to one step (or more if considered necessary by the investigator) higher than the OCS dose they were on when the exacerbation occurred or the investigator may decide to maintain the same OCS dose.

The subject's OCS dose should be stable for at least two weeks before entering the OCS dose reduction phase.

Reduction phase
If a subject experiences an exacerbation during the reduction phase, after the OCS bolus/burst is

complete, the subject may be returned to one step (or more if considered necessary by the investigator) higher than the OCS dose they were on when the exacerbation occurred or the investigator may decide to maintain the same OCS dose and kept stable for at least two weeks. Further dose reductions during the reduction phase can be considered in the opinion of the Investigator. However, no further dose reductions should be performed after week 36.

Maintenance phase
If a subject experiences an exacerbation during the maintenance phase, after the OCS bolus/burst is complete, the subject may be returned to one step (or more if considered necessary by the investigator) higher than the OCS dose they were on when the exacerbation occurred or the investigator may decide to maintain the same OCS dose throughout the maintenance phase.

8.1.3 Spirometry

8.1.3.1 General requirements

Lung function (FEV_1 and forced vital capacity [FVC]) will be measured by spirometry at the study site using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to ATS/ERS guidelines (Miller et al 2005).

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by each site meets ATS/ERS recommendations, and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedure manual.

Subjects should be instructed to follow the required restrictions for performing spirometry as described in sections 5.3 and Table **6**. If the required restrictions have not been adhered to, the investigator should reschedule the visit to the earliest opportunity within the allowed visit window.

Spirometry testing must be performed according to the schedule provided in SoA. All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the baseline Pre-BD spirometry was performed.

8.1.3.2 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. A signed and dated copy of the spirogram printout must be kept at the study site for source data verification.

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

8.1.3.3 Post-BD spirometry and FEV_1 reversibility assessment

Post-BD spirometry procedures will be performed according to the SoA and will be described in a separate spirometry procedure manual. Bronchodilatation can be induced using albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) up to a maximum of 4 inhalations. 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. Levalbuterol will not be supplied by the sponsor. It is highly recommended to use a spacer device for this procedure. Nebulizer should not be used. A lower total dose (e.g., 2 inhalations instead 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.

If FEV_1 reversibility has not been documented in the previous 12 months prior to or at visit 1, further assessments to meet the reversibility criteria may be performed at visit 2. It is acceptable to stop further reversibility assessments once the criteria for reversibility are met.

The highest 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

8.1.4 Home PEF testing

An electronic, hand-held spirometer (AM3G+™) to measure PEF (ePEF meter) will be provided to the subject at visit 1.

Subjects will be trained on at-home use of the ePEF meter at visit 1. Training will include explanation of device functionality and proper use of the ePEF meter.

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 1 until the morning of visit 18 (week 48). 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 use of the PEF meter as shown in SoA.

8.1.5 Fractional exhaled nitric oxide (FENO)

Airway inflammation will be evaluated using a standardized single-breath FENO test in accordance with the SoA. The 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 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 measure FENO. Instructions for use of this monitor will be provided in a separate users' 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 FENO measurements will be blinded for sites, subjects and sponsor throughout the study.

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

8.1.6 Patient reported outcomes

Patient reported outcomes (PRO) data will be captured electronically using a handheld device (eDiary). Site personnel will be trained on using the eDiary. Detailed procedures for using eDiary and training the subjects will be described in a separate instruction manual. Subjects will be trained on at-home use of the eDiary at visit 1. Training will include explanation of device functionality and its proper use. The subject will also be asked to verify completion of training on the eDiary. The site staff will set assessment reminder alarms on the device. At-home PRO assessment will start the evening of visit 1 and continue thereafter at every morning and evening until study completion as per the SoA. Subjects will be asked to bring the device back at each study visit. At site PRO questionnaires should be completed prior to any other assessments. The Investigator/authorized delegate will check subject's adherence to the completing PRO at each visit and even in between as shown in SoA.

8.1.6.1 Asthma Daily Diary

The daily diary will be completed each day from the evening of visit 1 to the morning of visit 18. The morning eDiary will include: Asthma Symptom Diary (ASD) morning items, questions about rescue medication, night time 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 eDiary to alert the subjects to signs of worsening of asthma and to contact their physician, please refer to Table 11. The subject should contact the investigator (or vice versa) for evaluation after receiving a diary alert.

Asthma Symptom Diary

Asthma symptoms will be recorded using the ASD (Globe et al 2015). The ASD comprises 10 items (5 items in the morning; 5 items in the evening). The morning items assess night time symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and the frequency of night time 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 night time 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 eDiary twice daily (i.e., in the morning and evening) beginning the evening of visit 1 until the morning of visit 18. 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.

