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Study Title: A Multicentre, Single-arm, Phase 3b Efficacy and Safety Study of Tezepelumab 210 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Participants with Severe Asthma on High-dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Long-term Oral Corticosteroid Therapy (WAYFINDER)

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Clinical Study Protocol	
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A Multicentre, Single-arm, Phase 3b Efficacy and Safety Study of Tezepelumab 210 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Participants with Severe Asthma on High-dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Long-term Oral Corticosteroid Therapy (WAYFINDER)

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Study Intervention: Tezepelumab

Study Phase: 3b

Short Title: A single-arm, Phase 3b efficacy and safety study of tezepelumab 210 mg subcutaneous, to reduce oral corticosteroid (OCS) use in severe asthmatic participants on high-dose inhaled corticosteroids plus long-acting β_2 agonist and long-term OCS therapy (WAYFINDER)

Study Physician Name and Contact Information will be provided separately

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.

International Co-ordinating Investigator: PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2.0	10 Nov 2022
Amendment 1.0	15 Nov 2021
Original Protocol	14 Oct 2021

Amendment 2.0: 10 November 2022

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main changes introduced by this amendment are the addition of a potential interim analysis (for publication purposes) and an alternative method of hypothalamic-pituitary--adrenal axis evaluation for sites where tetracosactides are not available.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 4.1 Overall Design Section 6.5 Prior and Concomitant Therapy Section 8.1.2 OCS Dose Titration Section 8.2.1 Hypothalamic-pituitary-adrenal Axis Evaluation Section 8.2.1.1 Morning Cortisol Test Section 8.2.1.2 Adrenocorticotropic Hormone Stimulation Test Appendix M Alternative Method for Hypothalamic-pituitary-adrenal Axis Evaluation	An alternative method has been included in case tetracosactides would not be available for the ACTH stimulation test.	Tetracosactides (required for performing ACTH stimulation test) are not registered in some countries involved in the study.	Non-substantial
Section 1.1 Synopsis Section 3 Objectives and Endpoints	Composite strategy updated to hypothetical strategy for handling intercurrent event	To correct the name of the strategy.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4.1 General Considerations	of therapy initiation with another biologic for treatment of asthma in statistical analyses.		
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 4.1 Overall Design Section 5.1 Inclusion Criteria Section 8.1.2.1 Asthma Worsening or Exacerbation Preventing OCS Down-titration Section 8.1.3 Assessment of Asthma Exacerbation	Asthma exacerbation definition has been edited.	To be aligned with AstraZeneca standards related to asthma exacerbations.	Non-substantial
Section 1.1 Synopsis Section 4.1 Overall Design Section 9.2 Sample Size DeterminationSection 9.5 Interim Analyses	An interim analysis has been added.	For publication to inform clinical practise about the interim results related to key efficacy and safety objectives.	Non-substantial
Section 1.3 Schedule of Activities	It has been clarified in the Schedule of Activities that morning cortisol test and ACTH stimulation test could be performed as soon as Visit 3.	Typographical error	Non-substantial
Section 1.3 Schedule of Activities	A footnote has been added in the Schedule of Activities to clarify that tezepelumab administration should be the last procedure performed during on site visit.	Clarification edit	Non-substantial
Section 1.3 Schedule of Activities Section 8.1.5.5 Sino-nasal Outcome Test	It has been clarified that presence of chronic sinusitis symptoms at screening will be used to determine which participants have to complete the SNOT-22 questionnaire.	Clarification edit	Non-substantial
Section 1.3 Schedule of Activities	Assessments of SNOT-22 and AIRQ™ have been added at the IPD visit	Typographical error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 Schedule of Activities Section 8.1.5 Patient-reported Outcomes Section 8.1.5.1 Asthma Control Questionnaire 6 Section 8.1.5.2 St. George's Respiratory Questionnaire Section 8.1.5.3 Asthma Quality of Life Questionnaire for 12 Years and Older Section 8.1.5.4 Asthma Impairment and Risk Questionnaire Section8.1.5.5 Sino-nasal Outcome Test Section 8.1.5.6 Participant Perception of OCS	It has been clarified that the programmed window for PRO assessments may or may not coincide with on-site visit date.	Clarification edit	Non-substantial
Section 1.3 Schedule of Activities	It has been clarified that for participants who prematurely discontinue study drug and do not want to undergo further study assessments, ePRO device should be returned at the IPD visit	Last visit on site for these participants.	Non-substantial
Section 3 Objectives and Endpoints	Change from baseline in AIRQ™ and proportions of AIRQ™ responders at Week 28 have been deleted from exploratory endpoints.	This study will use the past 12-month recall for AIRQ™, making change from baseline at Week 28 not relevant.	Non-substantial
Section 4.1 Overall Design Section 8.2.1 Hypothalamic-pituitary-adrenal Axis Evaluation Section 8.2.1.2 Adrenocorticotropic Hormone Stimulation Test	Details on the products used for ACTH stimulation test and their sourcing have been added.	To allow the use of a product other than Synacthen for this test, improve comfort of the participants during the injection, and to facilitate sourcing of these products.	Non-substantial
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of	Restriction has been added regarding at-home	Administration of tezepelumab at	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Civil Crisis, Natural Disaster, or Public Health Crisis Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	administration of tezepelumab.	participant home is not allowed in France.	
Section 5.2 Exclusion Criteria Section 5.4.1 Re-screening	Asthma exacerbation and its treatment with additional corticosteroid have been added in exclusion criterion #4 and circumstances for re-screening.	Exacerbation of asthma is often linked to respiratory tract infections.	Non-substantial
Section 6.1 Study Intervention Administered	Type of intervention has been clarified.	To include accessorised pre-filled syringe.	Non-substantial
Section 6.2.3 Dose Administration	Requirements for injection-site reactions have been removed.	There is no specific collection of injection-site reaction in this study (injection-site reactions will only be collected if they are SAEs or DAEs).	Non-substantial
Section 6.7 Intervention After the End of the Study	Potential access to the Patient Assistance Program has been added for participants enrolled in the UK.	To be aligned with UK requirements.	Non-substantial
Section 1.3 Schedule of Activities Section 8.3.6 Adverse Events of Special Interest	One AESI (serious cardiac events) has been added.	For consistency with the updated Investigator Brochure	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Participants who discontinues IP with option 1 or 2 are allowed to further reduce their OCS dose following the same protocol-specified OCS dose reductions scheme as participants being still on treatment.	Clarification edit	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.1 Assessment of OCS Dose	Circumstances under which OCS dose should be slowed down or stopped have been summarized.	Clarification edit	Non-substantial
Section 8.3.2 Follow-up of AEs and SAEs	The list of variables to be collected for SAE, DAE, and AESI has been updated.	To collect maximum intensity of the event.	Non-substantial
Section 8.3.14 Medical Device Deficiencies Appendix K Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies	Section 8.3.14 has been added and Appendix K edited.	To be aligned with AstraZeneca standards related to medical device deficiency management.	Non-substantial
Section 9.3.3 Currently or Historically Elevated EOS Population	Clarification added to the definition of currently or historically elevated EOS population.	Clarification edit	Non-substantial
Section 9.4.1 General Considerations	Two-sided 95% CI of the mean will not be calculated for demographics, participants characteristics, and continuous endpoints.	Clarification edit	Non-substantial
Section 9.4.1 General Considerations	Clarification and correction provided to the strategies of handling intercurrent events.	Clarification and correction edit	Non-substantial
Section 9.4.1 General Considerations	Clarification added that start date of all treatment periods is the date of first IP dose.	Clarification edit	Non-substantial
Section 9.4.2 Global/Country Situation Considerations, Including COVID-19	COVID-19 considerations had been replaced by global/country situation to assess impacts on this trial and its endpoints.	To be aligned with new AstraZeneca standards of capturing and presenting data.	Non-substantial
Section 9.4.3.2 Secondary Endpoints	Statistical model used for change from baseline for continuous endpoints has been modified from “a mixed model for repeated	To emphasise a random component is not used in a model for repeated measures.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	measures" to "a model for repeated measures".		
Section 9.4.3.2 Secondary Endpoints	Further details on combining exacerbation events have been added.	To be aligned with new AstraZeneca standards of capturing and presenting data.	Non-substantial
Section 9.4.4 Safety	Intensity of SAEs, DAEs, and AESIs will be listed and not summarised	Clarification edit	Non-substantial
Appendix E Prednisone/Prednisolone Doses < 5 mg in Relation to Available Oral Formulations	Appendix E has been modified.	To better align Appendix E to the OCS dose titration schedule in the protocol, and to accommodate titration when 1 mg tablets are not available.	Non-substantial
Appendix H 1 Chain of Custody	Details about samples taken for further use have been deleted.	There will be no biobanking in this study	Non-substantial
Throughout	Minor editorial and document formatting revisions.	-	Non-substantial

Abbreviations: ACTH = adrenocorticotropic hormone; AESI = adverse event of special interest; AIRQ™ = Asthma Impairment and Risk Questionnaire; CI = confidence interval; COVID-19 = Coronavirus disease 2019; DAE = discontinuation of investigational product due to adverse event; ePRO = electronic patient-reported outcome; EOS = end of study; IP = investigational product; IPD = premature investigational product discontinuation; OCS = Oral Corticosteroid; SAE = serious adverse event; SNOT-22 = Sino-nasal Outcome Test 22.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicentre, Single-arm, Phase 3b Efficacy and Safety Study of Tezepelumab 210 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Participants with Severe Asthma on High-dose Inhaled Corticosteroid plus Long-acting β2 Agonist and Long-Term Oral Corticosteroid Therapy (WAYFINDER)

Short Title: A single-arm, Phase 3b efficacy and safety study of tezepelumab 210 mg subcutaneous, to reduce oral corticosteroid (OCS) use in severe asthmatic participants on high-dose inhaled corticosteroids plus long-acting β_2 agonist and long-term OCS therapy (WAYFINDER)

Rationale: The purpose of WAYFINDER is, in oral corticosteroid (OCS)-dependent participants with severe asthma on high-dose inhaled corticosteroids (ICS) plus long-acting β2 agonist (LABA) and long-term OCS therapy, to assess the proportion of participants that are able to discontinue OCS completely or reduce to ≤ 5 mg/day. Participants will receive tezepelumab 210 mg on an open-label basis every 4 weeks (Q4W). Investigators will initiate the tapering of the OCS dose while maintaining asthma control and testing for adrenal insufficiency (AI).

Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary objectives	
To assess the ability of tezepelumab 210 mg subcutaneous (SC) to reduce prescribed OCS dose (≤ 5 mg/day) without loss of asthma control[a] in adult participants with OCS-dependent asthma	Endpoints • Proportion of participants who discontinued OCS without loss of asthma control[a] at Week 28 and Week 52 • Proportion of participants who reduced daily prescribed maintenance OCS dose to ≤ 5 mg/day without loss of asthma control[a] at Week 28 and Week 52
	Population: Adult with OCS-dependent asthma requiring high-dose ICS plus a LABA with or without additional asthma controller and with at least 1 asthma exacerbation in the prior year who received at least one dose of tezepelumab
	Intercurrent events: Treatment discontinuation, change in background therapy (other than OCS): All data will be included in the analysis according to treatment policy estimand.

	Initiate therapy with another biologic for treatment of asthma: hypothetical strategy; final dose for analysis will be defined as last reported OCS dose received by participant with asthma stability verified, achieved prior to initiation of another biologic.
	Summary measures: Proportion of participants and corresponding 95% confidence interval (CI) at Week 28 and Week 52
Secondary objectives	
To assess the ability of tezepelumab 210 mg SC to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction	• Annualised asthma exacerbation rate (AAER) over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation or emergency room (ER) visit over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation over 28 weeks and over 52 weeks
To assess the ability of tezepelumab 210mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]	• Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 and Week 52 • Categorised percent reduction from baseline in the daily maintenance OCS dose (categories: ≥ 90% to ≤ 100% reduction, ≥ 75% to < 90% reduction, ≥ 50% to < 75% reduction, > 0% to < 50% reduction, no change or any increase) at Week 28 and Week 52 • Absolute and percent change from baseline in daily maintenance OCS dose at Week 28 and Week 52
To assess the ability of tezepelumab to improve lung function	• Change from baseline in post-bronchodilator forced expiratory volume in 1 second at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma control[a]	• Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52

To assess the ability of tezepelumab to improve asthma related quality of life	• Change from baseline in standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[s]+12) total score at Week 28 and Week 52 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 28 and Week 52
Safety objective	
To describe the safety and tolerability of tezepelumab	• Serious adverse events (SAEs), discontinuation of investigational product due to an adverse event (DAEs), and adverse events of special interest (AESI)

[a] Loss of asthma control is defined as asthma worsening or exacerbation. Asthma worsening will be defined by an increase of ACQ-6 score ≥ 0.5 from baseline (see Section 8.1.2.1). Asthma exacerbation will be defined by worsening of asthma symptoms that leads to temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days (a single depo-injectable dose of corticosteroids being considered equivalent to a 3-day bolus/burst of systemic corticosteroids), and/or an emergency room (ER) or urgent care visit requiring systemic corticosteroid, and/or inpatient hospitalisation, both due to asthma (see Section 8.1.3).

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a single-arm, multicentre study in participants with severe asthma who are receiving high-dose ICS/LABAs and OCS with or without additional asthma controller(s). Participants should be maintained on their currently prescribed ICS plus LABAs with or without other asthma controller therapy, without change, until the end of treatment (EOT) visit.

The study will be divided in 4 periods: Screening, induction phase, OCS reduction and maintenance phase, and follow-up.

1. **Screening – From Week -4 to Week 0 (up to 4 weeks):** Eligibility criteria assessment and laboratory tests. Participants who are taking an alternative systemic steroid and not taking prednisone/prednisolone as their OCS treatment will be switched to a bioequivalent dose of prednisone/prednisolone (see Appendix D). For participants who switched to prednisone/prednisolone, dose will have to remain stable for at least 2 weeks before Week 0.
2. **Induction phase – From Week 0 to Week 4:** After confirmation of eligibility criteria, participants will be given their first tezepelumab dose at Week 0 (baseline). Participants should remain stable on their baseline OCS dose during this 4-week phase.
3. **Oral corticosteroid reduction and maintenance phase – From Week 4 to Week 52:** Participants will first reduce their dosage of OCS according to the schema defined in Table A for each baseline OCS dose until they reach the lowest stable dose or until Week 48. Participants will be considered as having reached the lowest stable dose when they have discontinued OCS or no further OCS reduction is possible

because of loss of asthma control and/or evidence of AI, as measured by cortisol levels (morning cortisol level or adrenocorticotropic hormone [ACTH] stimulation test).

Table A Oral Corticosteroid Titration Schema Until Reaching 5 mg/day

Baseline OCS dose	OCS down-titration schema until reaching 5 mg/day (without worsening of asthma)
> 20 mg/day	Reductions of 5 mg of the daily dose every 1 week until reaching a dose of 20 mg/day; followed by reductions of 5 mg every 2 weeks (Q2W) until a dose of 10 mg/day is reached; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 10 to ≤ 20 mg/day	Reductions of 5 mg of the daily dose Q2W until reaching a dose of 10 mg/day; followed by reductions of 2.5 mg Q2W until reaching a dose of 7.5 mg/day; and then reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 7.5 to ≤ 10 mg/day	Reductions of 2.5 mg of the daily dose Q2W until reaching a dose of 7.5 mg/day followed by reductions of 2.5 mg Q4W until reaching a dose of 5 mg/day
> 5 to ≤ 7.5 mg/day	Reductions of 2.5 mg of the daily dose Q4W until reaching a dose of 5 mg/day

Abbreviations: OCS = oral corticosteroids; Q2W = every two weeks; Q4W = every four weeks.

Once a participant reaches the lowest stable dose, the participant will be considered in maintenance. From Week 48 to Week 52, all participants will remain on their stable daily OCS dose, except if an asthma deterioration or exacerbation occurs. No further down-titration will be allowed from Week 48 onwards.

For all participants, hypothalamic-pituitary-adrenal axis integrity will be evaluated when they have been on 5 mg/day for 4 weeks and prior to any further tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction phase). A screening method with morning serum cortisol will be done (8 to 9 am morning cortisol level) for all participants, to determinate whether the participants have normal cortisol levels, complete AI, or indeterminate results. Participants with normal morning cortisol levels will continue down-titration. Participants with complete AI will delay titration and repeat the test 3 months later. For participants showing indeterminate results, an ACTH stimulation test will be performed and decisions regarding how to continue OCS down-titration will be based on results of this test (see Table B).

Table B Adrenocorticotropic Hormone Stimulation Testing

	ACTH stimulation test results		
	Normal (> 450 nmol/L[a])	**Partial AI (250-450 nmol/L[b])**	**Complete AI (< 250 nmol/L[c])**
OCS down-titration	Reduction of 2.5 mg Q4W	Reduction of 1 mg Q4W	Continue on same OCS dose
Repeat morning cortisol test for further OCS down-titration	No need	2 months later	3 months later

Abbreviations: OCS = oral corticosteroids; Q2W = every two weeks; Q4W = every four weeks.
a. > 675 nmol/L for participants taking oestrogen-containing contraceptives
b. 375-675 nmol/L for participants taking oestrogen-containing contraceptives
c. < 375 nmol/L for participants taking oestrogen-containing contraceptives

For sites where no tetracosactide is available/registered, an alternative method to identify AI is provided (see Appendix M).

In addition to a participant's asthma symptoms, investigators will use the participant's weekly ACQ-6 scores (completed by the participant at home by means of a handheld electronic participant-reported outcome device), and will further reduce the OCS dose unless asthma control is lost (deterioration or exacerbation as described below) or AI prevents further dose reduction.

Asthma deterioration will be defined by an increase of ACQ-6 score ≥ 0.5 from baseline. Asthma exacerbation will be defined by worsening of asthma symptoms that leads to:

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
- Or, an ER or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or in an urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
- Or, an in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

After recovery from the first exacerbation or asthma deterioration, the participant will be allowed to proceed with another attempt to reduce OCS dose; however, this must follow a lower speed of OCS down-titration (reductions Q4W). In case of a second

exacerbation or asthma deterioration, no further OCS daily dose reduction will be allowed, and the participant will continue on the same OCS dose or will return to a one-step higher dose level (or more as considered necessary by the investigator). The new OCS dose established after a second asthma exacerbation or deterioration should be maintained until the EOT visit. Further details are provided in Sections 6.5.1.1 and 8.1.3.

4. **Follow-up (Week 64):** A follow-up contact (phone call) will be scheduled at Week 64 or 16 weeks (± 5 days) after the last dose of tezepelumab.

All participants who prematurely discontinue tezepelumab or discontinue from the study should return to the study site and complete the procedures described for the premature investigational product discontinuation (IPD) visit within 4 weeks (± 7 days) after the last dose of tezepelumab. In addition, participants who prematurely discontinue tezepelumab will be encouraged to remain in the study and complete all subsequent scheduled study visits, procedures, and assessments through study completion.

Participants who have partial or complete AI at EOT should be followed up by an endocrinologist or other appropriate specialist.

Disclosure Statement: This is a single-arm study.

Masking: No masking

Number of Participants:

Approximately 300 participants from around 90 sites in approximately 10 countries will enter the induction phase.

The distribution of participants across the range of screening eosinophil (EOS) levels will be operationally controlled by ensuring that approximately the following ratios are met:

- 80% of participants with blood EOS count at screening ≥ 150 cells/µL
- 10% of participants with blood EOS count at screening < 150 cells/µL and documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1
- 10% of participants with blood EOS count at screening < 150 cells/µL without documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 (ie, participants with documented EOS < 300 cells/µL over the last 12 months prior to Visit 1, or undocumented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 or unknown EOS counts within 12 months prior to Visit 1).

Intervention Groups and Duration:

Single-arm study.