Night time awakenings

Night time awakenings due to asthma symptoms will be recorded by the subject in the eDiary each morning, beginning in the morning after visit 1 until the morning of visit 18, by answering the question whether he/she woke up during the night due to asthma symptoms with a "yes" or "no" response.

Maintenance medication

Maintenance medication compliance will be recorded in the eDiary once daily in the morning, beginning in the morning after visit 1 until the morning of Visit 18. There will be separate questions for checking compliance with OCS.

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 eDiary in accordance with the SoA. For IPD subjects ACQ-6 can be completed at home as well.

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 patients. The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Patients 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 eDiary in accordance with the SoA. For IPD subjects AQLQ(S)+12 can be completed at home as well.

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 at the beginning of site visit using eDiary in accordance with the SoA.

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

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

The 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 eDiary in accordance with the SoA.

8.1.6.6 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.

WPAI+CIQ will be completed at the beginning of site visits using eDiary in accordance with the SoA. For IPD subjects WPAI + CIQ can be completed at home as well.

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 12 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments (including serology, pregnancy and FSH test), must be conducted in accordance with the laboratory manual and the SoA. Subjects should be fasting for at least 12 hours prior to blood collection.

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 site 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.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

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

Table 12 **Laboratory safety variables**

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S-Alkaline phosphatase (ALP)
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Hematocrit	S-Blood urea nitrogen
B-Mean corpuscular volume	S-Calcium, total
B-Red blood cell (RBC) count	S-Chloride
B-HbA1C	S-Creatinine
	S-Creatinine kinase (CK)
Urinalysis (dipstick)	S-C Reactive Protein (CRP)
U-Hb/Erythrocytes/Blood	S-Gamma-glutamyl transpeptidase (GGT)
U-Protein/Albumin	S-Glucose
U-Glucose	S-Phosphorus
	S-Potassium
	S-Sodium
U-Microscopy and culture as required*	S-Total cholesterol
	S-Low density lipoprotein (LDL)
	S-Uric acid

*Urine samples will be first analysed locally using dipstick 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 0 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

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 centimetres. 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, musculo-skeletal (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, 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. Subjects should be observed for a minimum of 2 hours after administration of the first two IP doses 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.

Blood pressure and pulse measurements will be assessed in a 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 ECG will be taken in supine position after resting for at least 15 minutes, prior to blood draw, FeNO, 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.

8.2.6 Glucocorticoid toxicity index

Glucocorticoid Toxicity Index (GTI) will be assessed as described by Miloslavsky et al 2016 (see Appendix H for details). The composite GTI captures common glucocorticoid (GC) toxicities that are sensitive to differing cumulative GC doses over the period of a typical clinical trial (6 months to 3 years). The individual items within the GTI are weighted relative to each other for severity, and the instrument has the capability of measuring not only worsening of GC toxicity over baseline, but also improvement.

The composite GTI measures change in GC toxicity rather than absolute GC toxicity in order to account for the effects of prior GC therapy. Scoring should be performed as per SoA, using the randomisation assessment as the baseline. The GTI items were ranked in order of severity within each domain. The relative weights for each toxicity item were derived using multicriteria decision analysis (MCDA). MCDA has been used for the creation of multiple classification criteria sets in a variety of inflammatory diseases, including rheumatoid arthritis (Neogi T et al 2010), systemic sclerosis (Johnson SR et al 2014), systemic lupus erythematosus (Tedeschi SK et al 2017). IgG4-Related Disease classification criteria is presently under development (JH Stone; personal communication).

The composite GTI will be assessed at the timepoints given in the SoA. The following items will be assessed: BMI, glucose tolerance (HbA1c), blood pressure, LDL, steroid myopathy, skin toxicity, neuropsychiatric toxicity and Infection.

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 0.

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

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

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in 0. 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 may 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 0.

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 collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- 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 Investigational Product 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 7 to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values or 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 unless unequivocally related to the disease under study, see section 8.3.10.

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 investigational product. 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
- Adrenal crisis

8.3.9 Hy's law

Cases where a subject shows elevations 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 0 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.10 Disease under study

Symptoms of the disease under study

Asthma symptoms or signs, such as, wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, see 0
- the subject discontinues IP due to the sign or symptom, and/or
- the sign or symptom is new to the subject or not consistent with the subject's pre-existing asthma history (defined as within 1 year of visit 1) as judged by the Investigator

Asthma exacerbations should not be recorded as AEs, unless it fulfils any of the above criteria. All asthma exacerbations should be recorded in the EXACATE module as per Section 8.1.2.

If a subject discontinues IP due to a study specific discontinuation criterion, this should always be recorded as 'Development of study specific withdrawal' on the Discontinuation of Investigational Product eCRF. In addition, the Investigator must assess whether the asthma deterioration should also be reported as an AE leading to discontinuation of IP (DAE)/AE leading to withdrawal from study on the AE form.

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 investigational product, 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 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 works 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 is undertaken immediately. Investigators or other site personnel 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 eCRF, an automated email alert is sent to the designated AstraZeneca representative.

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

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

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see 0 of the Clinical Study Protocol.

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

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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 informs 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

For this study, any dose greater than 280 mg within a 2-week period will be considered an overdose. There is currently no specific treatment in the event of overdose of IP, and possible symptom of 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 8.4.1. 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 8.4.1) 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. 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 6 and 7, subjects should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, subjects will be observed for a minimum of 1 hour after IP administration for any such reaction.

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

8.4.6 Independent adjudication committee

An independent adjudication committee will provide an external independent assessment of blinded data to confirm the diagnosis of MACE (to be defined in the charter) and investigator reported malignancies that occur from randomization up to the end of the follow-up period. The 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, that occur from randomization until the end of the follow-up period to confirm that any such event is due to a worsening of asthma. The committee will operate in accordance with dedicated adjudication committee charter/manual of operations.

8.4.7 Data safety monitoring board (DSMB)

DSMB is an independent expert advisory group commissioned and charged with the responsibility of assessing safety aspects in the study. The DSMB will evaluate cumulative safety and other clinical trial data at regular intervals and make 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.

8.5 Pharmacokinetics

8.5.1 Collection of samples and drug concentration

Serum samples for determination of tezepelumab will be collected pre-dose according to SoA, Table 2. Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual. Samples for determination of tezepelumab concentration in serum will be analysed 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 sample to measure for the presence of ADAs

The presence of Anti-drug antibodies (ADAs) will be assessed in serum samples according to the SoA, Table 2. Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for tezepelumab using validated assays. Samples with confirmed ADAs positive will be analysed 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 (section 8.8)

8.7 Genetics

8.7.1 Optional exploratory genetic sample

Whole blood will be collected from 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 35 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 in SoA. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

See 0 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in 0 or in the Laboratory Manual.

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

Biomarker analysis may include (but not limited to) serum biomarkers, analysis of blood eosinophils, FENO (section 8.1.4), IgE (FEIA), total IgE (section 8.8.2) and transcriptomics (section 8.8.3).

Biomarker analysis will be performed to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to asthma, Th2 high and Th2 low inflammation, TSLP pathway and various phases of OCS dose reduction. Biomarkers will also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab.

Serum samples for biomarker analysis will be collected according to the schedule in Table 2. Specific serum biomarkers that may be analyzed are cytokines, chemokines and inflammatory mediators associated with asthma and the TSLP pathway, including but not limited to TSLP, IL-33 and TARC.

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

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 disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacodynamic samples to further evaluate pharmacology of tezepelumab. 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 SoA. Instruction 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.

8.9 Healthcare Resource Utilization and Health Economics

Healthcare resource utilization (HRU) 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, 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 at the 0.05 significance level. All other hypothesis testing in this study will be considered exploratory.

Primary endpoint

H01: Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (tezepelumab/placebo) = 1

versus

H11: Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (tezepelumab/placebo) ≠ 1.

For 5 ordered categories, there are 4 possible cumulative odds for each treatment group, corresponding to the 4 different possible binary splits, which are defined as follows:

- Category 1 versus categories (2,3,4,5)
- Categories (1,2) versus categories (3,4,5)
- Categories (1,2,3) versus categories (4,5)
- Categories (1,2,3,4) versus category 5,

where the ordered categories for OCS daily dose reduction are in turn defined as:

- Category 1: 90% - 100% reduction
- Category 2: 75% - <90% reduction
- Category 3: 50% - <75% reduction
- Category 4: >0% - <50% reduction

- Category 5: no reduction or an increase.

The above hypothesis assumes that the 4 possible odds ratios between the 2 treatments as defined above are the same (this is the proportional odds assumption).

The direction of superiority of tezepelumab is indicated by an odds ratio greater than 1.