- The total duration of the study for each participant could be up to 68 weeks:
  - Screening: up to 4 weeks
  - Induction phase: 4 weeks
  - OCS reduction and maintenance phase: 48 weeks
  - Follow-up: 12 weeks.
- Participants will receive up to 13 SC injections of tezepelumab 210 mg, with the first injection at Week 0 and the last injection at Week 48 (injection Q4W).

Scientific Committee: Yes

Statistical Methods:

There is no predefined study hypothesis to test in this study. The sample size for this study is based on the ability to provide sufficient precision in point estimates, both in the Full Analysis Set and subsets for statistical analysis.

The primary outcomes variables, the proportion of participants who have discontinued OCS without loss of asthma control and the proportion of participants who reduced OCS dose to ≤ 5 mg/day without loss of asthma control are expected to be ≥ 50%. For the sample size estimation, a success rate of 50% is assumed. Estimate precision is expressed in a two-sided 95% CI distance from the point estimate of a 50% success rate to confidence limit for a total of approximately 300 participants.

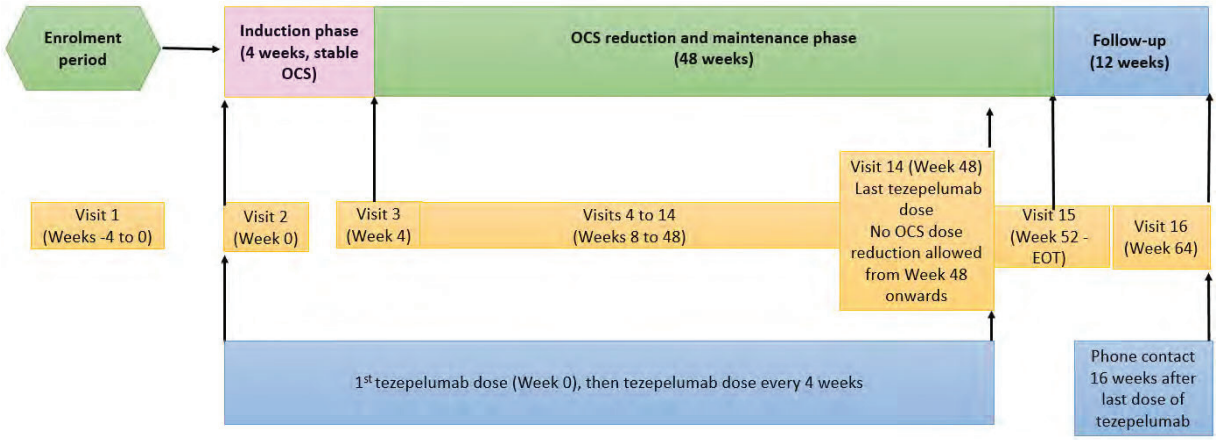
Safety will be assessed by describing the number and percentage of participants with AEs and SAEs.

An interim analysis may be performed if approximately 50 participants complete Visit 4 before a data cut-off date planned on mid-April 2023. The Statistical Analysis Plan (SAP) will be amended to describe the interim analysis in more details.

There will be 2 database locks (DBLs). The primary DBL will be carried out after approximately 300 participants have completed 28 weeks. All data available at that time may be analysed with the main focus on estimates of a subset of the pre-planned analysis outputs at Week 28. The final DBL will be conducted once the last participant has completed the safety follow-up visit (Week 64), with the main focus on estimates on Week 52 (EOT). Further details regarding DBLs will be specified in the Data Management Plan (DMP). The SAP will provide details of statistical analysis. Both documents will be developed and finalised (for the SAP) or signed off (for the DMP) before first participant enrolled.

1.2 Schema

Figure 1 Study Design



Abbreviations: EOT = end of treatment; OCS = oral corticosteroids

1.3 Schedule of Activities

Table 1 Schedule of Activities

	Screening	Induction phase	OCS dose reduction and maintenance phase[a]							IPD[b]	Follow-up	Unscheduled visit	Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6-8 (every 4 weeks)**	**V9**	**V10-14 (every 4 weeks)**	**V15 EOT[c]**		**V16 (by phone)**		
Week	**Week -4 to 0**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16 to 24**	**Week 28**	**Week 32 to 48**	**Week 52**		**Week 64**		
Visit window (days)			**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 7**	**± 5**		
Informed consent	X												Section 5.1
Registration of the participant's enrolment via IxRS	X												Section 6.3
Inclusion/exclusion criteria	X	X											Sections 5.1 and 5.2
Routine Clinical Procedures													
Demography	X												
Complete physical examination	X												Section 8.2.2
Brief physical examination		X					X		X	X			Section 8.2.2
Medical/surgical and asthma history	X												
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Weight and height[d]	X	X					X		X	X			Section 8.2.4.1

	Screening	Induction phase	OCS dose reduction and maintenance phase[a]							IPD[b]	Follow-up	Unscheduled visit	Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6-8 (every 4 weeks)**	**V9**	**V10-14 (every 4 weeks)**	**V15 EOT[c]**		**V16 (by phone)**		
Week	**Week -4 to 0**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16 to 24**	**Week 28**	**Week 32 to 48**	**Week 52**		**Week 64**		
Visit window (days)			**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 7**	**± 5**		
Routine Safety Measurements													
Serum sample for pregnancy (β-hCG) test (WOCBP only) and FSH test (to confirm postmenopausal status, when needed)[o]	X												Section 8.2.3
Urine pregnancy test (dipstick - WOCBP only)		X							X	X			Section 8.2.3
Clinical safety laboratory assessments (serum sample for clinical chemistry & blood sample for haematology)	X												Section 8.2.3
Serum for serology for Hep B and C	X												Section 8.2.3

	Screening	Induction phase	OCS dose reduction and maintenance phase[a]							IPD[b]	Follow-up	Unscheduled visit	Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6-8 (every 4 weeks)**	**V9**	**V10-14 (every 4 weeks)**	**V15 EOT[c]**		**V16 (by phone)**		
Week	**Week -4 to 0**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16 to 24**	**Week 28**	**Week 32 to 48**	**Week 52**		**Week 64**		
Visit window (days)			**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 7**	**± 5**		
Conditional morning serum sample for cortisol[e]			To be conducted when a participant reaches 5 mg as described in Section 8.2.1.1 or 8.2.1.2										Section 8.2.1.1
Conditional serum sample for ACTH stimulation test or alternative method[e,f]			To be conducted when a participant reaches 5 mg as described in Section 8.2.1.1 or 8.2.1.2										Section 8.2.1.2
Assessment of SAEs, DAEs, and AESIs[g]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Pregnancy report												X	Section 8.3.11.2
Overdose report												X	Section 8.4
Medication error report												X	Section 8.3.12
Asthma Assessments													
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.3
Spirometry (post-bronchodilator FEV_1)		X	X		X		X		X	X			Section 8.1.4

	Screening	Induction phase	OCS dose reduction and maintenance phase[a]							IPD[b]	Follow-up	Unscheduled visit	Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6-8 (every 4 weeks)**	**V9**	**V10-14 (every 4 weeks)**	**V15 EOT[c]**		**V16 (by phone)**		
Week	**Week -4 to 0**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16 to 24**	**Week 28**	**Week 32 to 48**	**Week 52**		**Week 64**		
Visit window (days)			**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 7**	**± 5**		
FeNO		X	X	X	X		X		X	X			Section 8.6.1
Blood for eosinophil count	X	X	X	X	X		X		X	X			Section 8.6.3
Serum sample for total IgE	X	X					X		X	X			Section 8.6.2
Serum sample for specific IgE	X												Section 8.6.2
Dispense ePRO device and provide instructions		X											
Assessment of ACQ-6 [h,i]		X	Completed weekly at home using the ePRO device							X			Section 8.1.5.1
Assessment of AQLQ(s)+12 [h,j]		X	X				X		X	X			Section 8.1.5.3
Assessment of SGRQ[h,j]		X					X		X	X			Section 8.1.5.2
Assessment of AIRQ™ [h]		X							X	X			Section 8.1.5.4
Assessment of SNOT-22 [h,j] (only for participants with symptoms of chronic		X					X		X	X			Section 8.1.5.5

	Screening	Induction phase	OCS dose reduction and maintenance phase[a]							IPD[b]	Follow-up	Unscheduled visit	Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6-8 (every 4 weeks)**	**V9**	**V10-14 (every 4 weeks)**	**V15 EOT[c]**		**V16 (by phone)**		
Week	**Week -4 to 0**	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Week 16 to 24**	**Week 28**	**Week 32 to 48**	**Week 52**		**Week 64**		
Visit window (days)			**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 5**	**± 7**	**± 5**		
sinusitis at screening)													
Assessment of PPOCS [h,j]		X					X		X	X			Section 8.1.5.6
Review of ePRO assessments/compliance			X	X	X	X	X	X	X	X			
Return ePRO device									X	X[m]			
Study Treatments													
Switch to prednisone/ prednisolone	X												Section 8.1.2
Prescribed daily OCS dose reduction[k]			X	X	X	X	X	X[l]					Section 8.1.2
Administration of tezepelumab		X[n]	X	X	X	X	X	X					Section 6.1

Abbreviations: ACQ-6 = Asthma Control Questionnaire 6; ACTH = adrenocorticotropic hormone; AESI = adverse event of special interest; AIRQ = Asthma Impairment and Risk Questionnaire; AQLQ(s)+12 = standardised Asthma Quality of Life Questionnaire for 12 years and older; CSP = Clinical Study Protocol; DAE = discontinuation of investigational product due to adverse event; ePRO = electronic patient-reported outcome; EOT = end of treatment; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; FSH = follicle-stimulating hormone; β-hCG = β- human chorionic gonadotropin; IgE = immunoglobulin E; IPD = premature investigative product discontinuation; IxRS = interactive (voice or web) response system; OCS = oral corticosteroid; PPOCS = participant perception of oral corticosteroid; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; SNOT-22 = Sino-nasal Outcome Test; WOCBP = woman of childbearing potential.

[a] Participants will remain on their stable maintenance OCS dose reached during reduction and maintenance phase from Week 48 to Week 52. No further down-titration will be allowed from Week 48 onwards.

[b] The IPD Visit will occur within 4 weeks (± 7 days) after last tezepelumab administration.
[c] The EOT visit will occur 4 weeks (± 5 days) after the last dose of tezepelumab. Participants who prematurely discontinue study intervention should return to the study site and complete the procedures described for the IPD Visit within 4 weeks (± 7 days) after the last dose of tezepelumab. Completion of the treatment will be registered in IxRS at the EOT visit for each participant.
[d] Height at Visit 1, only.
[e] For participants who have reached OCS doses equal to 5 mg/day, hypothalamic-pituitary-adrenal (HPA) axis integrity will be assessed at the end of a 4-week period on 5 mg/day using the 8 to 9 am morning cortisol level. If the morning cortisol level is indeterminate, then an ACTH stimulation or alternative method is required within approximately 1 week. For those participants who had a baseline OCS dose equal to 5 mg/day, HPA axis integrity will be assessed 4 weeks after first dose of tezepelumab administration and before initiation of the OCS reduction and maintenance phase.
[f] For sites where no tetracosactide is available/registered, an alternative method to identify adrenal insufficiency is provided (see Appendix M).
[g] Only events that fall into the following categories are collected in this study: SAEs, DAEs, and AESIs. AEs of special interest in this study fall into the following categories: serious hypersensitivity reactions (see Appendix G), serious infections (including serious opportunistic infections), helminth infections, serious cardiac events, malignancy, Guillain Barre syndrome, and adrenal crisis.
[h] At Visit 2, assessment should be performed before any other study procedures. After Visit 2, any available PROs which have not been completed prior to the site visit, should be completed at the site prior to any other study procedure.
[i] The ACQ-6 will be completed every 1 week at home on the handheld device.
[j] AQLQ(s)+12, SGRQ, SNOT-22 and PPOCS are to be completed at home as per Schedule of Activities (within a defined window of ± 2 days; this defined window may or may not coincide with the on-site visit).
[k] Oral corticosteroid dose reduction is for participants who have not reached the lowest possible stable dose, and who have not lost asthma control. No further OCS dose reduction will be allowed from Week 48 onwards. Note that for participants who must reduce OCS dose more frequently than every 4 weeks or between site visits (see reduction scheme in Table 7), OCS dose reduction may occur remotely (eg, by telephone) instead of a clinic visit.
[l] Oral corticosteroid dose reduction not allowed at Week 48.
[m] For participants who prematurely discontinue study drug and do not want to undergo further study assessments, apart from phone call 52 weeks after baseline (see Section 7.1).
[n] At Visit 2, all assessments should be done before tezepelumab administration to ensure proper calculation of baseline values.
[o] Serum pregnancy (β-hCG) test only for WOCBP. FSH test done only in women < 50 years who have been amenorrhoeic for ≥ 12 months to confirm postmenopausal status.

2 INTRODUCTION

Tezepelumab is a fully human immunoglobulin 2λ monoclonal antibody (IgG2λ mAb) directed against thymic stromal lymphopoietin (TSLP), which is an epithelial cytokine that is produced in response to proinflammatory stimuli and drives inflammatory responses, primarily through its activity on dendritic, Type 2 innate lymphoid cells and mast cells. Targeting TSLP may serve to inhibit multiple biologic pathways involved in asthma and other diseases.

The molecule is a heterotetramer consisting of 2 heavy chains of the immunoglobulin G2 subclass and 2 light chains of the λ subclass, which are covalently linked through disulfide bonds. Tezepelumab binds with human TSLP and prevents its interaction with TSLP receptor (TSLPR) complex.

Tezepelumab is currently being developed as a potential treatment for asthma.

Asthma is a syndrome characterised by airway inflammation, reversible airway obstruction, and airway hyper-responsiveness. Patients present clinically with recurrent wheezing, shortness of breath, cough, and chest tightness. Asthma is a leading cause of morbidity with a global prevalence of approximately 300 million; it is estimated that the number of people with asthma may increase to 400 to 450 million people worldwide by 2025 (Masoli et al, 2004).

2.1 Study Rationale

The current approach to anti-inflammatory controller therapy in asthma is based on a step-wise intensification of a daily maintenance regimen primarily centred around inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs), with the addition of long-acting β_2 agonists (LABAs) in patients with more severe asthma (NAEPP 2020; GINA 2020). Approximately 5% to 10% of persons with asthma have a severe form of disease that is usually managed with high-dose inhaled glucocorticoids (GCs) and bronchodilators (BDs; Bateman et al, 2010; Chung et al, 2014). Within this group, 12% to 45% of persons rely on frequent or maintenance use of oral GC (oral corticosteroids [OCS]) therapy (Moore et al, 2007; Shaw et al, 2015; Miloslavsky et al, 2017). Biologics targeting interleukin (IL)-5, IL-5R, IL-4R, and immunoglobulin E (IgE) are now included in international treatment guidelines as an add-on treatment to patients uncontrolled with ICS/LABA treatment (GINA 2020).

Although OCS therapy can be effective at treating several inflammatory diseases, it adversely affects health-related quality of life (Swedin et al, 2017; Sweeney et al, 2016) and is associated with several side-effects, including osteoporosis, hypertension, and depression (Dinsen et al, 2013). Long-term use of OCS suppresses the hypothalamicpituitary-adrenal (HPA) axis and prevents cortisol production (Neogi et al, 2010; Nicholas et al, 2018). Upon withdrawal of OCS, restoration of the HPA axis may take a longer time, thus leading to

adrenal insufficiency (AI) in approximately 50% of patients (Dinsen et al, 2013). Symptoms and signs of AI are often nonspecific and can include fatigue and nausea; moreover, impairment of the cortisol-induced stress response can be life-threatening (adrenal crisis) in physiologically traumatic situations such as during surgery, bodily injury, or severe systemic infections (Alves et al, 2008; Dinsen et al, 2013; Johnson et al, 2014; Joseph et al, 2016). It is therefore important to screen and monitor patients for AI while down-titrating their OCS dose, especially once the patient has reached a physiological dose, which is defined as approximately 5 mg per day of oral prednisone (Alves et al, 2008).

The SIRIUS trial of mepolizumab, ZONDA trial of benralizumab, and VENTURE trial of dupilumab all demonstrated the efficacy of biologics to reduce the dose of OCS in OCS--dependent patients compared to placebo without loss of asthma control (Doroudchi et al, 2019). In the PONENTE phase 3b open-label trial (Menzies-Gow et al, 2019), 62% of patients with OCS-dependent severe asthma treated with benralizumab eliminated OCS use during the OCS reduction phase. In addition, 81% of patients eliminated daily OCS or achieved a daily OCS dose of 5 mg or less when further reduction was not possible due to AI. These results were seen irrespective of baseline eosinophil (EOS) levels among the patients enrolled (all of whom had prior evidence of eosinophilic inflammation). PONENTE provided and demonstrated the implementation of a personalised OCS tapering algorithm, based on initial OCS dose, for faster reductions in daily OCS doses, with systematic assessments of adrenal status when OCS doses reached 5 mg/day.

SOURCE was a phase 3, randomised, placebo-controlled trial to test the efficacy of tezepelumab to reduce OCS dose in OCS-dependent patients (Wechsler et al, 2021). The SOURCE trial was uniquely designed to maximise the number of OCS-dependent patients able to discontinue OCS therapy without loss of asthma control. The primary endpoint in SOURCE was not met (the cumulative odds ratio of 1.28 favoured tezepelumab, but was not statistically significant). In SOURCE, many patients were able to achieve a ≥ 90% reduction in OCS dose in both treatment groups (54.1% on tezepelumab and 46.1% on placebo), demonstrating a large placebo effect. Two key contributing factors to the large placebo response were the long duration of OCS reduction phase and the possibility of multiple down -titration attempts, both unique features of the SOURCE design.

As demonstrated in the PATHWAY and NAVIGATOR studies (Corren et al, 2017; Menzies-Gow et al, 2021), tezepelumab is the first and only biologic to demonstrate consistent exacerbation reduction in a broad population of severe asthma patients across phenotypes and irrespective of biomarker levels, with 56% annualised asthma exacerbation rate (AAER) reduction in the overall patient population in NAVIGATOR.

The purpose of WAYFINDER is, in OCS-dependent participants with severe asthma on high-dose ICS plus LABA and long-term OCS therapy, to assess the proportion of participants

that are able to discontinue OCS completely or reduce to ≤ 5 mg/day. Participants will receive tezepelumab 210 mg on an open-label basis, every 4 weeks (Q4W) after the first tezepelumab dose at Visit 2 (baseline). Investigators will initiate the tapering of the OCS dose at Visit 3 (4 weeks after first tezepelumab dose).

2.2 Background

Biologic therapies have been shown to reduce AAER in severe asthma patients who are uncontrolled with medium- to high-dose ICS and additional asthma controller medications. Omalizumab provided benefit for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum IgE levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2021). Four additional biologics, mepolizumab, reslizumab, benralizumab, and dupilumab, have recently been approved for severe asthma with an eosinophilic phenotype (NUCALA US PI 2020; CINQAIR US PI 2020; FASENRA US PI; DUPIXENT US PI). Biologics targeting IgE, IL-5/5R, and IL-4R are now included in international treatment guidelines (GINA 2017) as an add-on treatment to patients uncontrolled with ICS/LABA treatment. However, patients without an allergic or eosinophilic phenotype (not OCS dependent) are ineligible for these agents. Additionally, among those receiving 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, there is still a clear unmet medical need for additional treatments among patients with severe asthma, independent of allergic or eosinophilic status.

Thymic stromal lymphopoietin, an epithelial cytokine, occupies an upstream position in the asthma inflammatory cascade and plays a central role in the initiation and persistence of airway inflammation in asthma. Thymic stromal lymphopoietin regulates immunity at the airway barrier surface, affecting dendritic cells and other innate and adaptive immune cells, and inducing downstream inflammatory processes and bronchial hyper-responsiveness. Thymic stromal lymphopoietin has also been shown to have effects on airway structural cells (eg, fibroblasts and airway smooth muscle) (Gauvreau GM et al, 2020). In asthma, both allergic and non-allergic triggers induce TSLP production.