Key secondary endpoints

H02: AAER ratio over 48 weeks (tezepelumab/placebo) = 1

versus

H12: AAER ratio over 48 weeks (tezepelumab/placebo) ≠ 1

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

9.2 Sample size determination

Approximately 152 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 randomised subjects as far as possible, no need is envisaged to adjust the number of subjects planned to be randomised in order to obtain a number of evaluable subjects.

With 76 subjects per treatment group it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint will be at least 90%, assuming:

- An odds ratio of 2.75 and the proportional odds assumption (see Section 9.1)

- The proportion of subjects in the 5 different dose reduction categories is similar to what was observed in the Steroid Reduction with mepolizumab Study (SIRIUS) (Bel et al 2014). The following proportions have been assumed for placebo:

  - Category 1 (90% - 100% reduction): 10% of subjects
  - Category 2 (75% - <90% reduction): 10% of subjects
  - Category 3 (50% - <75% reduction): 15% of subjects
  - Category 4 (>0% - <50% reduction): 15% of subjects
  - Category 5 (no reduction or an increase): 50% of subjects

The minimal detectable odds ratio still being significant with the above assumptions is 1.86.

For the key secondary endpoint, 76 subjects per group has >80% power to reject the null hypothesis for rate ratios up to 0.39, using a 2-sided 5% significance level, and assuming:

- A placebo rate of 1.3 exacerbations/year in this study population
- A conservative assumption on the dispersion parameter (2.4)
- Uniform dropout of 10%

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 randomised 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 last subject completes Week 48, and the final DBL will be conducted once all patients have completed the last safety follow-up visit (Week 60). All analyses of the primary and secondary objectives will be performed based on the primary DBL data. Following the primary DBL, data summaries created will be presented as an addendum to the CSR.

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 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 finalised 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 prior to unblinding and summarised 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 SAP, and may include (but not necessarily limited to): subjects who were randomised to study treatment without fulfilling key entry criteria; subjects who received prohibited or restricted concomitant medications while on IP, subjects who received the incorrect study treatment or study dose at any time during the 48-week double-blind treatment period.

9.4.1 Multiple testing procedure

To account for multiplicity when testing the primary and the secondary endpoints, the following hierarchical testing procedure will be applied, with the hypotheses tested as defined in Section 9.1:

1. First the null hypothesis H01 will be tested at a 2-sided 5% significance with regard to the primary endpoint (percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control)
2. If H01 is rejected, then the null hypothesis H02 will be tested at a 2-sided 5% significance level with regard to the key secondary endpoint (AAER ratio over 48 weeks)

9.4.2 Definition of baseline

In general, the last measurement at or prior to randomization will serve as the baseline measurement. If there is no value at or prior to randomization, then the baseline value will not be imputed and will be set to missing.

The baseline OCS dose for the primary and secondary variables related to OCS reduction during the reduction and maintenance periods is defined as the most recent prescribed daily dose prior to randomization.

For weekly means derived from subject diaries, baseline is defined as the mean of the available data in the most recent week prior to randomization. If more than 3 days within that period is missing, then the baseline will be considered to be missing. For titration of the OCS dose baseline values for optimization phase are calculated from completed eDiary records of a minimum of 10 out of 14 days before visit 2. Similarly baseline values for the reduction phase will be calculated from a minimum of 10 out of 14 days before randomization visit.

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

9.4.3 Efficacy analyses

9.4.3.1 Analysis of the primary efficacy endpoint

The primary analysis of the primary efficacy endpoint will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received. This analysis will therefore include all available data after treatment discontinuation for subjects who continue to attend monthly visits either at site or by telephone. Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 48-week period even after premature discontinuation of IP.

The primary endpoint is the percentage reduction from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (as per Table 10), by defined categories, where percent change from baseline is defined as {(final dose-baseline dose}/baseline dose)*100. Percent change from baseline will then be categorized per the categories in Section 3.

The final OCS dose is defined based on the prescribed dose, expressed as a dose per day, at week 48. If the subject is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the subject is on an every other day regimen, then the OCS dose is defined as the average amount prescribed to be taken each day.

Further details on deriving the final OCS dose in specific situations including asthma deterioration, discontinuation from study, and premature discontinuation from IP (with different options for subject follow up), will be specified in the SAP.

The primary endpoint in the tezepelumab group will be compared to that in the placebo group using a proportional odds (ordinal logistic regression) model. This model will be used to perform the statistical test specified in Section 9.1, and to estimate the treatment effect and its 95% confidence interval. The response variable in the model will be the ordered category number (1-

5) at Week 48 as defined in Section 9.1. Treatment and region will be included as factors in this model. Baseline OCS dose will also be included in the model as a continuous (linear) covariate.

Frequency tables of the number and proportion of subjects in each of the response categories will be presented. Cumulative responder (percentage reduction) plots will be presented to aid interpretation of the primary analysis. In addition, the number and proportion of subjects with final daily oral corticosteroid dose >0 and ≤5 mg, unable to reduce the OCS dose further due to adrenal insufficiency will be tabulated.

As further support to the primary analysis, the actual percentage reduction in daily OCS dose at Week 48 will be summarized descriptively and compared between treatments using a Wilcoxon rank sum test stratified by region (van Elteren test).

The consistency of treatment effect across baseline biomarkers and demographic variables will be evaluated descriptively, given the possible limitations of sample size on statistical modelling approaches in this trial. Any further requirements for subgroup analysis, 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 48 weeks

- The impact of different imputation strategies for the final OCS dose including switching to other asthma treatments

- An investigation into the proportional odds assumption, and if necessary further analyses which make fewer restrictions with regards to this assumption and/or analyses using different response category definitions

- Analysis in which additional factors or covariates are included.

9.4.3.2 Analysis of the key secondary efficacy endpoints

The main analysis of the key secondary endpoint (AAER over 48 weeks) will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received. 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 48-week period even after premature discontinuation of IP.

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 estimate the rate ratio and its 95% confidence interval. The response variable in the model will be the number of asthma exacerbations experienced by a subject over the 48-week treatment period (or shorter duration if not followed up for the full 48 weeks). Treatment, region 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 AAER will also be presented.

Sensitivity analyses on the key secondary endpoint will be performed, and will be fully specified in the SAP. These may include, but not necessarily be limited to, similar items considered for the primary endpoint (where relevant).

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 and analysed similarly.

A sensitivity analysis may be performed where adjudication outcome of the ER or urgent care visits, hospitalizations and all deaths will be considered.

9.4.3.3 Analysis of other efficacy endpoints

Binary (responder) endpoints which support the primary objective with regards to OCS dose reduction will be summarized using frequency tables. The odds ratio (tezepelumab/placebo) and its 95% confidence interval will be estimated for each endpoint from a logistic regression model with factors for treatment and region, and baseline OCS dose included as a continuous (linear) covariate.

Other binary endpoints will be summarized and analysed similarly; these analyses will be adjusted for region and baseline of the corresponding endpoint.

Changes from baseline in continuous variables will generally be analysed using a mixed model for repeated measures (MMRM) model for each endpoint. This model will be used to estimate the treatment effect at Week 48 and its 95% confidence interval. The response variable in the model will be the change from baseline at each scheduled post-randomisation visit up to and including Week 48, and irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region and treatment by visit interaction will be included as factors in this model. The baseline of the corresponding endpoint will also be included in the model as a continuous 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 continuous endpoints will also be presented. Adjusted means from the MMRM model above will be displayed graphically over time.

Time to first asthma exacerbation will be summarised graphically using Kaplan-Meier estimates, and analysed using a Cox proportional hazards model with factors for treatment and region.

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 full analysis set. 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) will also be summarised 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.

The composite glucocorticoid toxicity index will be presented descriptively using summary statistics.

9.4.5 Other analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalised 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 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 8.4.7.

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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 authorised representative and answer all questions regarding the study.

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

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date and time the written consent was obtained. The authorised 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 authorised representative.

If a 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 authorised 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 analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

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

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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised 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
- Adrenal crisis

B 6 Intensity rating scale:

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

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

B 7 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

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

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

B 8 Medication Error

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 at each centre 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 analysed, 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 Principal 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, a blood sample 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 a 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 discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood samples for genetic research will be obtained from the subjects as per SoA. 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/randomisation 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 discontinue 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) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 7.1 of the Clinical Study Protocol.

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

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

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

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

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

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

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

E 3 Identification of potential Hy's Law cases

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

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

Central laboratories being used:

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

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

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

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

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
    - Subsequent to this contact the Investigator will:
        - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
        - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.
        - Complete the three Liver CRF Modules as information becomes available

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

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

E 6 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended 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

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

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

Estimated OCS dose therapy equivalence

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg

Appendix G Anaphylaxis: signs and symptoms, management

G 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic [IgE-mediated and non-IgE-mediated (e.g. IgG and immune complex mediated) and nonimmunologic (Johansson et al, 2004). The clinical criteria for defining anaphylaxis for this study are listed in 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 (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

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

G 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

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

G 4 Management of Acute Anaphylaxis

Immediate intervention

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

Possibly appropriate, subsequent measures depending on response to epinephrine

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

(f) Establish and maintain airway.