Tezepelumab is a fully human IgG2λ mAb directed against TSLP. Tezepelumab binds to human TSLP and prevents its interaction with TSLPR (Corren et al, 2017; Gauvreau et al, 2014) . Owing to the central role of TSLP in initiating and maintaining asthma inflammation, anti-TSLP therapy may provide an opportunity to treat the upstream underlying mechanisms of asthma by reversing the established inflammatory responses to asthma triggers. Tezepelumab reduces the initiation and persistence of airway inflammation in asthma by interfering with multiple downstream inflammatory pathways, as evidenced by the reduction from baseline in multiple biomarkers and cytokines (eg, EOS, IgE, fractional

exhaled nitric oxide [FeNO], IL-5, and IL-13) in severe asthma participants (Corren et al, 2017; Pham et al, 2019).

The phase 3 NAVIGATOR study (Menzies-Gow et al, 2021) was a randomised, placebo-controlled trial that evaluated the efficacy and safety of tezepelumab in 1059 adults and adolescents with severe, uncontrolled asthma. In NAVIGATOR, a 56% reduction in the annualised asthma exacerbation rate was observed in the overall study population. Importantly, clinically meaningful and consistent reductions in exacerbations were observed across biomarker subgroups including blood EOS count (ranging from < 150 to ≥ 450 cells/μL), FeNO, and IgE; in patients with allergic asthma; in patients receiving maintenance oral corticosteroids; and irrespective of age at asthma diagnosis. Tezepelumab also significantly reduced exacerbations that required hospitalisation or an emergency department visit by 79%. Based on these data and earlier findings from the phase 2b PATHWAY study (Corren et al, 2017), tezepelumab is the first and only biologic to demonstrate consistent efficacy in reducing exacerbations in a broad population of patients with severe asthma, across phenotypes and irrespective of inflammatory biomarker levels.

In addition to its effects on exacerbations, tezepelumab demonstrated rapid and sustained effects on lung function (forced expiratory volume in 1 second [FEV_1]), asthma control, and health-related quality of life, observed as early as Week 2 and sustained until the end of the study. Tezepelumab also reduced levels of inflammatory biomarkers including blood EOS counts, FeNO, and IgE. Consistent with findings from the PATHWAY study, tezepelumab was well tolerated during NAVIGATOR and no meaningful differences in safety results were observed compared with placebo.

The SOURCE trial was designed to maximise the number of OCS-dependent patients able to discontinue OCS therapy without loss of asthma control. The primary endpoint was not met in SOURCE. Compared with placebo, more patients receiving tezepelumab achieved a reduction from baseline in maintenance OCS dose without losing asthma control (cumulative OR = 1.28; 95% confidence interval [CI] 0.69, 2.35), but the difference was not statistically significant.

Many patients in SOURCE were able to achieve a ≥ 90% reduction in OCS dose in both treatment groups (54.1% on tezepelumab and 46.1% on placebo), demonstrating a large placebo effect. Differences in SOURCE trial design compared to other trials contributed to the large placebo response for OCS down-titration. Specifically, the long duration of OCS reduction phase (36 weeks compared to 16 to 20 weeks in previous trials) and the multiple down-titration attempts. Although patients in SOURCE were on maintenance OCS at baseline, many were apparently not truly OCS-dependent, as demonstrated by the number of patients who discontinued OCS without loss of asthma control in the placebo group.

In SOURCE, treatment with tezepelumab resulted in fewer exacerbations and improvements

in FEV_1 and patient-reported outcomes compared with placebo. Results are consistent with improvements seen in pooled, post hoc analyses of OCS-dependent patients from PATHWAY and NAVIGATOR. No safety concerns were observed.

Based on the totality of the evidence from the NAVIGATOR and PATHWAY studies, tezepelumab has the potential to transform care for a broad population of patients with severe asthma irrespective of asthma phenotype and biomarker levels.

2.3 Benefit/Risk Assessment

In order to evaluate the clinical benefit-risk balance for tezepelumab, preclinical and clinical data have been taken into consideration, as well as a review of the available information for monoclonal antibodies that are approved for and are in development for the treatment of severe asthma. Benefits for tezepelumab over placebo include a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics. Tezepelumab has been well tolerated in studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the phase 2 and 3 programme. The frequency and type of adverse events (AEs) and serious adverse events (SAEs) were similar between the tezepelumab and placebo treatment groups in the phase 2 and phase 3 studies. Although TSLP suppression could theoretically have unanticipated immune-related side-effects impairing host defence 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 programme. The benefit/risk assessment for tezepelumab in severe asthma based on the development programme is favourable.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tezepelumab may be found in the investigator brochure (IB).

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary objectives	
To assess the ability of tezepelumab 210 mg subcutaneous (SC) to reduce the prescribed OCS dose (≤ 5 mg/day) without loss of asthma control[a] in adult participants with OCS-dependent asthma	Endpoints • Proportion of participants who discontinued OCS without loss of asthma control[a] at Week 28 and Week 52 • Proportion of participants who reduced daily prescribed maintenance OCS dose to ≤ 5 mg/day without loss of asthma control[a] at Week 28 and Week 52
	Population: Adult with OCS-dependent asthma requiring high-dose ICS plus a LABA with or without additional asthma controller and with at least 1 asthma exacerbation in the prior year who received at least one dose of tezepelumab
	Intercurrent events: Treatment discontinuation, change in background therapy (other than OCS): All data will be included in the analysis according to treatment policy estimand. Initiate therapy with another biologic for treatment of asthma: hypothetical strategy; final dose for analysis will be defined as last reported OCS dose received by participant with asthma stability verified, achieved prior to initiation of another biologic.
	Summary measures: Proportion of participants and corresponding 95% CI at Week 28 and Week 52
Secondary objectives	
To assess the ability of tezepelumab 210 mg SC to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction	• The AAER over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation or emergency room (ER) visit over 28 weeks and over 52 weeks • Rate of asthma exacerbation associated with hospitalisation over 28 weeks and over 52 weeks

	• Proportion of participants who did not experience an exacerbation over 28 weeks and over 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit over 28 weeks and 52 weeks • Proportion of participants who did not experience an exacerbation associated with hospitalisation over 28 weeks and over 52 weeks
To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]	• Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 and Week 52 • Categorised percent reduction from baseline in the daily maintenance OCS dose (categories: ≥ 90% to ≤ 100% reduction, ≥ 75% to < 90% reduction, ≥ 50% to < 75% reduction, > 0% to < 50% reduction, no change or any increase) at Week 28 and Week 52 • Absolute and percent change from baseline in daily maintenance OCS dose at Week 28 and Week 52
To assess the ability of tezepelumab to improve lung function	• Change from baseline in post-BD FEV_1 at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma control[a]	• Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma related quality of life	• Change from baseline in standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ[s]+12) total score at Week 28 and Week 52 • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 28 and Week 52
Safety objective	
To describe the safety and tolerability of tezepelumab	• Serious adverse events (SAEs), discontinuation of investigational product due to an adverse event (DAEs), and adverse events of special interest (AESI)

Exploratory objectives	
To describe changes from baseline in biomarker levels	• Change from baseline in biomarker levels at Week 28 and Week 52
To assess the ability of tezepelumab 210 mg SC to allow reduction of the prescribed OCS dose without loss of asthma control[a]	• Time to 50% reduction of OCS dose at Week 28 and Week 52 • Time to 100% reduction of OCS dose at Week 28 and Week 52
To describe the occurrence of AI	• Proportion of participants with normal, partial, complete AI at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma control[a]	• Proportion of ACQ-6 responders at Week 28 and Week 52
To assess the ability of tezepelumab to improve asthma related quality of life	• Proportion of AQLQ(s)+12 responders at Week 28 and Week 52 Proportion of SGRQ responders at Week 28 and Week 52
To describe the ability of tezepelumab to improve Asthma Impairment and Risk Questionnaire (AIRQ™)	• Change from baseline in AIRQ at Week 52 • Proportions of AIRQ responders at Week 52
To describe the ability of tezepelumab to improve Sino-nasal Outcome Test (SNOT-22)	• Change from baseline in Sino-nasal Outcome Test (SNOT-22) at Week 28 and Week 52 • Proportion of SNOT-22 responders at Week 28 and Week 52
To describe participant satisfaction with change in daily OCS use	• Change from baseline in Participant Perception of OCS (PPOCS) score at Week 28 and Week 52
To evaluate the ability of tezepelumab to reduce exposure to SCS	• Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 and 52 weeks

[a] Loss of asthma control is defined as asthma worsening or exacerbation. Asthma worsening will be defined by an increase of ACQ-6 score ≥ 0.5 from baseline (see Section 8.1.2.1). Asthma exacerbation will be defined by worsening of asthma symptoms that leads to temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days (a single depo-injectable dose of corticosteroids being considered equivalent to a 3-day bolus/burst of systemic corticosteroids), and/or an ER or urgent care visit requiring systemic corticosteroids, and/or inpatient hospitalisation, both due to asthma (see Section 8.1.3).

4 STUDY DESIGN

4.1 Overall Design

This is a phase 3b, single-arm, multicentre study in adult participants with severe asthma on high-dose ICS plus LABA and long-term OCS therapy. Participants may be treated with or without additional asthma controller(s). Each participant must have been receiving an average daily OCS dose equivalent to ≥ 5 mg of prednisone/prednisolone for the last 3 months before study entry.

Approximately 300 participants from around 90 sites in approximately 10 countries will enter the induction phase. The distribution of participants across the range of screening blood EOS levels will be operationally controlled by ensuring that approximately the following ratios are met:

- 80% of participants with blood EOS count at screening ≥ 150 cells/μL
- 10% of participants with blood EOS count at screening < 150 cells/μL and documented history of EOS ≥ 300 cells/μL within 12 months prior to Visit 1
- 10% of participants with blood EOS count at screening < 150 cells/μL without documented history of EOS ≥ 300 cells/μL within 12 months prior to Visit 1 (ie, participants with documented EOS < 300 cells/μL over the last 12 months prior to Visit 1, or undocumented history of EOS ≥ 300 cells/μL within 12 months prior to Visit 1 or unknown EOS counts within 12 months prior to Visit 1).

When the target percentage of participants for the eosinophil subgroup in a country/region is reached, consideration will be given to closing the IxRS enrolment for that subgroup, which may be performed either overall or within a specific country/region.

The study aims at evaluating the efficacy and safety of reducing OCS use after initiation of a 210 mg dose of SC tezepelumab Q4W.

The total duration of the study for each participant will be up to approximately 68 weeks.

Study will be divided in 4 periods, with site visits planned Q4W:

1. **Screening – From Week -4 to Week 0 (up to 4 weeks):** Eligibility criteria will be checked at Visit 1. At Visit 1, participants will continue with or be switched to prednisone/prednisolone. Participants who are taking an alternative systemic steroid and not taking prednisone/prednisolone as their OCS treatment will be switched to a bioequivalent dose of prednisone/prednisolone (see Appendix D). In participants who switched to prednisone/prednisolone, dose has to remain stable for at least 2 weeks before Week 0.

2. **Induction phase – From Week 0 to 4:** After confirmation of eligibility criteria, participants will start receiving tezepelumab treatment at Visit 2/Week 0 (baseline) and should remain stable on their baseline OCS dose during this phase.
3. **Oral corticosteroid reduction and maintenance phase – From Week 4 to Week 52:** Site visits will occur Q4W. Participants will reduce their dosage of OCS according to the schema defined in Table 7 for each baseline OCS dose until they reach the lowest stable OCS dose or until Week 48. The first OCS dose reduction may occur at Visit 3. OCS dose reduction may occur remotely if the scheduled dose reduction does not coincide with a site visit.

   Participants will be considered as having reached the lowest stable dose when they have discontinued OCS or no further OCS reduction is possible because of loss of asthma control and/or evidence of AI (as confirmed by morning cortisol test or adrenocorticotropic hormone [ACTH] stimulation test).

   Once they reach the lowest stable dose, participants will be considered in maintenance. From Week 48 to Week 52, all participants will remain on their stable daily OCS dose, except if an asthma deterioration or exacerbation occurs. No further down-titration will be allowed from Week 48 onwards.

   HPA axis integrity will be evaluated for all participants who have been on 5 mg/day OCS for 4 weeks and prior to any further tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction and maintenance phase). A screening method with morning serum cortisol (see Section 8.2.1.1) will be done (8 to 9 am morning cortisol level), to evaluate whether the participant has normal cortisol levels or complete AI. Cortisol levels from the morning cortisol test that will be below normal range and above the complete AI range will be considered ‘indeterminate’ and will require additional testing (ACTH stimulation test or alternative method, as described in Appendix M).

   Depending on the morning cortisol level results, the participant will continue per the following guidance:

   - Cortisol levels within normal range (Table 9):
     - Participant exhibits absence of signs and/or symptoms of AI: continue OCS down-titration by 2.5 mg Q4W
     - Participant exhibits signs and/or symptoms of AI: continue OCS down-titration at a slower pace (1 mg Q4W)
   - Cortisol levels are indeterminate (Table 9): participant will be instructed to maintain the current OCS dose and will undergo the ACTH stimulation testing (or alternative method, see Appendix M). Decisions regarding how to continue

OCS down-titration will be based on the results of the ACTH stimulation testing (or alternative method, see Appendix M).

- If complete AI is confirmed (Table 9): participant will be instructed to maintain the current OCS dose until there is evidence of recovery from the complete AI without worsening of asthma control. The morning cortisol test will be repeated 3 months later.

If the morning cortisol is in the indeterminate range, the ACTH stimulation test will be done within approximately 1 week (see Section 8.2.1.2 for details). The ACTH stimulation test (Table 10) can determine whether the participant has:

- Normal cortisol levels
- Complete AI
- Partial AI

Decisions regarding how to continue OCS down-titration will be based on results of this test (Table 3).

Table 3 OCS Down-titration Scheme Using ACTH Stimulation Test

	Normal (> 450 nmol/L[a])	**Partial AI (250-450 nmol/L[b])**	**Complete AI (< 250 nmol/L[c])**
OCS down-titration	Reduction of 2.5 mg Q4W	Reduction of 1 mg Q4W	Continue on same OCS dose
Repeat morning cortisol test for further OCS down-titration	No need	2 months later	3 months later

Abbreviations: ACTH = adrenocorticotropic hormone; OCS = oral corticosteroids; Q2W = every two weeks; Q4W = every four weeks.

a. > 675 nmol/L for participants taking oestrogen-containing contraceptives
b. 375-675 nmol/L for participants taking oestrogen-containing contraceptives
c. < 375 nmol/L for participants taking oestrogen-containing contraceptives

For sites where tetracosactide is not available or not registered, an alternative method to identify AI is provided (see Appendix M).

At each visit, in addition to the participant's asthma symptoms, investigators will use the participant's weekly ACQ-6 scores (completed by the participant at home by means of a handheld electronic participant-reported outcome device [ePRO]), and will further reduce the OCS dose unless asthma control is lost (deterioration or exacerbation as described below) or AI prevents further dose reduction.

Asthma deterioration will be defined by an increase of ACQ-6 score ≥ 0.5 from baseline. Asthma exacerbation will be defined by worsening of asthma symptoms that leads:

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
- An ER or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or in an urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
- An in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

After recovery from the first exacerbation or asthma deterioration, the participant will be allowed to proceed with another attempt to reduce OCS dose; however, this must follow a lower speed of OCS down-titration (reductions Q4W). In case of a second exacerbation or asthma deterioration, no further OCS dose reduction will be allowed, and the participant will continue on the same OCS dose or will return to a one-step higher dose level (or more as considered necessary by the investigator). The new OCS dose established after a second asthma exacerbation or deterioration will be maintained until Week 52. Further details are provided in Sections 6.5.1.1 and 8.1.3.

4. **Follow-up (Week 64):** A follow-up contact (phone call) will be scheduled at Week 64 or 16 weeks (± 5 days) after the last dose of tezepelumab.

All participants who prematurely discontinue tezepelumab or discontinue from the study should return to the study site and complete the procedures described for the IPD visit within 4 weeks (± 7 days) after the last dose of tezepelumab. In addition, participants who prematurely discontinue tezepelumab will be encouraged to remain in the study and complete all subsequent scheduled study visits, procedures, and assessments through study completion (see Section 7.1).

An interim analysis may be performed if approximately 50 participants complete Visit 4 before a data cut-off date planned on mid-April 2023.

There will be 2 DBLs. The primary DBL will be carried out after approximately 300 participants having completed 28 weeks. All data available at that time may be analysed with the main focus on estimates of a subset of the pre-planned analysis outputs at Week 28. The final DBL will be conducted once the last participant has completed the safety follow-up

visit (Week 64) with the main focus on estimates on Week 52 (end of treatment [EOT]). Further details regarding DBLs will be specified in the Data Management Plan (DMP). The Statistical Analysis Plan (SAP) will provide details of statistical analysis. Both documents will be developed and finalised (for SAP) or signed off (for DMP) before first participant enrolled.

A Scientific Committee will be involved in the study (see Appendix A 5).

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: In Germany, this guidance is applicable only in connection with the Coronavirus disease 2019 (COVID-19) pandemic.

The guidance given should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study.

The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Additional re-screening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The screening period may also be extended. Both re-screening and screening extension options should be discussed with the designated contract research organisation (CRO) study physician. Before randomisation, the principal investigator (PI) must ensure that all of the eligibility criteria are fulfilled. The investigator should confirm with the designated CRO study physician which option can be used.
- Home or Remote visit: Performed by a qualified Health Care Professional (HCP).

- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home investigational product (IP) administration: Performed by a qualified HCP, except in Germany and France, where at-home administration of tezepelumab is not allowed. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix C.

4.2 Scientific Rationale for Study Design

Severe asthma is defined as asthma requiring high-dose ICS plus a second maintenance medication and/or systemic steroids to prevent becoming uncontrolled or remaining uncontrolled despite this therapy (Doroudchi et al, 2019).

The purpose of this study is to assess the potential for reducing the use of maintenance OCS in systemic corticosteroid-dependent asthma participants treated with tezepelumab 210 mg. This study will allow participants to reduce their OCS dose to the lowest stable OCS dose that is physiologically possible (given the possibility of AI in this population of participants) and will assess whether a faster OCS down-titration compared with what has been previously studied (Nair et al, 2017) is appropriate. Participants will start maintenance 4 weeks after their OCS dose has been reduced to the lowest OCS dose possible. Lowest OCS dose possible is the maintenance dose prescribed in case no further OCS down-titration is allowed because of the presence of AI (as measured by ACTH stimulation test or alternative method, see Appendix M) or in case of inadequate asthma control. This maintenance dose will assess the ability of tezepelumab to maintain clinical benefits after OCS withdrawal.

Participants will receive open-label tezepelumab 210 mg from a 110 mg/mL solution for injection in an accessorised pre-filled syringe (APFS). It will be administered subcutaneously at the study site as Q4W dosing. This dose is aligned with the current prescribing information for tezepelumab, and an open-label design allows for a real-world assessment of OCS down-titration as it relates specifically to tezepelumab effectiveness.

The study will target the enrolment of 80% of participants with blood EOS count at screening ≥ 150 cells/µL because eosinophilic asthma is known to be associated with recurrent exacerbations (Chung et al, 2014).

Measured variables such as AAER, FEV_1, and FeNO are well-established outcomes in asthma clinical trials (Doroudchi et al, 2019).

Upon withdrawal of OCS, restoration of the HPA axis may take a longer time, thus leading to AI. Therefore, participants will be monitored for AI while down-titrating their OCS dose,

especially once they have reached a physiological dose, which is defined as approximately 5 mg per day of oral prednisone (Alves et al, 2008).

Clear guidance is in place for rescue therapy and management of asthma exacerbations during treatment period (see Section 6.5.1) as well as for study discontinuation (see Section 7).

The safety of tezepelumab compared to placebo has been assessed in randomised controlled trials compared to placebo. The frequencies and types of adverse events did not differ meaningfully between the tezepelumab and placebo groups (Corren et al, 2017; Menzies-Gow et al, 2021). This single-arm study is not expected to provide meaningful new safety information; therefore, only SAEs, discontinuation of investigational product due to an adverse events (DAEs), and adverse events of special interest (AESIs) will be recorded.