(g) Administer oxygen.

(h) Establish venous access.

(i) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(j) Consider epinephrine infusion.

(k) Consider H1 and H2 antihistamines.

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

(m) Consider systemic corticosteroids.

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

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

(p) Consider atropine for symptomatic bradycardia.

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

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

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

Appendix H Glucocorticoid toxicity index

Any untoward medical occurrences captured as part of the GTI assessment should be reported as an adverse event. This includes but is not limited to any clinically significant worsening of a subject's pre-existing condition (i.e. worsening of glucose tolerance, etc.).

Eight domains and 28 items are included in the composite glucocorticoid toxicity index (GTI).

For item weights please see table below. Details for scoring each item is provided at the end of the table.

Adapted from Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Ann Rheum Dis Published Online First:29 July 2016 doi:10.1136/annrheumdis-2016-210002

The Glucocorticoid Toxicity Index (GTI)	
Composite GTI	**Item weight**
BMI	
• Improvement in BMI	–8
• No change in BMI	0
• Moderate increase in BMI	21
• Major increase in BMI	36
Glucose tolerance	
• Improvement in glucose tolerance	–8
• No change in glucose tolerance	0
• Worsening of glucose tolerance	32
• Worsening of glucose tolerance despite treatment	44
Blood pressure	
• Improvement in blood pressure	−10
• No change in blood pressure	0
• Worsening hypertension	19
• Worsening hypertension despite treatment	44
Lipids	
• Improvement in lipids	−9
• No change in lipids	0
• Worsening hyperlipidaemia	10
• Worsening hyperlipidaemia despite treatment	30
Steroid myopathy	
• No steroid myopathy	0
• Mild steroid myopathy	9
• Moderate steroid myopathy or greater	63
Skin toxicity	
• No skin toxicity	0
• Mild skin toxicity	8
• Moderate skin toxicity or greater	26
Neuropsychiatric toxicity	

• No neuropsychiatric symptoms	0
• Mild neuropsychiatric symptoms	11
• Moderate neuropsychiatric symptoms or greater	74
Infection	
• No significant infection	0
• Oral/vaginal candidiasis or uncomplicated zoster	19
• Grade III infection or greater	93
Total	−35 to 410

1. **Body Mass Index (BMI) (compared to baseline)**
   a. Improvement in the direction of the normal range by more than 2 BMI units (normal range = 18.5-24.9 kg/m^2)
   b. No significant change (BMI remains within +/- 2 BMI units compared with baseline) OR BMI remains within the normal range
   c. Moderate increase in BMI (increase by more than 2 but less that 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2])
   d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m^2])
2. **Glucose Tolerance (compared to baseline)**
   a. Improvement in glucose tolerance:
      - HbA1c declined >10% from baseline without medication increase
        OR
      - Decrease in diabetic medication without an increase in HbA1c of >10% or HbA1c < 5.7%

   b. No significant change in glucose tolerance:
      - HbA1c within 10% of baseline or HbA1c < 5.7% AND no change in medication
        OR
      - HbA1c increased to > 10% of baseline with a decrease in medication
        OR
      - HbA1c decreased by > 10% of baseline with an increase in medication

   c. Worsening of glucose tolerance or medication status:
      - HbA1c > 5.7% and increased to >10% of baseline without a change in medication
        OR
      - Increase in diabetic medication with < 10% increase in HbA1c

   d. Worsening of glucose tolerance despite increased treatment:
      - HbA1c > 5.7% AND increased to >10% of baseline AND an increase in diabetic medication
3. **Blood Pressure (BP) (compared to baseline)**
   a. Improvement in BP:
      - Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

OR
- Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

b. No significant change in BP:
- BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication
OR
- Increase in either systolic or diastolic BP >10% with a decrease in medication
OR
- Improvement in systolic or diastolic BP of > 10% with an increase in medication

c. Worsening of hypertension:
- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication
OR
- An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP

d. Worsening of hypertension despite treatment:
- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication

4. **Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)**

a. Improvement in lipids:
- Decrease in LDL concentration >10% of baseline toward the target range without medication increase
OR
- Decrease in medication without an increase in LDL of >10% or LDL remains within target range

b. No significant change in LDL:
- LDL within 10% of baseline or within the target range for patient AND no change in medication
OR
- Increase in LDL > 10% with a decrease in medication
OR
- Improvement in LDL of > 10% with an increase in medication

c. Worsening of LDL or medication status:
- Increase in LDL of >10% to above target range without a change in medication
OR
- Increase in medication with <10% change in LDL

d. Worsening of LDL despite treatment:
- Increase in LDL of >10% AND an increase in medication