4.2.1 Participant Input into Design

The study design concept was reviewed by participants. Their request for a simple explanation of the study design and rationale will be incorporated into the ICF.

4.3 Justification for Dose

The selection of the 210 mg SC Q4W dose was based on efficacy and safety results from the phase 2b PATHWAY study (Corren et al, 2017). In PATHWAY, 210 mg tezepelumab Q4W led to numerically improved efficacy compared with 70 mg Q4W, whereas the 280-mg dose every 2 weeks (Q2W) did not increase efficacy further with the 210-mg Q4W dose. Tezepelumab was well tolerated at all 3 doses and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship to AEs. Efficacy and safety of the 210-mg SC Q4W dose was further confirmed in the phase 3 NAVIGATOR study in adults and adolescents with severe asthma (Menzies-Gow et al, 2021).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled contact.

The end of the study is defined as the date of the last scheduled contact for the last participant in the study globally.

5 STUDY POPULATION

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

The distribution of participants across the range of screening EOS levels will be operationally controlled by ensuring that approximately the following ratios are met:

- 80% of participants with blood EOS count at screening ≥ 150 cells/µL
- 10% of participants with blood EOS count at screening < 150 cells/µL and documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1
- 10% of participants with blood EOS count at screening < 150 cells/µL without documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 (ie, participants with documented EOS < 300 cells/µL over the last 12 months prior to Visit 1, or undocumented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 or unknown EOS counts within 12 months prior to Visit 1).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be 18 to 80 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 History of physician diagnosed asthma that requires continuous treatment with high-dose ICS (high-dose ICS is the highest approved dose in a country; see Appendix I) plus a LABA for at least 6 months prior to Visit 1 (to be documented in medical records). The ICS and LABA can be contained within a combination product or given by separate inhalers:

(a) For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.

Note: Additional maintenance asthma controller medications (eg, LTRAs, tiotropium, cromone, theophylline) are allowed (see Table 5).

3 Long-term OCS therapy for asthma, equivalent to a daily dose of at least 5 mg and up to 40 mg of prednisone/prednisolone for at least 3 continuous months directly preceding Visit 1 (to be documented in medical records).

Note: Alternate intake of OCS (ie, every other day) or other frequency is allowed provided the average daily dose is equivalent to at least 5 mg of prednisone/prednisolone and the participant is switched to a daily intake of prednisone/prednisolone at Visit 1. Systemic corticosteroid doses administered by any route other than oral cannot be used to determine the average daily dose preceding Visit 1.

4 Participant should be on a stable maintenance OCS dose for at least 4 weeks prior to Visit 1. If taking a type of OCS other than prednisone/prednisolone at Visit 1, then the participant must agree to switch to prednisone/prednisolone as their OCS by Visit 2 and for the duration of the study.

5 Documented history of at least 1 asthma exacerbation event within 12 months prior to Visit 1. An asthma exacerbation will be defined as a worsening of asthma symptoms that leads to any of the following:

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

(b) Or, an ER or urgent care visit (defined as evaluation and treatment for < 24 hours in ER or urgent care centre) due to asthma that required systemic corticosteroids (as per above)

(c) 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).

Weight

6 Body weight ≥ 40 kg at Visit 1.

Sex

7 Male and female

Female participants:

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

- Women of non-childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned start date of the induction phase without an alternative medical cause. The following age-specific requirements apply:
  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Women of childbearing potential (WOCBP) must be willing to use one of the methods of contraception described hereafter, from the time of signing the informed consent throughout the study and 16 weeks thereafter:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner (vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success
- Sexual abstinence: it is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Cessation of contraception after this point should be discussed with a responsible physician.

Informed Consent

8 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1 Any clinically important pulmonary disease other than asthma (eg, active lung infection, Chronic Obstructive Pulmonary Disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral EOS counts (eg, 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, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could:

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

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

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

3 History of cancer:

(a) Participants who have had basal cell carcinoma, localised 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.

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

4 History of a clinically significant infection, including upper (URTI), lower respiratory tract infection (LRTI) or asthma exacerbation, requiring treatment with antibiotics, antiviral, or additional corticosteroid medications finalised < 2 weeks before Visit 1.

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

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

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

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

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

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

11 Coexistent inflammatory conditions for which long-term OCS doses are part of their maintenance treatment such as, but not limited, giant cell arteritis or polymyalgia rheumatic.

12 Coexistent endocrine conditions for which glucocorticoid replacement therapy is required.

13 Evidence of COVID-19 within 4 weeks prior to screening or ongoing clinically significant COVID-19 sequalae.

Prior/Concomitant Therapy

14 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 nonbiologic agent within 30 days or 5 half-lives (whichever is longest) prior to Visit 1.

Note 1: Participants enrolled in current or previous tezepelumab studies will not be included.

Note 2: Participants on previous biologics treatment are allowed to enter the study provided the appropriate washout period is fulfilled (see Table 6).

15 Receipt of more than 2-week treatment with macrolides, antivirals, or azole therapies within 30 days or 5 half-lives, whichever is the longer, prior to screening.

16 Treatment with systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine, etc.), except for OCS used in the treatment of asthma/asthma exacerbations, within the last 12 weeks or 5 half-lives (whichever is longer) prior to Visit 1.

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

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

19 Receipt of live attenuated vaccines 30 days prior to the date of Visit 1 and during the study including the follow-up period.

20 Receipt of COVID-19 vaccine (regardless of vaccine delivery platform) within 28 days prior to date of first tezepelumab administration at Visit 2.

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

Prior/Concurrent Clinical Study Experience

22 Known history of sensitivity to any component of the tezepelumab formulation or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

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

24 Concurrent enrolment in another clinical study involving an IP.

Diagnostic Assessments

25 Any clinically meaningful abnormal finding in physical examination, haematology, clinical chemistry at Visit 1 which, in the opinion of the investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete the entire duration of the study.

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

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

Other Exclusions

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

29 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

30 For women only: Pregnant, breastfeeding, or lactating women. A serum β- human chorionic gonadotropin (HCG) pregnancy test must be drawn for WOCBP at the screening visit. If the results of the serum β-HCG cannot be obtained prior to dosing of the IP, a participant 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 participant should be excluded. Since urine and serum tests may miss a pregnancy in the first days after conception, relevant menstrual history and sexual history, including methods of contraception, should be considered. Any participant whose menstrual and/or sexual history suggests the possibility of early pregnancy should be excluded.

5.3 Lifestyle Considerations

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

No other lifestyle restrictions will be required in this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study because of not meeting required inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information including demography, screen failure details, eligibility criteria, and any SAE will be entered into the electronic Case Report Form (eCRF).

5.4.1 Re-screening

Re-screening of a participant for any other reason will be allowed only upon approval of the

CRO study physician. A documented approval for re-screening should be filed in the Investigator Study File (ISF).

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

- Participants with a clinically significant infection, including URTI, LRTI, or asthma exacerbation, requiring treatment with antibiotics, antiviral, or additional corticosteroid medications within 14 days prior to Visit 1 or during the screening period (before Visit 2), may extend their screening period to accommodate the time needed to recover and return to Visit 2.

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

- If the reason for screen failure was the blood EOS count and the investigator believes that the participant may qualify for the study if tested at a later date.

- Participants who had evidence of COVID-19 within 2 weeks prior to or during screening and are screened failed may be re-evaluated after approximately 4 weeks of clinical recovery/diagnosis for potential re-screening upon discussion with CRO study physician.

- Participants who experience an asthma exacerbation during the screening period (before Visit 2), may extend their screening period to accommodate the time needed for a short course (5-7 days) of systemic corticosteroids treatment and return to Visit 2 no sooner than 4 weeks after the last dose of systemic corticosteroids.

Re-screened participants should be assigned the same participant number as for the initial screening. It means that participant should keep the same E-code as was originally assigned.

Re-screening should be documented so that its effect on study results, if any, can be assessed. A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 7 days from the previous ICF signature date. All assessments must be repeated for re-screening unless they are within 28 days of enrolment.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol.

6.1 Study Intervention Administered

Table 4 Investigational Products

Intervention name	Tezepelumab
Type	Biologic plus device combination
Dose formulation	110 mg/mL in 10 mM acetate, 3.0% (w/v) L-proline, 0.01 % (w/v) polysorbate 80, pH 5.2
Unit Dose Strength(s)	210 mg
Dosage level(s)	210 mg Q4W
Route of administration	Subcutaneous injection
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor or designee.
Packaging and labelling	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into the local language where applicable.
Former name(s) or alias(es)	AMG 157 or MEDI9929

Abbreviations: APFS = accessorised pre-filled syringe; GMP = Good Manufacturing Practice; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; Q4W = every 4 weeks

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

The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 2.25 mL pre-filled syringe barrel with a 1/2-inch 27-gauge thin wall staked in needle, rigid needle shield, plunger stopper) and a safety device.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation and Handling

Study intervention will be supplied to the site in a kit with one tezepelumab APFS. Each kit has a unique number that is printed on all labels within the kit (ie, 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 study intervention.

The study intervention is to be stored at the study site in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log while study intervention is stored at the study site. The study intervention must be kept in the original outer container and under conditions specified on the label (between 2°C to 8°C [36°F to 46°F], protected from light).

In the following cases neither the site staff should use the affected study intervention and should immediately contact an AstraZeneca representative for further guidance:

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

Damaged study intervention should be documented via the interactive (voice or web) response system (IxRS; refer to the IxRS manual for further details).

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

Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.2.2 Dose Preparation

Preparation of the study intervention must be performed by a qualified person (eg, pharmacist, investigator or nurse) at the site. The APFS should be visually inspected prior to dose preparation. If defects are noted with the study intervention, the investigator and site monitor should be notified immediately.

The study intervention does not contain preservatives and any unused portion must be discarded. Total in-use storage time from removal of the study intervention from the refrigerator to start of administration must not exceed 8 hours. If storage time exceeds this limit, a new dose must be prepared with a new study intervention kit.

To prepare the participant’s dose, a study intervention kit will be selected for administration according to the kit identification number assigned by the IxRS.

Dose preparation steps:

1. Allow the study intervention to equilibrate to room temperature for at least 60 minutes prior to dose administration. Ensure that the APFS is adequately protected from light during the warming process.
2. To prepare the study intervention for administration, remove the syringe from the carton by holding the middle of the syringe body.
3. Unwrap, but do not detach, the wrap-around label attached to syringe body to view the syringe contents.
4. Look at the liquid through the viewing window. The liquid should be clear to slightly opalescent, colourless to light yellow liquid, practically free from particles. Do not inject the study intervention if the liquid is cloudy, discoloured, or contains large particles.
5. Re-wrap the label around the syringe body.

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

6.2.3 Dose Administration

The investigator or authorised delegate will assess the injection site as per standards of medical care. For WOCBP, a urine pregnancy test will be performed, and first study intervention administration will be done when the result of the test is negative (Section 8.2.3).

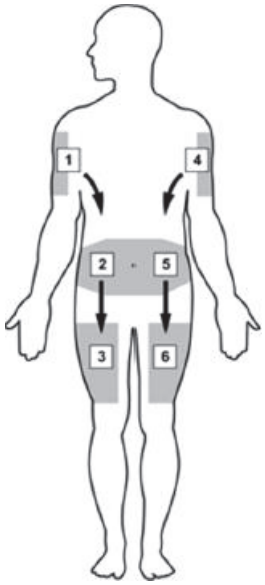
The administration of tezepelumab should be recorded in the appropriate sections of the eCRF. Tezepelumab will be administered at the study site but at home administration by an HCP can also take place, if deemed necessary (see Appendix C). In case of at home administration, the HCP administering the dose will also fill out the source documentation to capture that the dose was successfully administered. Both the completed source documentation and the used device are to be returned to the site once the visit is completed for study intervention accountability.

The study intervention will be administered by the investigator/authorised delegate as specified in Table 1.

Each participant will receive tezepelumab 210 mg (one 1.91 mL injection), administered SC Q4W for 13 doses in the abdomen, thigh, or upper arm by APFS. The person administering the dose will wipe the skin surface of the upper arm, anterior thigh, or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be fully inserted at a 45-degree angle approximately into the SC tissue. The injection site should not be rubbed after each injection.

It is advised that the site of injection of the study intervention be rotated such that the participant receives study intervention at a different anatomical site at each treatment visit. The suggested injection site rotation sequence is presented in Figure 2.

Figure 2 Suggested Schema of Rotation of Injection Sites



After study drug administration

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

Conditions that will require rescheduling of study drug administration

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

- The participant received allergen immunotherapy injection on the same day as scheduled study intervention administration.
- The participant has an intercurrent illness that in the opinion of the investigator and/or medical monitor may compromise the safety of the participant in the study (eg, viral illnesses).
- The participant is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to study intervention administration.
- The participant is confirmed to have an active COVID-19 infection based on positive SARS-CoV-2 test results.

- The participant has received COVID-19 vaccine within 28 days prior to study intervention administration.

    – If COVID-19 vaccination is in the best interest of the participant and he/she is vaccinated during the study, study intervention dosing can continue but study intervention is not recommended to be administered within 14 days before or 28 days after a dose of vaccine.

    – Thus, if the participant receives a COVID-19 vaccination during the treatment period, it is recommended that the COVID-19 vaccination be administered at least 14 days from the last study intervention dose, and that the next study intervention administration be rescheduled or skipped to ensure the next study intervention dose is at least 28 days after the vaccine administration.

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

6.2.4 Reporting Product Complaints

Any defects with the study intervention must be reported immediately to the site monitor. All defects will be communicated to the sponsor and investigated further with the AstraZeneca Supply Chain Group.

During the investigation of the product complaint, all study interventions must be stored at labelled conditions 2°C to 8°C (36°F to 46°F), separated from other study intervention kits, unless otherwise instructed.

6.2.5 Reporting Product Defects

Product defects may be related to component, product, or packaging and labelling issues prior to or during use. Product defects should be reported to the study monitor. The list below includes the 3 categories of product complaints that should be reported as defects. Descriptions of product complaints in these 3 categories include, but are not limited to:

- **Component Issue:** Defect in container or dosing mechanism of the study intervention. The component defect may be damaged, missing, or broken. For the APFS, component examples include syringes and the accessory housing the syringe.

- **Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallisation, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description in the study intervention handling instructions.
- **Packaging/Labelling Issue**: Defect in the packaging or labelling of the product. The packaging (eg, carton, thermo-fitted tray, or tamper-evident seal) or labelling defects may be damaged or unreadable, or the label may be missing.

6.2.6 Single Use APFS Device Malfunction

An APFS malfunction is when the APFS appeared normal during verification of shipment and then does not work during administration, eg, the safety feature activated prematurely, part of the device (finger flange, plunger rod, etc.) came off or broke, needle shield could not be removed only partial dose administered, needle guard safety feature did not activate, or needle bent or broke upon use.

Device malfunctions should be reported using the Product Complaint Intake Form and the study monitor should be notified.

If a device malfunction is identified at the study site:

- Before study intervention administration has started, another study intervention kit (replacement) should be dispensed to perform study intervention administration.
- After study intervention administration has started and participant has been administered unknown dose of study intervention, another study intervention kit must not be dispensed, and participant must not be administered with another study intervention kit. The CRO study physician and study monitor should be notified.

If it is determined that a replacement should be issued based on the same guidance for device malfunction at study site described above, the HCP will return to the study site to obtain the replacement device.

For definitions and procedures for recording, evaluating, follow-up, and reporting of medical device AEs, SAEs and deficiencies in medical device studies, please see Section 8.3.14 and Appendix K.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study with no placebo or active comparator; as such, no blinding or randomisation is required. However, the investigator will assign each potential participant a unique enrolment number, beginning with ‘E#’ via the IxRS.

The distribution of participants across the range of screening EOS levels will be operationally controlled by ensuring that approximately the following ratios are met:

- 80% of participants with blood EOS count at screening ≥ 150 cells/µL
- 10% of participants with blood EOS count at screening < 150 cells/µL and documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1
- 10% of participants with blood EOS count at screening < 150 cells/µL without documented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 (ie, participants with documented EOS < 300 cells/µL over the last 12 months prior to Visit 1, or undocumented history of EOS ≥ 300 cells/µL within 12 months prior to Visit 1 or unknown EOS counts).

When the target percentage of participants for the eosinophil subgroup in a country/region is reached, consideration will be given to closing the IxRS enrolment for that subgroup, which may be performed either overall or within a specific country/region.

Before the study is initiated, the telephone number and call-in directions for the IxRS will be provided to each site. Specific information concerning the use of the IxRS will be provided in a separate manual.

If a participant withdraws from participation in the study, then his/her enrolment code cannot be reused. Following successful screening/enrolment on the study, withdrawn participants will not be replaced in the study.

Study intervention will be dispensed at the study visits summarised in the Schedule of Activities (SoA; see Table 1).

6.4 Study Intervention Compliance

Participants will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Prior and Concomitant Therapy

Information about any treatments received in the 6 months prior to the date of informed consent and all the concomitant treatments given during the study (through follow-up period) with reason for the treatment will be collected by the investigator/authorised delegate at each visit (as shown in Table 1) and recorded in the eCRF.

In order to satisfy inclusion criterion 3, a history of long-term OCS therapy equivalent to a daily dose of at least 5 mg and up to 40 mg of prednisone/prednisolone for at least 3 months prior to Visit 1 should be documented in source and recorded in the eCRF.

In order to satisfy with inclusion criterion 2, a history of continuous treatment with high-dose ICS (high-dose ICS is the highest approved dose in a country) plus a LABA for at least 6 months prior to Visit 1 should be documented in source and recorded in the eCRF.

Use of ICS/LABA as a reliever (eg, Symbicort Maintenance and Reliever Treatment) that was part of the participant's usual asthma controller regimen at baseline is allowed; however, it should also be withheld before any morning cortisol and ACTH stimulation test as described in Section 8.2.1 and Appendix M. Any maintenance therapy (in addition to ICS/LABA) such as long-acting muscarinic antagonists used prior to study entry should not be changed during the study. The 'as-needed' use of short-acting BDs for relief of acute asthma symptoms is permitted throughout the study.

Asthma exacerbations should be treated with oral or other systemic corticosteroids according to standard practice (see Section 6.5.1.1).

Table 5 and Table 6 describe the concomitant medications allowed and prohibited during the study period.

Medications will be classified according to the World Health Organization (WHO) Drug Dictionary.

Before any morning cortisol or ACTH stimulation test is performed:

- Prednisone/prednisolone should not be taken at least 24 hours prior to morning cortisol level/ACTH stimulation test
- No high-dose ICS (or ICS/LABA if in single inhaler) treatment on the morning of the morning cortisol level/ACTH stimulation testing (for participants taking a once-daily ICS/LABA formulation, eg, fluticasone furoate/vilanterol, participants must not take the treatment ≤ 24 hours prior to the morning of the morning cortisol level/ACTH stimulation test).

The visit should be rescheduled if the above medications are not withheld properly (note: short-acting β-agonist [SABA] rescue is allowed throughout the study).

Table 5 Restricted Medications

Medication/Class of drug	Usage
Maintenance treatment with ICS and long-acting BDs (including ICS/LABA combinations)	No changes in either dose or regimen are allowed from Visit 1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. The ICS (including ICS/LABA combinations) should be withheld the morning of any morning cortisol level/ACTH stimulation test. For participants taking a once-daily ICS/LABA formulation, eg, fluticasone furoate/vilanterol, participants must not take the treatment ≤ 24 hours prior to the morning of any morning cortisol level/ACTH stimulation test. Participants will not need a washout of their asthma medications for unscheduled visits due to asthma worsening.
Short-acting β-agonists	Regular scheduled use of SABA is not allowed from Visit 1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP. Short-acting β-agonist rescue use is allowed if needed.