5. **Glucocorticoid-induced myopathy**

a. No steroid myopathy
b. Mild steroid myopathy (weakness WITHOUT functional limitation)
c. Moderate steroid myopathy (weakness WITH functional limitation)

See Steroid Myopathy definitions, below

6. **Skin**

a. No skin toxicity
b. Mild skin toxicity
c. Moderate skin toxicity

See Skin definitions, below
7. **Neuropsychiatric toxicity** a. No neuropsychiatric symptoms b. Mild neuropsychiatric symptoms c. Moderate neuropsychiatric symptoms **See Neuropsychiatry definitions, below**
8. **Infection (since last assessment)** a. No significant infection b. Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster) c. Grade 3 or complicated herpes zoster **See Infection definitions, below**

Glucocorticoid-induced myopathy definitions

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

Mild and moderate severity of myopathy are defined by a muscle strength of 4 on the standard Medical Research Council rating scale. A 4 means weaker than normal but greater than antigravity strength against resistance.

"Mild" is mild weakness (Grade 4) that does NOT functionally limit the patient.

"Moderate" is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severity of glucocorticoid toxicity in the skin

Manifestations to be considered:

• Acneiform rash	• Atrophy/striae
• Easy Bruising	• Erosions/tears/ulcerations
• Hirsutism	

Skin 6b. Mild	Skin 6c. Moderate
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)
Easy bruising (Grade 1)	Easy bruising (Grade 2)
Hirsutism (Grade 1)	Hirsutism (Grade 2)
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)

Skin Definitions (from National Cancer Institute Common Terminology Criteria for Adverse Events):

Acneiform rash
- Grade 1 - Papules and/or pustules covering <10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2 – Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental Activity of Daily Living (ADL)
- Grade 3 - Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self-care ADL; OR associated with local superinfection with oral antibiotics indicated

Easy bruising
- Grade 1 – Localized or in a dependent area
- Grade 2 - Generalized

Hirsutism - In women, increase in length, thickness or density of hair in a male distribution
- Grade 1 - Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2 - Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact

Atrophy / Striae
- Grade 1 - Covering <10% BSA; OR associated with telangiectasias or changes in skin color
- Grade 2 – Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss

Erosions / Tears / Ulcerations
- Grade 1 – Combined area of ulcers <1 cm; OR non-blanchable erythema of intact skin associated with warmth or erythema
- Grade 2 – Combined area of ulcers 1 - 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat

Severity of neuropsychiatric glucocorticoid toxicity

Manifestations to be considered:

• Insomnia	• Cognitive Impairment
• Mania	• Depression

7b. Mild	7c. Moderate
Insomnia – (Grade 1)	Insomnia – (Grade 2)
Mania (Grade 1)	Mania (Grade 2)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)
Depression (Grade 1)	Depression (Grade 2)

Definitions of severity within the neuropsychiatric domain

Insomnia - Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening

- Grade 1: not associated with functional impairment
- Grade 2: associated with functional impairment

Mania

- Grade 1: Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 2: Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

Cognitive impairment

- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids.
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids.

Depression

- Grade 1: Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 2: Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.

Infection Definitions

No significant infection = No specific infections or serious infections, grade 3 or greater

Specific Infections – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement

Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

References

Medical Research Council of the United Kingdom. Guide to Examination of the Peripheral Nervous System: Memorandum No 45. Palo Alto, Calif: Pedragon House; 1978. National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication # 09-7473.

Appendix I Prednisone/Prednisolone doses < 5 mg in relation to available tablet strengths (scored tablets)

Daily dose	Available tablet strength	Administered # of tablets and frequency
1 mg	1 mg	1 tablet each day
1.25 mg	2.5 mg	½ tablet every day or 1 tablet every 2nd day
1.25 mg	5 mg	½ tablet every 2nd day
1.875 mg	2.5 mg	1 tablet every 2nd day and ½ tablet every 2nd day
2 mg	1 mg	2 tablets each day
2.5 mg	5 mg	½ tablet each day or 1 tablet every 2nd day
2.5 mg	1 mg	2 ½ tablets each day OR 2 tablets every 2nd day and 3 tablets every 2nd day
2.5 mg	5 mg	½ tablet each day
3 mg	1 mg	3 tablets each day
3.125 mg	2.5 mg	1 ½ tablet every 2nd day and 1 tablet every 2nd day
3.75 mg	2.5 mg	1 tablet every 2nd day and 2 tablets every 2nd day
3.75 mg	5 mg	½ tablet every 2nd day and 1 tablet every 2nd day
4 mg	1 mg	4 tablets each day