Additional maintenance controllers	Participants on theophyllines should have blood concentration levels within therapeutic range documented before proceeding in the study.
Inactive/killed vaccinations (eg, inactive influenza)	Allowed provided they are not administered within 5 days before or after any study visit.
Allergen immunotherapy	Allowed if participant has been receiving stable therapy for at least 30 days prior to Visit 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as study drug
Prednisone/prednisolone	Allowed provided it is not administered at least 24 hours prior to any morning cortisol/ACTH stimulation test
High-dose ICS (see Appendix I)	Allowed; however, ICS (or ICS/LABA if in single inhaler) treatment should not be administered on the same day as morning cortisol/ACTH stimulation test (for participants taking a once-daily ICS/LABA formulation, eg, fluticasone furoate/vilanterol; participants must not take the treatment the night prior or the morning of any morning cortisol/ACTH stimulation test).
Immunosuppressive medication	Topical or nasal administration may be allowed at the discretion of the investigator
COVID-19 vaccination	If COVID-19 vaccination is in the best interest of the participant and they are vaccinated during the study, IP dosing can continue but IP is not recommended to be administered within 14 days before or 28 days after a dose of vaccine. Thus, if the participant receives a COVID-19 vaccination during the treatment period, it is recommended that the vaccination occurs at least 14 days from the last IP dose, and that the next IP administration be rescheduled or skipped to ensure the next IP dose is at least 28 days after the vaccine administration. The participant's COVID-19 vaccination schedule should follow country-specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the IP dosing/COVID-19 vaccination intervals are maintained.

Table 6 Prohibited Medications

Prohibited medication/Class of drug	Usage
Macrolides, antivirals, and azole therapies	Chronic treatment with macrolides, antivirals, or azole therapies are not allowed during the study. If a participant has been receiving long-term (> 2 weeks) treatment of these therapies, all such medications need to be stopped 30 days or 5 half-lives, whichever is the longer, prior to the date informed consent is obtained. If a participant requires short courses of these medications (short course defined as ≤ 2 weeks), they should be stopped at least 1 week prior to any morning cortisol level/ACTH stimulation test.
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed within 15 days prior to Visit 1 and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Live attenuated vaccines	Not allowed 30 days prior to the date of Visit 1, and during the study including the follow-up period.
Immunosuppressive medications	Use of immunosuppressive medications (including, but not limited to, methotrexate, troleandomycin, cyclosporine, azathioprine, intramuscular long-acting depot corticosteroid, any experimental anti-inflammatory therapy, or oral/parenteral/intra-articular corticosteroids for reasons other than asthma) is not allowed except maintenance use of OCS for asthma if present at baseline and rescue use of systemic corticosteroids (oral, intravenous, or intramuscular) to treat an asthma exacerbation. Immunosuppressive medications must be discontinued 3 months or 5 half-lives (whichever is longer) prior to Visit 1; during the treatment period; and 3 months or 5 half-lives (whichever is longer) after the last dose. For flare-ups of non-asthma related indications (eg, arthritis, crohn's disease, AD) or AE/SAE requiring temporary OCS use (or temporary increase in maintenance OCS), a short course of OCS (≤ 2 weeks) use is allowed anytime during the study. Use of OCS for nasal polyposis, allergic rhinitis, or related eosinophilic conditions is not allowed.
Immunoglobulin or blood products	Receipt of immunoglobulin or blood products is not allowed within 30 days prior to Visit 1 and throughout the entire treatment period.
Any marketed (eg, omalizumab, mepolizumab, reslizumab) or to be marketed or investigational biologic treatment	Not allowed 4 months or 5 half-lives (whichever is longer) prior to the date of Visit 1, throughout the entire, period (even if the participant has discontinued IP) and until the follow-up visit (Week 64).

Other investigational products (including investigational use of an approved drug)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to Visit 1, and throughout the IP treatment and until the follow-up visit (Week 64).
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, and throughout the IP treatment and preferably 4 weeks after the last dose of IP.

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

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

If the participant received one (or more) COVID-19 vaccination(s) prior to enrolment, this needs to be recorded in the eCRF.

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medicine

6.5.1.1 Management of Asthma Exacerbations During Treatment Period

Participants who experience an exacerbation during the treatment period may remain on the study drug at the investigator's discretion. Asthma exacerbations will be treated with oral or other systemic corticosteroids according to standard clinical practice.

- **Induction phase:** If a participant experiences an exacerbation during the induction phase, the start of the OCS dose reductions may be delayed. After the OCS bolus/burst to treat an exacerbation is complete, the participant may be returned to a one-step higher dose level (or more if considered necessary by the investigator) than what was prescribed when the exacerbation occurred. The investigator may decide to maintain the same OCS dose. The participant's OCS dose should be stable for at least 2 weeks before entering the OCS reduction phase
- **Oral corticosteroids reduction and maintenance phase:** If a participant experiences an exacerbation during the OCS reduction and maintenance phase, the investigator may do one of the following for at least 2 weeks after completion of the OCS bolus/burst:
  - The participant may be returned to a one-step higher dose level (or more if considered necessary by the investigator) than what was prescribed when the exacerbation occurred

or

- The same OCS dose may be maintained at a stable dosage and then OCS down-titration may be continued once the participant recovers from the exacerbation.

Further dose reductions during this phase will be considered as per the investigator's opinion (except from Week 48 onwards, when no further OCS dose reduction is allowed). After recovery from the first exacerbation, the participant will be allowed to proceed with another attempt to reduce their OCS dose; however, they would follow a lower speed of OCS down-titration (reductions Q4W; Table 8).

In case of a second exacerbation, no further OCS daily dose reduction will be allowed, and the participant will continue the same dose or will return to a one-step higher dose level (or more as considered necessary by the investigator) than what was prescribed when the exacerbation occurred. The participant will then continue the same dose through the end of the study.

6.5.1.2 Other Rescue Medicine

Rescue use of SABA administered via nebulisation is discouraged, except as urgent treatment during an asthma exacerbation.

6.5.2 Bronchial Thermoplasty

Participants should not be treated with bronchial thermoplasty during the study or for 12 months before Visit 1.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Participants who complete Visit 16 should be given standard of care, including commercially available tezepelumab, at the discretion of the investigator. In the UK, participants who complete the study are eligible to apply to the UK Tezspire[1] Patient Assistance Program for

[1] Tezepelumab trade name.

access to tezepelumab in case it is not yet commercially available.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) tezepelumab.

Reasons for discontinuation of study intervention may include:

- Participant decision: The participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Incorrectly enrolled/dosed participant in whom the inclusion/exclusion criteria violation would put the participant at undue risk.
- Adverse event for which the investigator judges continued treatment may put the participant at undue risk.
- Severe noncompliance with the Clinical Study Protocol (CSP).
- Pregnancy (see Section 8.3.11).
- Development of any study specific criteria for discontinuation, including:
  - An anaphylactic reaction to the IP requiring administration of epinephrine
  - A helminth parasitic infestation not responding to anti-helminth treatment
  - Any malignancy except participants who develop basal cell carcinoma or localised 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 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase of ≥ 8 × ULN
  - Confirmed ALT or AST increase of ≥ 5 × ULN for more than 2 weeks
  - Confirmed ALT or AST increase of ≥ 3 × ULN and total bilirubin of ≥ 2 × ULN
  - ALT or AST of ≥ 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%).

For discontinuation pertaining to COVID-19, please see Appendix C.

A participant who decides to discontinue study drug will always be asked about the reason(s)

and the presence of any AEs. The reason for premature discontinuation of tezepelumab should be documented in the source documentation and recorded in the eCRF.

All participants who prematurely discontinue study drug should:

- **return to the study site and complete the procedures described for the IPD Visit within 4 weeks (± 7 days) after last tezepelumab administration,**
- **and have a follow-up visit 16 weeks after last tezepelumab administration (± 5 days) (see Table 1, Visit 16).**

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

At the IPD Visit the participants will be given the following 3 options as to how they will be followed:

1. The participant should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding IP administration) until the EOT visit at Week 52 (± 5 days).
2. The participant will be offered follow-up on a monthly basis via telephone calls while continuing ePRO data collection on the handheld device at home (no further procedure will be performed) until the participant completes the on-site EOT visit at Week 52 (± 5 days).
3. If the participant cannot or does not wish to comply with any of the options above (or any component of them such as only telephone-based visits without completion of the ePRO data), the investigator will contact the participant via telephone at 52 weeks after baseline. No other study assessments will be performed prior to this contact.

Participants who discontinue IP with option 1 or 2 are allowed to further reduce their OCS dose following the same protocol-specified OCS dose reductions scheme as participants being still on-treatment.

If the last study intervention administration was after Week 36 for options 1 or 2, the participant will return to the clinic for an EOT visit at Week 52 (± 5 days). For option 3, the investigator will contact the participant at 52 weeks post baseline.

If a participant chooses option 1, all assessments will be completed as per the SoA as indicated in Table 1. If a participant chooses option 2 or 3, the key information to be collected during the telephone calls are AESIs/DAEs/SAEs, changes in concomitant medication, and asthma exacerbation information.

Participants who initially choose options 1 or 2 and subsequently cannot or do not wish to comply with the requirements of their option can continue with a less intensive option

(ie, participants initially choosing option 1 can continue with options 2 or 3, participants initially choosing option 2 can continue with option 3).

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

Note that discontinuation from study intervention is NOT the same as a withdrawal from the study. The EOT visit will be completed immediately in the case of subsequent early withdrawal from the study. Participants who do not wish to have any follow-up contacts will be discontinued from the study. All participants who withdraw from the study must return the ePRO at the EOT visit (and at IPD visit for participants choosing option 3 above).

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an IPD Visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
    - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

The participants will return the study supplied equipment.

7.3 Lost to Follow-up

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

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

study visit:

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

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

8.1 Efficacy Assessments

8.1.1 Assessment of OCS Dose

All participants who meet eligibility criteria and enter the study will receive open-label

tezepelumab during the induction phase (Week 0 to Week 4). During this phase, participants should remain stable on their baseline (Week 0) OCS dose.

During the OCS reduction and maintenance phase, participants will reduce their OCS dose until the participant discontinues OCS or reaches the lowest OCS dose possible. OCS dose reduction may be slowed down in case of a first test result indicating complete AI, an elevated ACQ-6 score, or a first asthma exacerbation. OCS dose reduction will be stopped for the duration of the trial in case of a second test result confirming complete AI or a second asthma exacerbation (details provided in Section 8.1.2, Appendix M, and the schedule provided in Table 7).

No further reductions will be made to OCS dose from Week 48 onwards.

In case of exacerbations, participants will be managed as per details provided in Section 6.5.1.1. Additionally, in case the participant experiences asthma deterioration or an exacerbation, increase in the maintenance OCS daily dose is permitted per investigator discretion. Once the participant recovers from the first asthma exacerbation, further OCS dose reductions will be allowed at a slower pace during the reduction and maintenance phase as described in Table 8. No reductions are allowed after a second exacerbation.

All OCS dose changes, including temporary or permanent interruption of OCS reduction, will be documented in the source documentation and recorded in the appropriate eCRF form, along with reason for change.

8.1.2 OCS Dose Titration

At screening visit, participants will continue with or be switched to prednisone/prednisolone. For participants not previously receiving prednisone/prednisolone as OCS, the conversion table shown in Appendix D will be used to calculate the equivalent prednisone/prednisolone dose for dose titration.

The OCS dose titration in the reduction phase will be followed as per Table 7 depending on the initial OCS dose and HPA axis evaluation. Note: For participants who must reduce OCS dose more frequently than Q4W or if the scheduled dose reduction does not coincide with a clinic visit (see reduction scheme in Table 7), OCS dose reduction may occur remotely (eg, by telephone) instead of a clinic visit.

If Table 7 instructs to reduce dose by 5 mg increments, but the initial OCS dose is < 5 mg to the nearest dosing level, the 1st reduction would be smaller, rounding down to the nearest 5 mg, then continue on with 5 mg Q2W reductions (examples below):

- eg, 12.5 → 10 mg → etc.
- eg, 23 → 20→ 15→ 10 mg → etc.

- eg, 19 → 15 → 10 mg → etc.

If Table 7 instructs to reduce the initial dose by 2.5 mg increments, but the initial dose is < 2.5mg to the next dosing level, the 1st reduction would be smaller, rounding down to the nearest 2.5 mg, then continue on with 2.5 Q4W reductions (examples below):

- eg, 8 → 7.5 → 5 → etc.
- eg, 6.25 → 5 → etc.

Investigators may also choose to slow the down-titration to 1 mg Q4W once the participant reaches an OCS dose of 5 mg/day based on participant symptoms.

For all participants, HPA axis integrity will be evaluated after 4 weeks on 5 mg/day and prior to tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction and maintenance phase). See Section 8.2.1 for details.

Table 7 OCS Dose Titration Schedule During the OCS Reduction and Maintenance Phase

Initial OCS dose/day	**OCS down-titration to reach an OCS dose of:**				
	20 mg	**10 mg**	**7.5 mg**	**5 mg**	**0 mg**
> 20 mg	Reduction of 5 mg of the daily dose weekly until reaching dose of 20 mg/day	Reduction of 5 mg of the daily dose Q2W until reaching dose of 10 mg/day	2.5 mg of the daily dose Q2W until reaching dose of 7.5 mg/day	2.5 mg of the daily dose Q4W until reaching dose of 5 mg/day	**No AI:** reductions of 2.5 mg of the daily dose Q4W until reaching dose of 0 mg/day **Partial AI:** reductions of 1 mg of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
> 10 mg to ≤ 20 mg		Reduction of 5 mg of the daily dose Q2W until reaching dose of 10 mg/day	2.5 mg of the daily dose Q2W until reaching dose of 7.5 mg/day	2.5 mg of the daily dose Q4W until reaching dose of 5 mg/day	**No AI:** reductions of 2.5 mg of the daily dose Q4W until reaching dose of 0 mg/day **Partial AI:** reductions of 1 mg of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
> 7.5 mg to ≤ 10 mg			2.5 mg of the daily dose Q2W until reaching dose of 7.5 mg/day	2.5 mg of the daily dose Q4W until reaching dose of 5 mg/day	**No AI:** reductions of 2.5 mg of the daily dose Q4W until reaching dose of 0 mg/day **Partial AI:** reductions of 1 mg of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
> 5 mg to ≤ 7.5 mg				2.5 mg of the daily dose Q4W until reaching dose of 5 mg/day	**No AI:** reductions of 2.5 mg of the daily dose Q4W until reaching dose of 0 mg/day **Partial AI:** reductions of 1 mg of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
5 mg					**No AI**: reductions of 2.5 mg of the daily dose Q4W until reaching dose of 0 mg/day **Partial AI**: reductions of 1 mg of the daily dose Q4W and repeat test 2 months later[a] **Complete AI**: No OCS dose reduction and repeat test 3 months later[b]

[a] Partial AI cortisol testing confirmed with ACTH stimulation testing or the alternative method described in Appendix M. After repetition of the test 2 months later, the decision to further reduce OCS dose will be based on the morning cortisol test results. If test results are normal, the OCS dose may be reduced directly to 0 mg/day (if participant is receiving ≤ 3 mg); the participant will continue receiving 1 mg Q4W if still at risk. If complete AI is indicated, OCS dose will not be modified.
[b] If morning cortisol test results again indicate complete AI at 3 months, the OCS dose will not be modified as this is the final attempt. If morning cortisol test results indicate risk AI, then reductions will be 1 mg Q4W and, if normal, then reductions will be 2.5 mg Q4W.

Table 8 Rescue OCS Down-titration After Recovery From the First Event of an Asthma Exacerbation or Deterioration

Initial OCS dose/day	Rescue OCS down-titration after recovery from an asthma exacerbation or deterioration to reach an OCS dose of:		
	10 mg	**5 mg**	**0 mg**
> 20 mg	Reduction of 5 mg of the daily dose Q4W until reaching a dose of 10 mg/day	Reduction of 2.5 mg of the daily dose Q4W until reaching a dose of 5 mg/day	**No AI:** Reduction of 2.5 mg of the daily dose Q4W **Partial AI:** 1 mg/day of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
> 10 mg to ≤ 20 mg	Reduction of 5 mg of the daily dose Q4W until reaching a dose of 10 mg/day	Reduction of 2.5 mg of the daily dose Q4W until reaching a dose of 5 mg/day	**No AI:** Reduction of 2.5 mg of the daily dose Q4W **Partial AI:** 1 mg/day of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
> 5 mg to ≤ 10 mg		Reduction of 2.5 mg of the daily dose Q4W until reaching a dose of 5 mg/day	**No AI:** Reduction of 2.5 mg of the daily dose Q4W **Partial AI:** 1 mg/day of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]
5 mg			**No AI:** Reduction of 2.5 mg of the daily dose Q4W **Partial AI:** 1 mg/day of the daily dose Q4W and repeat test 2 months later[a] **Complete AI:** No OCS dose reduction and repeat test 3 months later[b]

[a] Partial AI cortisol testing confirmed with ACTH stimulation testing or the alternative method described in Appendix M. After repetition of the test 2 months later, the decision to further reduce OCS dose will be based on the morning cortisol test results. If test results are normal the OCS dose may be reduced directly to 0 mg/day (if participant was receiving ≤ 3 mg); the participant will continue receiving 1 mg Q4W if still at risk.

[b] If morning cortisol test results again indicate complete AI at 3 months, the OCS dose will not be modified as this is the last attempt. If morning cortisol test results indicate risk AI, then reductions will be 1 mg Q4W and, if normal, then reductions will be 2.5mg Q4W.

For prednisone/prednisolone 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 Appendix E for help dosing < 5 mg in relation to tablet strength.

8.1.2.1 Asthma Worsening or Exacerbation Preventing OCS Down-titration

The OCS dose titration will be interrupted in case of one of the following circumstances related to the asthma condition:

- Asthma deterioration will be assessed by the investigators when there is an increase in ACQ-6 scores of ≥ 0.5 from the value at Visit 2. If the ACQ-6 score at Visit 2 is missing, the 1st score recorded post-Visit 2 and pre-OCS reduction may be used as baseline value for the 0.5-point increase (however, it will not be used to impute the baseline for ACQ-6 analysis). At each visit, in addition to the participant's asthma symptoms, investigators will use the participant's weekly ACQ-6 scores and will further reduce the OCS dose unless asthma control is lost or AI prevents further dose reduction.

- In case of an asthma exacerbation that requires treatment with a temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days[2], in-patient hospitalisation, or ER admission, the OCS dose titration will be interrupted, and appropriate treatment will be administered as described in Section 6.5.1.1.

- After recovery from the first asthma deterioration or exacerbation, participants will be offered to continue OCS tapering down at a slower speed (ie, Q4W). If the first asthma deterioration or exacerbation occurs between Week 48 and Week 52, no further down-titration will be allowed.

[2] A single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.

In the case of a second event of asthma deterioration or exacerbation, the OCS reduction will be stopped, and the participant will continue on the same OCS dose or will return to a one-step higher dose level (or more as considered necessary by the investigator).

8.1.3 Assessment of Asthma Exacerbation

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

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
- An ER or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
- Inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours) due to asthma.

Note: Participants who experience an exacerbation during the screening period (between Visits 1 and 2) can be granted an extension of the screening period to ensure that the participant recovers from an asthma exacerbation and the OCS dose is stabilised.

The investigator must justify the decision for defining an event of worsening asthma as an exacerbation and record it in the source documents and eCRF.

The participant may remain in the study after an exacerbation and continue to receive study drug if the investigator judges that it is medically appropriate for the participant to do so and will be managed as per the details provided in Section 6.5.1.1.

Reasonable attempts should be made by the investigator to bring the participant into the study site for patient-initiated therapy for asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled visit or as part of a routine centre visit if the worsening happens to occur in line with a scheduled visit. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (eg, by the primary care provider or at an emergency department/hospital). Details should be entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medications due to exacerbations must be recorded in the appropriate module of the eCRF.

8.1.4 Spirometry

General requirements

Lung function (FEV_1) will be measured post-BD at the study site by spirometry using equipment provided by a central vendor. The central spirometry vendor will ensure that the spirometer meets American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations and that the study site personnel who will be performing the testing are properly certified.

Spirometry will be performed by the investigator, or designee, according to ATS/ERS guidelines (Graham et al, 2019).

Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual and in the monitoring plan.

- Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the study site.
- Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the study site.

Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the SoA (Table 1). It is recommended that all spirometry assessments are performed within ± 2 hours of the time of day that the Visit 2 spirometry is performed, if possible.

Post-BD spirometry technique

Post-BD spirometry procedures will be performed according to the SoA. Bronchodilation 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 participant has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45-µg metered dose; up to a maximum of 4 inhalations) can be used. 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 (eg, 2 inhalations instead of 4 puffs) can be used if there is a concern about any effect on the participant's heart rate, tremor or safety; the reason should be noted in the participant's medical record.

Further details on spirometry are provided in the spirometry manual.

Record keeping

A signed and dated copy of the spirometry printout must be kept at the study site for source

data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, and visit number.

Date and time (and result) of the spirometry data will be transcribed from source data into the electronic database.

8.1.5 Patient-reported Outcomes (PRO)

Patient-reported outcomes (PRO) data will be captured electronically at home using a handheld device (ePRO). The ePRO device is the only acceptable source; data from paper questionnaires are not acceptable. Site personnel will be trained on using the ePRO. Detailed procedures for using the ePRO and training the participants will be described in a separate instruction manual. Participants will be trained on at-home use of the ePRO at Visit 2. Training will include explanation of device functionality and its proper use. Participants will also be asked to verify completion of training on the ePRO. Participants will be asked to bring the device back at each study visit. Data for all PROs will be collected in accordance with Table 1. Participants should be informed that the recording made electronically cannot be retrospectively or prospectively entered and must be completed within a defined time window (± 2 days; this defined window may or may not coincide with the on-site visit). Participants will also be provided with information about when and where to request help if problems occur. The investigator/authorised delegate will check the participant's adherence to completing the ePRO as described in Table 1. There will be triggers in the PROs to alert investigators to signs of worsening of asthma and advising them to contact the participant for evaluation. Compliance alerts will remind participants to complete their assessments and notify investigators of poor compliance. These alerts will be described in a separate guide.

8.1.5.1 Asthma Control Questionnaire 6

The ACQ-6 is a shortened version of the ACQ that assesses asthma symptoms (night time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and use of short-acting β2 agonists), omitting the FEV_1 measurement from the original ACQ score.

Participants will be asked to recall how their asthma has been during the previous week by responding to 1 BD use question and 5 symptom questions.

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. Individual changes of ≥ 0.5 are considered to be clinically meaningful, and a decrease from baseline of at least 0.5 is the responder definition for ACQ-6.

From Visit 2 onwards, the participant will complete the ACQ-6 at home every 1 week as per the SoA (Section 1.3 and Section 8.1.5) until the EOT visit. The ePRO device will be set up with functionality to collect unscheduled ACQ-6 assessments on site if required by investigators at a visit.

At each visit, in addition to the information provided by the participant on his/her asthma disease, investigators will have access to the participant's ACQ-6 scores (completed by means of an ePRO) to evaluate whether the participant's condition has not significantly deteriorated (ie, increase in score of ≥ 0.5 from baseline [baseline defined as value at Visit 2 before tezepelumab administration]) and take the final decision to further reduce the OCS dose until the participant reaches the lowest OCS dose possible.

8.1.5.2 St. George's Respiratory Questionnaire

The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases (Jones et al, 1991). The questionnaire is divided into 2 parts: Part 1 consists of 8 items that pertain to the severity of respiratory symptoms in the preceding 4 weeks, and 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 component 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 component scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al, 1991). A decrease of 4 units in the SGRQ total score has been established as the criterion for minimal clinically meaningful difference (MCID) (Jones 2005). St. George's Respiratory Questionnaire responders will be those with ≥ 4 unit decreases compared to baseline in SGRQ total score.

The SGRQ will be completed at home, using the ePRO, as per the SoA (Section 1.3 and Section 8.1.5).

8.1.5.3 Asthma Quality of Life Questionnaire for 12 Years and Older

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma participants (Juniper et al, 1999; Juniper et al, 2005). The questionnaire comprises 4 separate domains (symptoms, activity limitations, emotional function, and environmental stimuli). Participants are asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores 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 home, using the ePRO, as per the SoA (Section 1.3 and Section 8.1.5).

8.1.5.4 Asthma Impairment and Risk Questionnaire

The AIRQ™ is a PRO tool intended to identify patients 12 years and older whose health may

be at risk because of uncontrolled asthma. It has 10 questions that ask about respiratory symptoms, activity limitation, sleep, rescue medication use, social activities, exercise, difficulty controlling asthma, and exacerbations. All items have a yes/no response option and the tool is scored by summing the total number of 'yes' responses. This sum score is used to assess level of asthma control where: 0 to 1 is well controlled, 2 to 4 is not well controlled, and 5 to 10 is very poorly controlled. Thus, a higher score indicates worse control status.

The AIRQ™ items have 2 different recall period: The first 7 impairment items are evaluated over the past 2 weeks and the last 3 risk items over the past 3 months or the past year. This study will use the past 12-month recall. The AIRQ™ will be administered and completed on the ePRO by the participant, on-site as per the SoA (Section 1.3). The AIRQ™ is estimated to take approximately 3 minutes to complete.

8.1.5.5 Sino-nasal Outcome Test

The Sino-Nasal Outcome Test 22 (SNOT-22) is a condition-specific HRQoL assessment which captures patient-reported physical problems, functional limitations, and emotional consequences of sino-nasal conditions (Piccirillo et al 2002, Hopkins et al 2009). Patient-reported symptom severity and symptom impact over the past 2 weeks are captured via a 6 -point scale (0- No Problem to 5- Problem as bad as it can be). The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes). A Minimal Importance Difference (MID) of 8.90 has been established for individual score change (Hopkins et al 2009).

The SNOT-22 will be completed only by participants with symptoms of chronic sinusitis (at screening), at home, as per the SoA (Section 1.3 and Section 8.1.5).

8.1.5.6 Participant Perception of OCS

This is a new survey to be developed for this study including one or 2 questions designed to learn about how participants feel about any change in their daily OCS dose (decrease or lack thereof) to be assessed, at home, as per the SoA (Section 1.3 and Section 8.1.5). Responses will be scored and change from baseline calculated.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.2.1 Hypothalamic-pituitary-adrenal Axis Evaluation

For all participants, HPA axis integrity will be evaluated after 4 weeks on 5 mg/day and prior to tapering down the OCS dose (for participants with baseline OCS doses equal to 5 mg/day, this will be assessed 4 weeks after the first dose of tezepelumab administration and before initiation of the OCS reduction phase).

First, a screening method with morning serum cortisol is done (8-9 am morning cortisol level), to evaluate whether the participant has:

- Normal cortisol levels (Table 9)
- Complete AI (Table 9).

Cortisol levels from the morning cortisol test that are below normal range and above the complete AI range are considered 'indeterminate' (Table 9), and require additional testing described below (for sites where tetracosactide is not available or not registered, please see Appendix M).

If the morning cortisol is in the indeterminate range, then the ACTH stimulation test is done within approximately 1 week (see Section 8.2.1.2 for details). The ACTH stimulation test is more specific than the morning cortisol test, and can determine whether the participant has:

- Normal cortisol levels: > 450 nmol/L (> 675 nmol/L for participants taking oestrogen-containing contraceptives)
- Complete AI: < 250 nmol/L (< 375 nmol/L for participants taking oestrogen-containing contraceptives)
- Partial AI: 250 to 450 nmol/L (375 to 675 nmol/L for participants taking oestrogen-containing contraceptives).

For morning serum cortisol and ACTH stimulation tests, hold OCS dose and other concomitant medications that could interfere with cortisol results as follows (see Section 6.5):

- The last OCS dose should be taken ≥ 24 hours prior to testing
- Participants must not take ICS (or ICS/LABA if in single inhaler) treatment on the morning of the morning cortisol level/ACTH stimulation test (for participants taking a once-daily ICS/LABA formulation, eg, fluticasone furoate/vilanterol, participants must not take the treatment ≤ 24 hours prior to the morning of the morning cortisol level/ACTH stimulation test)
- If a participant requires a short course of macrolides, antivirals, or azoles, there must be a window of ≥ 1 week prior to the testing of cortisol levels.

The process will be as described in Figure 3.

Figure 3 Hypothalamic-pituitary-adrenal Axis Evaluation

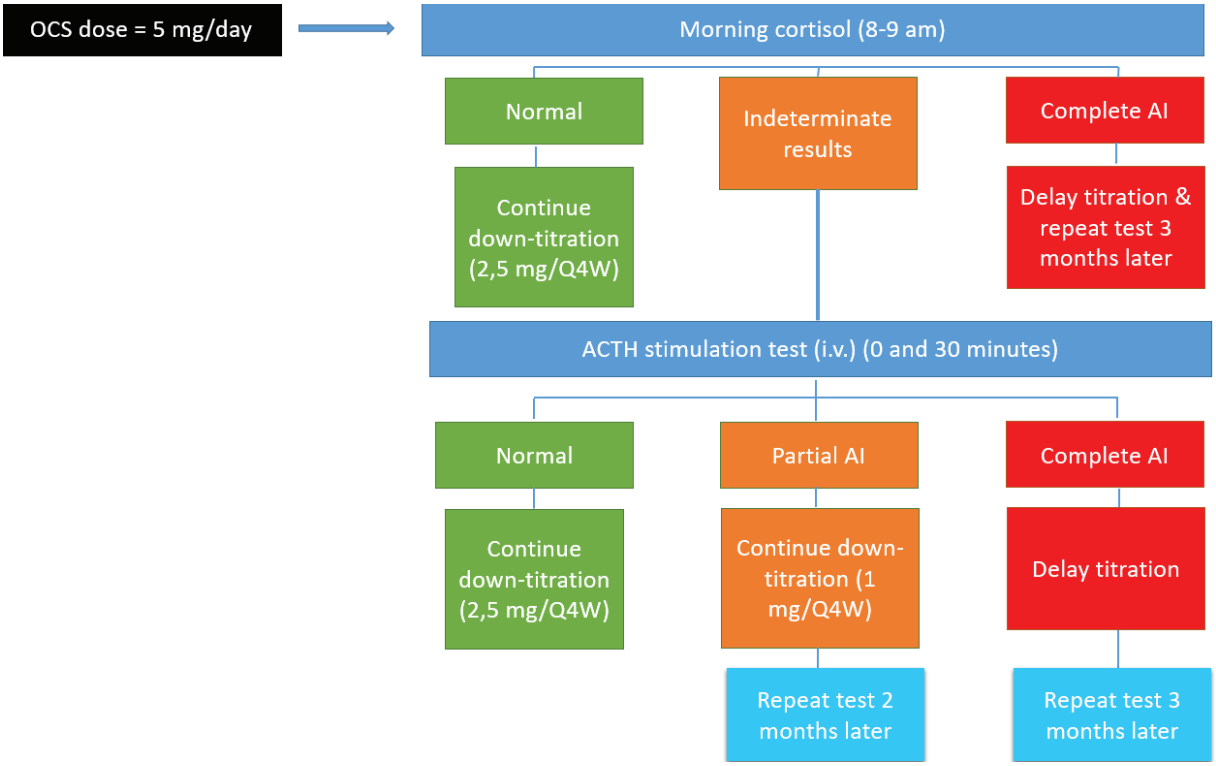


Figure 3: For normal cortisol levels with concurrent signs/symptoms of AI, OCS down-titration should continue at a slower pace (1 mg Q4W). For complete AI identified via morning cortisol testing, refer to Section 8.2.1.1 for instructions on 3-month repeat testing. For partial AI or complete AI identified via ACTH stimulation test see Section 8.2.1.2 for instructions on 2-month or 3-month repeat testing respectively.

8.2.1.1 Morning Cortisol Test

The morning cortisol test will be done in all participants 4 weeks after reaching the 5 mg dose of OCS, and before further dose reductions. It is also done 3 months after a participant has completed a test indicating complete AI.

Serum samples for cortisol will be collected between 8 and 9 am and will be sent to a central laboratory for evaluation.

The following values will be used to define AI status for the morning cortisol test:

Table 9 Cortisol Status

AI status	SI units	Participants taking oestrogen-containing contraceptives
Normal	>350 nmol/L	>700 nmol/L
Indeterminate results	100 - 350 nmol/L	200 - 700 nmol/L
Complete AI	<100 nmol/L	<200 nmol/L

Once the results are available, the site will inform the participant of the results via telephone. For sites where tetracosactides are available, and depending on the result, the actions that will be implemented are as follows:

- If cortisol levels are within normal range and the participant does not exhibit any signs and/or symptoms of AI, the participant will continue OCS down-titration by 2.5 mg Q4W
- If cortisol levels are within normal range but the participant exhibits signs and/or symptoms of AI, then OCS down-titration should continue at a slower pace (1 mg Q4W).
- If cortisol levels are below the normal range and above the complete AI range (indeterminate result), then the participant will be instructed to maintain the current OCS dose and come back to the site within 1 week for an ACTH stimulation test (Section 8.2.1.2)
- If complete AI is confirmed, sites will inform participant that the OCS dose will remain the same without further reduction until there is evidence of recovery from the complete AI without worsening of asthma control. The morning cortisol test and associated clinical assessments (see Table 1) will be repeated 3 months later. After the repeat morning cortisol test, the site will inform the participant based on the results as follows:
    - If morning cortisol results indicate normal cortisol values, then reductions will be 2.5 mg Q4W, and the participant would subsequently move to maintenance at the OCS lowest possible dose
    - If morning cortisol results are indeterminate, then reductions will be delayed further, and the participant would return approximately 1 week later for an ACTH stimulation test:
        - If normal result after ACTH stimulation (Table 10): reduce by 2.5 mg Q4W then move to maintenance at the lowest possible dose
        - If the result is partial AI after ACTH stimulation (Table 10): reduce by 1 mg Q4W then move to maintenance at the lowest possible dose
        - If complete AI result after ACTH stimulation (Table 10): OCS dose will not be reduced further, and participant will continue at the current OCS dose.
    - If morning cortisol tests again indicate complete AI at 3 months, the OCS dose will not be modified as this is the final attempt. The participant would move to maintenance at the current OCS dose.

For sites where tetracosactide is not available or not registered, please see Appendix M.

8.2.1.2 Adrenocorticotropic Hormone Stimulation Test

The tetracosactide (also known as Synacthen, Cortrosyn, or cosyntropin) ACTH stimulation test will be performed when morning cortisol levels are in the indeterminate range (for sites

where tetracosactide is not available or not registered, please see Appendix M).

Options for sourcing tetracosactide are provided below:

- Acquire Synacthen or Cortrosyn 250 mg for intravenous (IV) or intramuscular (IM) injection locally and submit invoices for reimbursement (preferred option, if possible).
- If the medication is available in your country but the site cannot directly acquire the medications, then Labcorp or AstraZeneca may arrange for delivery to the site.
- If the medication is available in your country, but delivery to the site is delayed, the site may request permission from Labcorp to use the alternative method described in Appendix M.
- Sites in countries where the medications are not registered must use the alternative method in Appendix M.

The following values will be used to define AI status for the ACTH stimulation test:

Table 10 ACTH Stimulation Status

AI status	SI units	Participants taking oestrogen-containing contraceptives
Normal	>450 nmol/L	>675 nmol/L
Indeterminate results	250 - 450 nmol/L	375 - 675 nmol/L
Complete AI	<250 nmol/L	<375 nmol/L

The sites will inform the participant of the morning cortisol results via phone call, and a visit will be scheduled within 1 week for the ACTH stimulation test.

An injection of the fast-acting ACTH stimulant will be given IV or IM. Serum samples for cortisol will be collected between 8 and 9 am and will be sent to a central laboratory for evaluation as follows: a blood sample for serum cortisol will be collected at 0 minutes (before IV or IM injection) and 30 minutes after the IV or IM injection. Peak cortisol response at 30 minutes will be selected to assess AI, and the OCS taper will follow the applicable scenario below:

- If a normal peak cortisol level is demonstrated at 30 minutes, the site will inform the participant via phone call, and the participant will continue OCS dose titration by 2.5 mg Q4W aiming for 0, and subsequently would move to maintenance at the lowest possible OCS dose

- If the peak cortisol level at 30 minutes is below the normal range yet above the level of complete AI (partial AI), or there are some signs/symptoms of AI or corticosteroid withdrawal syndrome, the site will inform the participant to continue OCS down-titration at a slower pace (1 mg Q4W). The morning cortisol test and associated clinical assessments (see Table 1) will be repeated 2 months later, as per the process described in Figure 3.
- If peak cortisol level at 30 minutes indicates complete AI, sites will inform participants that the OCS dose will remain the same without further reduction until there is evidence of recovery from the complete AI without worsening of asthma control. The morning cortisol test and associated clinical assessments (see Table 1) will be repeated 3 months later, as per the process described in Figure 3.

8.2.1.3 Management of Participants with Partial or Complete Adrenal Insufficiency

Any participant showing partial or complete AI at initial or subsequent morning serum cortisol or ACTH stimulation test, will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards.

In the absence of evidence of HPA axis recovery, participants should be instructed to carry some type of identification (worn around the neck or wrist or carried as a card) warning of their clinical status of corticosteroid dependence along with a medical report detailing the treatment measures needed, including IM hydrocortisone requirements. Corticosteroid supplementation is recommended during situations of stress (ie, fractures, surgery, trauma, labour, invasive dental procedures, severe systemic infections, major burns, and fever > 38.5ºC).

Additionally, participants who have partial or complete AI at EOT (or sooner if deemed appropriate) should be followed up by an endocrinologist or other appropriate specialist.

8.2.2 Physical Examinations

- A complete physical examination will be performed and include assessments of the following; general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the general appearance, abdomen, cardiovascular, and respiratory systems. For the brief physical examination, only information on whether the assessment was performed or not is to be recorded.

Physical examination will be performed at timepoints as specified in the SoA (Table 1).

8.2.3 Clinical Safety Laboratory Assessments

Blood samples will be collected for clinical safety laboratory assessments. Laboratory safety assessments (listed in Table 11) will be performed in a central laboratory. For information on methods of collection, assessment, labelling, storage, and shipment of samples, please refer to the separate laboratory manual. Safety samples will be collected at screening according to the schedule provided in Table 1. Laboratory results should be reviewed by the investigator/authorised delegate and evaluated for abnormalities. Any laboratory abnormalities considered to be significant in the investigator/authorised delegate's judgement should be reported if they meet the definition of an SAE (as defined in Appendix B 2), DAE, or AESI (see Section 8.3.6).

The copy of the laboratory results report should be signed and dated by the investigator/authorised delegate and retained at the study site.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

The following laboratory variables will be measured at screening:

Table 11 Laboratory Safety Variables at Screening

Haematology/Haemostasis (Whole Blood)	**Clinical Chemistry (Serum)**
Haemoglobin (Hb)	Sodium (Na^+)
Red blood cell count	Potassium (K^+)
Absolute leukocyte count (white blood cell count) and differential	Low-density lipoprotein
Platelet count	Gammaglutamyl transpeptidase (GGT)
Haematocrit (Hct)	Glucose
Glycated haemoglobin (HbA1c)	Creatinine
	Alkaline phosphatase (ALP)
	Alanine amino transferase (ALT)
	Aspartate amino transferase (AST)
	Bilirubin, total
Serology (serum)	
Hepatitis B surface antigen	
Hepatitis C antibody	

NB. In case a participant shows an AST **or** ALT ≥ 3 × upper limit of normal (ULN) together with total bilirubin ≥ 2 × ULN, please refer to Appendix F. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

The following tests are applicable to female participants only and will be conducted according to the schedule provided in Table 1.