Appendix J Abbreviations

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

Abbreviation or special term	Explanation
AAER	Annual Asthma Exacerbation Rate
AAERR	Annualized Asthma Exacerbation Reduction Rate
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibodies
ADL	Activities of Daily Living
AE	Adverse Event
AERR	Asthma Exacerbation Reduction Rate
AESI	Adverse Event of Special Interest
AI	Adrenal Insufficiency
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
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
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BTR	Best Test Report
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine Kinase
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease

Abbreviation or special term	Explanation
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form (electronic/paper)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome device
EQ-5D-5L	European Quality of Life - 5 Dimensions 5 Level
ER	Emergency Room
ERS	European Respiratory Society
FAS	Full Analysis Set
FEIA	Fluorescent Enzyme Immunoassay
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FSH	Follicle-Stimulating Hormone
FU	Follow Up
FVC	Forced Vital Capacity
GC	Glucocorticoid
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
GTI	Glucocorticoid Toxicity Index
Hb	Haemoglobin

Abbreviation or special term	Explanation
HCP	Health Care Professional
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HRU	Healthcare resource utilization
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
Ig	Immunoglobulin
IL	Interleukin
IP	Investigational Product
IPD	Investigational Product Discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
ITT	Intent-to-Treat
IUD/IUS	Intrauterine Device / Intrauterine System
IV	Intravenous
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 Antagonist
LAR	Late Asthmatic Response
LIMS	Laboratory Information Management System
LDL	Low-Density Lipoprotein
LRTI	Low Respiratory Tract Infection
LSLV	Last Subject Last Visit
LTRA	Leukotriene Receptor Antagonists
MAb	Monoclonal Antibody

Abbreviation or special term	Explanation
MACE	Major adverse cardiac events
MAR	Missing at Random
MCDA	Multicriteria Decision Analysis
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeat Measurements
MNAR	Missing-Not-at-Random
nAB	Neutralizing Antibodies
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PHL	Potential Hy's Law
PI	Prescribing information
PK	Pharmacokinetic(s)
PNV	Predicted Normal Value
ppb	Parts per billion
PRO	Patient Reported Outcome
Q4W	Every 4 Weeks
RNA	Ribonucleic Acid
SABA	Short-Acting β2-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDV	Source Data Verification
SGRQ	St. George's Respiratory Questionnaire
SNP	Single Nucleotide Polymorphism
SoA	Schedule of Assessment
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
Th2	T Helper 2 Cells
TSLP	Thymic Stromal Lymphopoietin

Abbreviation or special term	Explanation
TSLPR	Thymic Stromal Derived Lymphopoietin Receptor
ULN	Upper Limit of Normal
UNS	Unscheduled
URTI	Upper Respiratory Tract Infection
WBDC	Web Based Data Capture
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

Appendix K 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.

K 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 17) or without administration of IP for EOT Visit and Visits 19 and 20, 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 and urine sample according to the SoA
- Conduct urine pregnancy test (dipstick), prior to IP administration, if applicable
- eDiary data review/completion
- Evaluation of OCS dose (done by Investigator, can be done remotely after relevant data is reviewed)
- 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 D5180C00009 Study Re: COVID-19 for more information.

K 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 D5180C00009 Study Re: COVID-19 for more information.

K 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 control/exacerbation and healthcare resource utilization as well as assessment and adjustment of OCS dose based on available sources of information (see K 4) while minimizing the risk to subjects of COVID-19 exposure.

K 4 OCS Titration During the COVID-19 Pandemic

During the COVID-19 pandemic, the Investigator may make decisions on the OCS dose based on remote interview of subject, eDiary data and if applicable, home visit physical examination and vital signs.

If COVID-19 in any way interferes with OCS titration (e.g. suspected or confirmed COVID-19 infection or lack of sufficient information due to COVID-19 pandemic) and/or titration decision is influenced by anything else than described in CSP Section 8.1.1.2, it needs to be specified in the eCRF/OCSDOSE form by including "COVID-19" phrase in the justification for the decision.

K 5 End of Treatment Visit / Transition to the Extension Study D5180C00018

If the EOT visit at Week 48 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 54, Week 60) 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 the study safety follow-up (Week 60), a subject will not transition to the extension study. These cases should be discussed with the AstraZeneca study physician.

K 6 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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