- Serum β-HCG: To be done at screening visit (Visit 1) only for WOCBP and analysed at central laboratory.
- Follicle-stimulating hormone: To be done at screening visit (Visit 1) only for female participants < 50 years who have been amenorrhoeic for ≥ 12 months to confirm postmenopausal status
- Urine HCG: To be performed at the study site for WOCBP at timepoints indicated in the SoA (Table 1) using a dipstick before any invasive study procedures (eg, blood sampling) are performed and before study drug administration. Positive urine test result must be confirmed with serum β-HCG.

8.2.4 Other Safety Assessments

8.2.4.1 Weight and Height

Weight and height will be measured according to the schedule provided in Table 1. Height will be taken at screening, Visit 1, only. The participant's weight will be recorded in kilograms, and height in centimetres. Weight and height measurements will be performed in light clothing and with shoes off. Body mass index will be calculated, and not captured in the eCRF.

8.3 Adverse Events and Serious Adverse Events

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

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

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

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE to be collected in this study.

Only events that fall into the following categories will be collected in this study:

- SAEs (as defined in Appendix B 2)
- AEs leading to discontinuation of tezepelumab (DAEs)
- AESIs (see Section 8.3.6).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

SAEs, DAEs, and AESIs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (16 weeks after the last dose of IP).

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

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for SAE, DAE, and AESI:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused participant's withdrawal from study (yes or no)
- Outcome.

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

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

8.3.3 Causality Collection

The investigator should assess causal relationship between IP and/or investigational medical

device and AE and/or incident, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the IP?’.

For SAEs and serious incidents, causal relationship should also be assessed for other medication and study procedures and/or medical devices. 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.

8.3.4 Adverse Events Based on Signs and Symptoms

AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: ‘Have you had any health problems since the previous visit/you were last asked?’, or revealed by observation will be collected and recorded in the eCRF, if they meet the definition of an SAE (as defined in Appendix B 2), DAE, or AESI (see Section 8.3.6). When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in laboratory values, vital signs, or physical examinations performed as usual care during the study should only be reported as AEs if they fulfil the criteria for an SAE, DAE, or AESI.

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 (only if it fulfils any of the SAE, DAE, or AESI) and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator will use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

The signs and symptoms of AI will not be recorded unless they are an SAE, DAE, or AESI (eg, adrenal crisis, see Appendix J).

8.3.6 Adverse Events of Special Interest

An AESI is an event of scientific and medical interest towards improving the understanding of the IP. An AESI may be serious or non-serious. For this study, AESIs include:

- Serious hypersensitivity reactions (see Appendix G)
- Helminth infections
- Serious infections (including serious opportunistic infections)
- Malignancy
- Guillain Barre Syndrome
- Serious cardiac events
- Adrenal crisis (see Appendix J).

An AESI that meets one of the seriousness outcomes listed in Appendix B 2 will be categorised as an SAE for the purposes of follow-up responsibility and safety reporting. A non-serious AESI will be categorised as an AE.

8.3.7 Hy's Law

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

8.3.8 Disease Under Study

When collecting SAEs, DAEs, and AESIs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Symptoms of disease under study are those which might be expected to occur as a direct result of asthma (wheeze, cough, chest tightness, dyspnoea, breathlessness, and phlegm). These symptoms will be recorded as AEs only when:

- The sign or symptom is serious according to definitions; see Appendix B
- The participant discontinues the IP due to the sign or symptom.
- The sign or symptom is an AESI

Asthma exacerbations occurring during the treatment period should be recorded in the eCRF. An asthma exacerbation should be recorded as an AE only if it fulfils any of the above criteria for an SAE or DAE.

8.3.9 Reporting of SAEs

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

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day (ie, immediately but **no later than**

24 hours of when he/she becomes aware of it).

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours)** of when he/she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC; Medidata Rave® 2018.1.1) system, an automated email alert is sent to the designated AstraZeneca representative.

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

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

8.3.10 Reporting of SAEs/DAEs/AESIs in Relation to COVID-19

All SAEs/DAEs/AESIs should be reported in line with instructions for safety reporting documented in the CSP. For participants experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the AE will be recorded accordingly. If a participant presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

- If the test is positive, record “COVID-19 positive” in the SAE/DAE/AESI field.
- If the test is negative, record “COVID-19 negative” in the SAE/DAE/AESI field, along with the SAE/DAE/AESI signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the investigator, are suggestive of COVID-19 infection, record “COVID-19 suspected” in the SAE/DAE/AESI field. If the investigator has other concurrent diagnoses for the participant’s signs and symptoms (eg, pneumonia), these will be recorded as separate SAEs/DAEs/AESIs.

8.3.11 Pregnancy

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

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

8.3.11.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.11.2 Paternal Exposure

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

8.3.12 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** (ie, immediately but **no later than 24 hours** of when he/she becomes aware of it).

Medication errors should be documented in the Medication Error Report.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.3.13 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 recognise and treat anaphylaxis (Lieberman et al, 2010). Details on anaphylaxis management are provided in Appendix G.

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

- 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 (BP) or symptoms of end-organ dysfunction
- Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms and/or persistent gastrointestinal symptoms
- Reduced BP after exposure.

Participants will have had a pre-assessment (ie, lung function) prior to IP administration. At Visits 2 and 3, participants should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, participants will be observed for a minimum of 1 hour after IP administration for any such reaction.

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

8.3.14 Medical Device Deficiencies

A combination product with a device constituent is being used in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection

and documentation of events meeting the definition of a medical device deficiency that occur during the study with the APFS device constituent of the tezepelumab combination product.

Medical device deficiencies from this study will be collected and monitored to ensure the safety of participants and improve the safety and performance of the device.

Medical device deficiencies will not be presented in the CSR, but where required by local regulations, deficiencies will be summarised in the relevant periodic report.

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

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix K.

The AstraZeneca Product Complaint Intake Form will be used to collect the deficiency. For third-party medical devices, the deficiency will be reported to the manufacturer, who will be responsible for fulfilling their regulatory obligations.

8.3.14.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify AstraZeneca.

The method of documenting medical device deficiencies is provided in Appendix K.

8.3.14.2 Follow-up of Medical Device Deficiencies

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

8.3.14.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies will be reported to AstraZeneca within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The AstraZeneca Product Complaint Intake Form will be sent to AstraZeneca by email as follows:

  Reporting a Medical Device Deficiency to Clinical Supply Chain

  For all medical device deficiencies, the Product Complaint Intake Form will be sent to the Clinical Supply Chain Representative at the mailbox GCSCProductComplaintOriginators@astrazeneca.com

  Reporting a Medical Device Deficiency with an associated SAE to Participant Safety

  Where the medical device deficiency has caused an SAE, the Sponsor Study Representative works with the Study Site Investigator to complete the Clinical Study Medical Device/Device Constituent Report Form. The Sponsor Study Representative then forwards the Clinical Study Medical Device/Device Constituent Report Form to the Patient Safety Data Entry Site at the mailbox AEMailboxClinicalTrialTCS@astrazeneca.com 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.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.3.9.
- AstraZeneca will be the contact for the receipt of medical device deficiency reports.

8.3.14.4 Regulatory Reporting Requirements for Device Deficiencies

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

8.4 Overdose

For guidance refer to AstraZeneca SOP Reporting of Individual Safety Events in Clinical Studies.

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

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

An overdose with associated SAEs, DAEs, or AESIs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the Case Report Form and on the Overdose Case Report Form module.

An overdose without such associated symptoms is only reported on the Overdose eCRF 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/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 overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix H.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity will not be assessed in this study.

8.5.3 Pharmacodynamics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA. Instructions for sample collection, processing, storage, and

shipment can be found in the separate laboratory manual provided to the sites.

For storage, re-use, and destruction of biomarker samples, see Section 8.5 and Appendix H.

8.6.1 Fractional Exhaled Nitric Oxide

Airway inflammation will be evaluated using a standardised single-breath FeNO test in accordance with the SoA. A single exhalation technique recommended by the manufacturer will be followed (Alving et al, 2017). The change from baseline in FeNO will be evaluated descriptively for association with OCS dose reduction during treatment with tezepelumab.

Participants will be asked whether they have had a respiratory infection in the 2 weeks prior to the measurement. The FeNO measurements will not be performed within 2 weeks of a respiratory infection. The FeNO test will be performed prior to spirometry. Participants should not eat or drink 1 hour prior to having the FeNO test. 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.

All post-Visit 2 FeNO assessments should be performed within ± 2 hours of the time that the Visit 2 FeNO was performed.

8.6.2 Total Serum IgE and Specific IgE

Serum samples will be collected. The levels of total IgE and seasonal and perennial allergen-specific IgE will be tested by a central laboratory in accordance with the SoA (Table 1). Serum samples will be tested for seasonal and perennial specific IgE to identify subgroups of patients with sensitivities to these allergens. Primary and secondary endpoints may be evaluated in these subgroups. Serum samples will be tested for total IgE levels to descriptively evaluate their association with OCS-dose reduction during treatment with tezepelumab.

8.6.3 Peripheral Blood Eosinophils

Blood samples for the analysis of peripheral blood EOS will be analysed in a central laboratory as part of the routine haematology assessment (complete blood count) at timepoints specified in the SoA (Table 1). Blood samples will be tested to measure blood eosinophil counts. The blood eosinophil count at baseline will be used to define subgroups for evaluation of endpoints. In addition, the change from baseline in blood eosinophil count during the study will be used descriptively to evaluate an association with OCS-dose reduction during treatment with tezepelumab.

8.7 Optional Genomics Initiative Sample

Optional genomics initiative research is not applicable in this study.

8.8 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The statistical analyses will be fully described in the SAP, as appropriate. Statistical analyses for this study will be conducted using SAS® v9.4 or latest version in a secure and validated area.

There is no predefined study hypothesis to test in this study, as such, no multiplicity control strategy will apply.

9.2 Sample Size Determination

The sample size for this study is based on the ability to provide sufficient precision in point estimates, both in the Full Analysis Set (FAS) and subsets for statistical analysis.

The primary outcomes variables, the proportion of participants who have discontinued OCS without loss of asthma control and the proportion of participants who reduced OCS dose to ≤ 5 mg/day without loss of asthma control. For the sample size estimation, a success rate of 50% is assumed. Estimate precision is expressed in a two-sided 95% CI distance from the point estimate of a 50% success rate to confidence limit for a total of approximately 300 participants. Calculations were conducted using the exact Clopper-Pearson CI formula for a single proportion in R v.4.0.1 (function *binom.test()* from *stats* package).

A total sample size of approximately 300 participants entering the induction phase is expected to provide 95% CIs for a single proportion extending approximately 5.8% from the point estimate of a 50% success rate. Estimates of the 95% CI of a > 50% success rate are incrementally smaller, as is shown in Table 12.

Table 12 Expected Distance Between Observed Proportion and Confidence Limit (Clopper-Pearson 95% CI Width)

Proportion of participants	Sample size					
	50	**100**	**150**	**200**	**250**	**300**
50	± 14.5	± 10.25	± 8.3	± 7.1	± 6.4	± 5.8
60	-14.8 +13.6	-10.3 +9.7	-8.3 +7.9	-7.1 +6.8	-6.4 +6.1	-5.8 +5.6
70	-14.6 +12.1	-10.0 +8.8	-8.0 +7.2	-6.9 +6.3	-6.1 +5.6	-5.5 +5.1
80	-13.7 +10.0	-9.2 +7.3	-7.3 +6.1	-6.2 +5.3	-5.5 +4.8	-5.0 +4.4

The table also shows that the 95% CIs for subpopulation analyses as small as 50 are < 15% for proportions between 50% and 80%.

Note: The planned interim analysis does not impact the sample size calculation.

9.3 Populations for Analyses

The following statistical analysis sets will be defined:

9.3.1 All Participants Analysis Set

Comprises all participants screened for the study and will be used for reporting of disposition and screening failures.

9.3.2 Full Analysis Set

Includes all enrolled participants who received at least one dose of tezepelumab, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study will be included up to the date of their study termination. All efficacy, demographics, baseline characteristics, and safety analyses will be performed using the FAS.

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

9.3.3 Currently or Historically Elevated EOS Population

Includes participants who received at least one dose of tezepelumab and with peripheral blood EOS count of ≥ 150 cells/μL assessed by central laboratory at Visit 1 or documented EOS count of ≥ 300 cells/μL in the past 12 months. Participants will be analysed irrespective of whether they prematurely discontinue, according to the intent-to-treat principle. Participants who withdraw from the study will be included up to the date of their study termination. Primary efficacy analyses, key demographics, and baseline characteristics will also be presented using the currently or historically elevated EOS population in addition to the FAS.

9.4 Statistical Analyses

There will be 2 DBLs. The primary DBL will be carried out after approximately 300 participants have completed 28 weeks. All data available at that time may be analysed with the main focus on estimates of a subset of the pre-planned analysis outputs at Week 28. Further detailed description of the statistical analyses described in this section will be provided in the

SAP which will be developed and finalized before the first participant is enrolled. The final DBL will be conducted once the last participant has completed the safety follow-up visit (Week 64) with the main focus on estimates on Week 52 (EOT).

Details regarding both database locks will be provided in the DMP which will be developed and signed off prior to the first patient enrolled.

9.4.1 General Considerations

No formal hypothesis will be tested in this study, and no multiplicity adjustment will be applied in the statistical analysis. No imputation will be performed beyond the approach defined for outcome measures. Imputation for partial date will be detailed in the SAP document.

In general, the last measurement at or prior to Visit 2 will serve as the baseline measurement. If there is no value at or prior to Visit 2, then the baseline value will not be imputed and will be set to missing.

The baseline OCS dose is derived as the most recent prescribed, daily maintenance OCS dose prior to Visit 2 (ie, the daily dose regimen that a participant is prescribed at the time of Visit 2). If the OCS dose is administered every other day, the total OCS dose over the 2 days will be summed and averaged.

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

Absolute change from baseline is defined as *(post-baseline value – baseline value)*. The percent change from baseline is defined as *{(post-baseline value – baseline value}/baseline value)*100%.*

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

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

Relevant medical history/current medical conditions will be summarised by System Organ Class (SOC) and Preferred Term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary using frequency counts and percentage of participants in the FAS.

Prior and concomitant medications, categorised according to the WHO Drug Dictionary which employs the Anatomical Therapeutic Chemical classification system, will be summarised as frequency counts and percentage of participants reporting usage. Prior medications are defined as those which stopped before first dose of IP. Concomitant medications are defined as those which either started or continued after first dose of IP.

Important protocol deviations will be defined prior to first participants enrolled. Participants will not be excluded from analysis sets on the basis of any important protocol deviations. The definitions of each category of important protocol deviation will be fully specified in the SAP. Details regarding statistical analysis will be provided in the SAP. In general, continuous endpoints will be summarised using the mean, the standard deviation, median, minimum value, and maximum value, and the categorical endpoints will be summarised using frequency counts and percentages. Two-sided 95% CI for proportions computed using exact Clopper-Pearson method may also be presented. Time to event data will be presented graphically using Kaplan Meyer curve.

In general, all data up to Week 28 or Week 52 will be included in the analysis, even if a participant discontinues treatment or changes background therapy other than OCS (treatment policy strategy). If a participant initiates therapy with other biologic for treatment of asthma, then only data collected up until the initiation of the other biologic treatment will be included in the analysis (hypothetical strategy).

In general, efficacy analyses will be based on planned treatment period, starting on the date of first dose of IP and ending on the date of the Week 28 or Week 52 visit or earlier study withdrawal date.

Safety analyses will be based on-treatment and/or on-study period. Details will be specified in the SAP. On-treatment period starts on the date of first dose of IP and ends on minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal). On-study period (planned treatment and follow-up) starts on the date of first dose of IP and ends on the study completion or withdrawal date. Data will be listed in participant-level data listings.

9.4.2 Global/Country Situation Considerations, Including COVID-19

Descriptive summaries to assess global/country situation impacts will be provided for evaluating visits impacted (missing visits, type of visits), exposure impacts, and AEs. Additional descriptive analyses may be needed to evaluate the impact of the global/country situation on this trial and its endpoints. Further details will be included within the SAP document.

9.4.3 Efficacy

9.4.3.1 Primary Endpoints

The following outcomes are designed to support the primary objective of the study:

- Proportion of participants who discontinue OCS without loss of asthma control
- Proportion of participants who reduce OCS dose to ≤ 5 mg/day without loss of asthma control

The baseline OCS dose is defined in Section 9.4.1. The final OCS dose is defined based on the prescribed maintenance dose, expressed as a dose per day, at Week 28 or Week 52. If the participant is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the participant is on every other day regimen, then the OCS dose is defined as the average amount prescribed to be taken each day. Final daily OCS dose will be derived as described in Table 13. Further details may be specified in the SAP.

Table 13 Final Daily Maintenance OCS Derivation

Situation	Final daily maintenance OCS dose
Initiation of therapy with another biologic for treatment of asthma	Last reported OCS dose[a] received by participant with asthma stability verified[b] prior to initiation of another biologic.
Premature withdrawal from the study	Last reported OCS dose[a] received by participant with asthma stability verified[b] at the time of study withdrawal.
Any other situation	Last reported OCS dose[a] received by participant with asthma stability verified[b]

[a] daily OCS dose is based on information collected in ECSYSCRT eCRF.
[b] Asthma stability is defined as no change in OCS dose for at least 2 weeks.

Each primary endpoint will be summarised by number and proportion (with 95% CI) of participants. The 95% CIs for proportions will be calculated using the Clopper-Pearson exact method.

Analysis of the primary endpoints will be based on both the FAS population and the current or historical elevated EOS population. In addition, primary endpoints will be summarised by pre-specified subgroups using FAS population including (but not limited to):

- Baseline EOS group: < 300/μL, ≥ 300/μL
- Baseline EOS group: < 150/μL, ≥ 150/μL.

Any further requirements for subgroups analysis and exact definition of all relevant categories where needed, will be pre-specified in the SAP.

9.4.3.2 Secondary Endpoints

The following outcomes are designed to support the secondary objectives of the study:

- Rate of annualised asthma exacerbation (all exacerbations; exacerbations associated with hospitalisation or ER visit, and exacerbation associated with hospitalisation only) at Week 28 or Week 52
- Proportion of participants who did not experience an exacerbation over 28 or 52 weeks
- Proportion of participants who did not experience an exacerbation associated with hospitalisation or ER visit over 28 or 52 weeks
- Proportion of participants who did not experience an exacerbation associated with hospitalisation over 28 or 52 weeks
- Proportion of participants with ≥ 50% reduction from baseline in daily maintenance OCS dose at Week 28 or Week 52
- Proportion of participants for each pre-specified categories of percentage reduction from baseline in daily maintenance OCS dose at Week 28 or Week 52:
  - ≥ 90% to ≤ 100% reduction; ≥ 75% to < 90% reduction; ≥ 50% to < 75% reduction; > 0% to < 50% reduction; no change or any increase.
- Mean change from baseline over time in:
  - percentage reduction from baseline in daily maintenance OCS dose
  - post-BD FEV_1
  - ACQ-6 scores
  - AQLQ(s)+12 total scores
  - SGRQ total scores.

The number and proportion (with 95% CI) of participants who remained exacerbation free, those who did not experience an exacerbation associated with hospitalisation or ER visit or with hospitalisation only, reduced the OCS as per predefined categories, and those defined as responders (based on ACQ-6, AQLQ(s)+12 or SGRQ total scores) will be summarised using the same approach as for the primary endpoint.

AAER (all asthma exacerbation and uniquely exacerbations associated with hospitalisation or ER visits, or with hospitalisation only), calculated in years over the study treatment period of interest as the total number of exacerbations in the period of interest divided by the total time at risk of interest. The 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. AAER will be summarised descriptively. Any asthma exacerbation that occurs within 7 days of the last date of additional 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 for a prior asthma exacerbation will be combined and counted as a single

exacerbation event. Further details on combining exacerbation events will be provided in the SAP.

For continuous secondary endpoints, an absolute (and relative if appropriate) change from baseline (eg, daily OCS dose, post-BD FEV_1, ACQ-6, AQLQ(s)+12, and SGRQ) will be summarised by timepoint using descriptive statistics. In addition, the change from baseline in each endpoint will be analysed using a model for repeated measures with the approach to intercurrent events described in Section 3. Results from the model will be tabulated (least square mean with 95% CI) and presented graphically. The response variable in the model will be the change from baseline (absolute and percentage, as appropriate) at each scheduled visit. Baseline value of the corresponding endpoint and baseline blood EOS count will be included in the model as covariate. Visit might be also included as covariate in the model, if appropriate. Details will be provided in the SAP. Moreover, the model for daily OCS dose will include a baseline OCS dose as additional covariates. The analysis will be performed on those participants who have at least one non-missing post baseline value in the FAS. Participant will be included in the model using the REPEATED statement (no RANDOM statement will be specified). Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant. If the 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 model.

All secondary endpoint analyses will be based on the FAS. Data will be summarised for the overall population and by pre-specified subgroups including (but not limited to):

- Baseline EOS group: $< 300/\mu L$, $\geq 300/\mu L$
- Baseline EOS group: $< 150/\mu L$, $\geq 150/\mu L$.

9.4.3.3 Exploratory Endpoints

Statistical analysis for exploratory endpoints will be described in the SAP.

All exploratory analyses will be based on the FAS.

9.4.4 Safety

SAEs, DAEs, AESIs and medical/surgical history will be coded using the latest version of the MedDRA. Medications will be classified according to the WHO Drug Dictionary.

The number and percentage of participants with an SAE, DAE, and AESI will be presented by SOC and PT. SAEs and AESIs will be summarised separately for the on-treatment and on-study periods.

On-treatment SAEs, DAEs, and AESIs will also be summarised by SOC, PT, and causality/relatedness (as determined by the investigator). Maximum intensity of an event will be listed.

Laboratory data will be summarised by summary statistics (means, medians, quartiles, ranges) of observed values. The incidence of clinically notable laboratory abnormalities will be summarised.

All safety analyses will be based on the FAS.

9.4.5 Other Analyses

Not applicable.

9.5 Interim Analyses

An interim analysis may be performed if approximately 50 participants complete Visit 4 before a data cut-off date planned on mid-April 2023. In case of interim analysis, all data available for those participants will be included in summaries. The analysis will address key efficacy and safety objectives during the OCS titration period for the purpose of publication. The results will not be used to change any element of the study design and the study will continue regardless of the results of interim analysis. The SAP will be amended to describe the interim analysis in more details.

9.6 Data Monitoring Committee

Not applicable.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Conference on Harmonisation (ICH) GCP Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A Scientific Committee consisting of internal AstraZeneca and external experts (pulmonologists, allergists, and endocrinologists) who have been involved in the design of the clinical study will advise the sponsor on changes to the study design and provide recommendations on issues related to the study conduct, if required. In addition, the committee will be involved in the review and interpretation of the study results. The Scientific Committee will be governed by a charter, detailing roles and responsibilities and processes.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. The eCRF contains an electronic audit trail and is 21 CFR Part 11 compliant.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

A 9 Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

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

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

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

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

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

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

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

Life-threatening

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

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

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

Intensity Rating Scale:

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

It is important to distinguish between SAEs 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 an 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 an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a

causal relationship, the event(s) will be assessed as ‘not related’.

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

B 4 Medication Error

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

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IxRS, 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) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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

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

Appendix C Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

For Germany: Applicable only in connection with the COVID-19 pandemic.

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

C 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Appendix C 2 to C 6. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note: in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

C 2 Re-screening of Participants to Reconfirm Study Eligibility

Additional re-screening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 1.3, the participant will need to be re-screened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 4.1.1. The procedures detailed in Section 5.4.1 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

C 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site will visit the participants home/or other remote location as per local SOP, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

C 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, ePRO and other assessments at the discretion of the PI to be collected and entered on the source documents.

C 5 At-home or Remote Location IP Administration Instructions

Note: This section is not applicable for Germany and France.

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the participant or his/her caregiver. The option of at-home or remote location IP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by travelling to the site/clinic. This will also minimise interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

Note: Before initiating consent for home IP administration visit during study disruptions due to cases of civil crisis, natural disaster, or public health crisis, the participant must have received at least the first 3 IP administrations at the site.

Site must contact the participant by telephone to assess possible COVID-19 symptoms before initiating home visit.

C 5.1 At-home or Remote Location IP Administration by a Qualified HCP

Note: This section is not applicable for Germany and France.

A qualified HCP from the study site may administer the IP at the participant's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

C 6 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site in the source documents, or by the participant themselves.

Appendix D Estimated Oral Corticosteroid 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
For conversions of other OCS doses or other OCS products, please see local label of OCS product or online conversion calculators (eg, https://clincalc.com/corticosteroids/).	

Appendix E Prednisone/Prednisolone Doses < 5 mg in Relation to Available Oral Formulations*

Desirable daily dose	Available tablet strength	Administered number of tablets and frequency
1 mg	1 mg	1 tablet each day
1 mg	5 mg	¼ tablet each day or ½ tablet every other day
2 mg	1 mg	2 tablets each day
2 mg	5 mg	½ tablet each day, or 1 tablet every other day
2.5 mg	1 mg	If divisible – 2½ tablets each day If non-divisible – dose over 2 days as follows: 2 tablets on day 1 and 3 tablets on day 2
2.5 mg	5 mg	½ tablet each day, or 1 tablet every other day
3 mg	1 mg	3 tablets each day
3 mg	5 mg	½ tablet each day, or 1 tablet every other day
4 mg	1 mg	4 tablets each day
4 mg	5 mg	1 tablet each day

*Liquid or tablet formulations may be used. The table above is to be used for tablet formulations. For liquid formulations, please provide a dispenser or dosing cup, if not provided with the bottle; this will allow the patient easy access to the desirable daily dose.

Appendix F Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in Section 7.1 of the CSP.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential 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 total bilirubin (TBL) from a local laboratory.

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

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law 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 SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase 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, eg, elevated

ALP indicating cholestasis, viral hepatitis, another drug.

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

F 3 Identification of Potential Hy's Law Cases

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

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

Central Laboratories Being Used:

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

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

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

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

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

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria not met

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

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

F 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete the 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 HL laboratory kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

F 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from

date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

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

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

- If the alternative explanation is **not** an SAE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an SAE: update the previously submitted PHL SAE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

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

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

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

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

F 6 References

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

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix G Anaphylaxis: Signs, Symptoms, and Management

G 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The WHO has categorised anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic IgE-mediated and non-IgE-mediated (eg, immunoglobulin G 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 recognise and treat anaphylaxis according to local guidelines.

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

G 2 Clinical Criteria for Defining Anaphylaxis

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

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

AND AT LEAST ONE OF THE FOLLOWING:

a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

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

- Two or more of the following occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):

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

b) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

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

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

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

G 3 Signs, Symptoms, and Management of Acute Anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include the following:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhoea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhoea, abdominal cramps, and bloating
- Light headedness
- Headache
- Uterine cramps
- Generalised warmth.

G 4 Management of Acute Anaphylaxis

Immediate intervention

- Assessment of airway, breathing, circulation, and adequacy of mentation

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

Possibly appropriate, subsequent measures depending on response to epinephrine

a) Place participant in recumbent position and elevate lower extremities

b) Establish and maintain airway

c) Administer oxygen

d) Establish venous access

e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

a) Consider epinephrine infusion

b) Consider H1 and H2 antihistamines

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

d) Consider systemic corticosteroids

e) Consider vasopressor (eg, dopamine)

f) Consider glucagon for participant taking a β-blocker

g) Consider atropine for symptomatic bradycardia

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

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

Adapted from Kemp et al, 2008.

Appendix H Handling of Human Biological Samples

H 1 Chain of Custody

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

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

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

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

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.

H 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

The investigator:

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

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

H 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

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

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

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

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

Appendix I Estimated Daily Doses for Inhaled Corticosteroids

Asthma therapy (adults and adolescents 12 years and older)	Total daily dose (µg/day)[b]	
Inhaled corticosteroid[a]	**Medium**	**High**
Beclomethasone dipropionate CFC[c]	> 500 -1000	> 1000
Beclomethasone dipropionate HFA	> 200 - 400	> 400
Budesonide DPI	> 400 - 800	> 800
Ciclesonide HFA	> 160 - 320	> 320
Flunisolide[d]	2000	> 2000
Fluticasone furoate DPI (eg, Arnuity® Ellipta®)[d]	n.a.	200
Fluticasone propionate DPI	> 250 - 500	> 500
Fluticasone propionate HFA	> 250-500	> 500
Mometasone furoate	> 220 - 440	> 440
Triamcinolone acetonide	> 1000 - 2000	> 2000
Inhaled corticosteroid in ICS/LABA combination[d]	**Medium**	**High**
Beclomethasone dipropionate (eg, Fostair®)	400	> 400
Fluticasone furoate (eg, Relvar® Ellipta, Breo® Ellipta)	n.a.	184,200
Fluticasone propionate HFA (eg, Seretide®, Advair®)	> 320 - 460	> 460
Fluticasone propionate DPI (eg, Seretide Diskus®, Advair® Diskus®)	> 250 - 500	> 500
Budesonide HFA (eg, Symbicort®)	320 to < 640	640
Budesonide DPI (eg, Symbicort Turbuhaler®)	400 to <800	800
Mometasone furoate HFA (eg, Dulera®)	400	800
Mometasone DPI (eg, Asmanex® Twisthaler®)	330 – 440	> 440

Abbreviations: CFC = chlorofluorocarbon propellant; DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; n.a. = not applicable

a Modified from the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018. Available from: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention.

b. This protocol also allows any product with clinically comparable doses, including newer products and authorised generics. High-dose ICS via nebulised solution for inhalation is also allowed. For products not listed in this table, the highest approved maintenance ICS or ICS/LABA dose in the local country label will meet the protocol-defined criterion for "high-dose ICS." See Section 5.1. Additionally, in countries where the high-dose ICS or ICS/LABA is not available (eg, only the medium-dose ICS or ICS/LABA is available in that country), the highest approved maintenance dose in the local label will also meet this ICS criterion.

c. Beclomethasone dipropionate CFC is included for comparison with older literature.

d. See local label.

Note: Data provided from GINA 2018 is not a table of equivalence, but of estimated clinical comparability. Categories of "low," "medium," and "high" doses are based on published information and available studies (at the time of GINA 2018 publication), including direct comparisons where available. Doses may be country-specific depending on labelling requirements. Most of the clinical benefit from ICS is seen at low doses, and clear evidence of dose-response relationships is seldom available within the dose ranges evaluated for regulatory purposes. "High" doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects. For new preparations, manufacturer's information should be reviewed carefully; products containing the same molecule may not be clinical equivalent (GINA 2018).

Appendix J Adrenal Crisis Guidelines

Management of Acute Adrenal Insufficiency Secondary to Glucocorticoid Withdrawal

National or local guidelines for the management of acute AI (adrenal crisis), where they exist, should be followed. The following guidelines have been adapted from the guidelines of the Society for Endocrinology. They are intended for guidance subject to clinical judgement only.

The possibility of acute AI should be considered in any acutely unwell participant undergoing withdrawal of chronic systemic corticosteroid treatment.

Recognition

- Clinical signs and symptoms:
    - Fatigue, lack of energy, weight loss
    - Low BP, postural dizziness and hypotension (≥ 20 mmHg drop in systolic BP from supine to standing position), dizziness, collapse, and in severe cases hypovolaemic shock
    - Abdominal pain, tenderness and guarding, nausea, vomiting
    - Fever
    - Confusion, somnolence, in severe cases delirium or coma
    - Back and leg cramps/spasms may be reported.
- Lab findings:
    - Hyponatraemia
    - Pre-renal failure (increased serum creatinine due to hypovolaemia)
    - Normochromic anaemia, sometimes also lymphocytosis and eosinophilia
    - Hypoglycaemia.

Management

- Hydrocortisone (immediate bolus injection of 100 mg hydrocortisone IV or IM followed by continuous IV infusion of 200 mg of hydrocortisone per 24 hours; alternatively 50 mg of hydrocortisone per IV or IM injection every 6 hours).
- Rehydrate with IV 0.9% sodium chloride in hypotensive participants. The rate and total volume of infusate must be decided on an individual participant basis with continuous monitoring for fluid overload. Correction of hyponatraemia must be according to relevant local guidelines.
- Consider any other potential precipitating factors (in addition to corticosteroid withdrawal), eg, infection; investigate and treat as appropriate.

- Contact an endocrinologist at an early stage to advise on ongoing management.

Reference

Arlt W; Society for Endocrinology Clinical Committee. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect 2016;(5):G1-G3.

Appendix K Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European MDR 2017/745 for clinical device research (if applicable).

- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

- The detection and documentation procedures described in this protocol apply to the Tezepelumab APFS provided for use in the study.

K 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.

- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

K 2 Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it

were more severe.

- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to foetal distress, foetal death, or a congenital anomaly or birth defect

Serious ADE (SADE) definition

- A SADE is defined as an adverse medical device effect that has resulted in any of the consequences characteristic of an SAE.
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a serious adverse medical device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

K 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

K 4 Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

  A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and

each occurrence of each AE/SAE/medical device deficiency.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed form.

- The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

K 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 8.3.9.

NOTE: There are additional reporting obligations for SADEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any medical device deficiency that is associated with an SAE must be reported to AstraZeneca **within 24 hours** after the investigator determines that the event meets the definition of a medical device deficiency.
- In addition to the reporting process described in Section 8.3.9, the AstraZeneca Product Complaint Intake form will be used to capture details of the device and related deficiency.
- Facsimile transmission of the AstraZeneca Product Complaint Intake form is the preferred method to transmit this information to the Study Clinical Lead /SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the AstraZeneca Product Complaint Intake form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca Product Complaint Intake form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

Appendix L Protocol Amendment History

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

Amendment 1.0: 15 November 2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants (study did not start enrolment at the time of this amendment) nor the scientific value of the study.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Sections 1.3 Schedule of Activities and 8.1.5.5 SNOT-22	Completion of SNOT-22 is restricted to participants with history of chronic sinusitis at baseline.	Some questions in the SNOT-22 questionnaire are relevant only to participants with chronic sinusitis.	Non-substantial
Section 1.3 Schedule of Activities	Completion of AIRQ™ and SNOT-22 at the IPD visit has been added.	To be consistent with the requirements for the other questionnaires.	Non-substantial
Sections 1.3 Schedule of Activities, 8.3.5 Adverse Events Based on Examinations and Tests, and 8.3.6 Adverse Events of Special Interest	The list of AESIs has been modified.	Changes made to align the protocol to the IB v5.0.	Non-substantial
Section 3 Objectives and endpoints	Total cumulative prescribed OCS up to Week 28 and Week 52 has been deleted from exploratory endpoint list.	It is included in derivation of the endpoint Mean daily SCS exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 and 52 weeks.	Non-substantial
Section 5.4.1 Re-screening	Procedures to be performed during re-screening have been modified.	To reduce the inconvenience for participants who are re-screened.	Non-substantial
Section 6.2.6 Single Use APFS Device Malfunction	Reference to Appendix K for definition of medical device AEs, SAEs and deficiencies in medical device studies has been added as well as the corresponding appendix.	To clarify the process to be followed in case of medical device AEs, SAEs and deficiencies.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.5 Prior and Concomitant Therapy	Restrictions on background therapies (BD, short-acting β-agonists, LABA, LAMA , theophyllines) before FeNO assessment had been deleted in Table 5.	To more closely align the protocol with routine clinical practice.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Helminth parasitic infestation requiring hospitalisation has been replaced by helminth parasitic infestation not responding to anti-helminth treatment in the list of specific criteria for discontinuation.	Change made for consistency with the draft US label of tezepelumab	Non-substantial
Sections 8.1.4 Spirometry and 11 References	Reference for spirometry guidelines have been updated (Miller et al. 2005 has been replaced by Graham et al. 2019).	To use the most recent recommendations of the American Thoracic Society and European Respiratory Society.	Non-substantial
Sections 1.3 Schedule of Activities, 8.1.5.2 SGRQ, 8.1.5.3 AQLQ(S)+12, 8.1.5.4 AIRQ™, 8.1.5.5 SNOT-22, and 8.1.5.6 PPOCS	Time windows for questionnaires have been modified or specified (±5 days as been replaced by ±2 days.	To align the time windows for all questionnaires for consistency (±2 days).	Non-substantial
Section 8.2.4.1 Weight and Height	Mention of body mass index has been added.	To clarify that body mass index will be calculated and not captured in the eCRF.	Non-substantial
Section 8.3.5 Adverse Events Based on Examinations and Tests	Guidance for management of deterioration in laboratory values, physical exams, vital signs performed as usual care during the study has been added.	To clarify that such deteriorations should be reported as AEs only if they fulfil the criteria for an SAE, DAE, or AESI.	Non-substantial
	AESI has been added as a reason to record signs and symptoms of adrenal insufficiency.	To clarify that adrenal insufficiency signs and symptoms have to be recorded if the participant experiences an adrenal crisis, now listed as AESI.	Non-substantial
Section 8.6.1 FeNO	Time window for visits post	To gain consistency with time window required for	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Visit 2 has been modified.	spirometry assessments.	
Section 9.4.1 General Considerations	Definition of composite strategy to be applied for primary endpoint and other OCS endpoints has been updated.	To gain consistency across the document.	Non-substantial
	It has been specified that safety analyses will be done based on on-treatment and/or on-study period.	To provide additional clarification.	Non-substantial
Section 9.4.3.1 Primary Endpoints	Description of final OCS derivation has been updated.	To provide additional clarification of final OCS dose derivation.	Non-substantial
Section 9.4.3.2 Secondary Endpoints	Description of the statistical model for continuous secondary endpoints has been updated.	To provide additional clarification.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarised.	Non-substantial

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AIRQ™ = Asthma Impairment and Risk Questionnaire; APFS = accessorised pre-filled syringe; AQLQ(s)+12 = standardised Asthma Quality of Life Questionnaire for 12 years and older; BD = bronchodilator; eCRF = electronic Case Report Form; FeNO = Fractional exhaled nitric oxide; IB = Investigator Brochure; IPD = premature investigational product discontinuation; LAMA = long-lasting muscarinic antagonist; LABA = long acting β2 agonist; OCS = oral corticosteroid; PPOCS = participant perception of oral corticosteroid; SAE = serious adverse event; SCS = Systemic Corticosteroid; SGRQ = St. George's Respiratory Questionnaire; SNOT-22 = Sino-nasal Outcome Test 22.

Appendix M Alternative Method for Hypothalamic-pituitary-adrenal Axis Evaluation

FOR USE ONLY IF TETRACOSACTIDE IS NOT REGISTERED IN YOUR COUNTRY OR **WITH PERMISSION FROM LABCORP** IF TETRACOSACTIDE IS NOT AVAILABLE AT YOUR SITE

First test (before reducing the maintenance OCS dose below 5 mg per day)

Sample	8–9am cortisol cortisol[a]	Action	Status
1	>350 nmol/L	Continue down-titration (2.5 mg every 4 weeks to zero)	No AI
	100–350 nmol/L	Repeat 8–9am cortisol approximately 1 week later (instead of performing ACTH stimulation test) and interpret according to sample 2 below	Indeterminate
	<100 nmol/L	Delay titration and repeat test in 3 months[b]	Complete AI

Second test - Approximately 1 week after the first test in case the first test was indeterminate

Sample	8–9am cortisol cortisol[a]	Action	Status
2	>350 nmol/L	continue down-titration (2.5 mg every 4 weeks to zero)	No AI
	≤350 nmol/L or when signs or symptoms of AI are present	If serum cortisol ≥250 nmol/L on either sample 1 or sample 2, proceed with slow titration (1 mg every 4 weeks) until the participant reaches a prednisolone / prednisone dosage of 3 mg per day and then repeat testing[b] (ie, at 2 months – see 3rd test below)	Partial AI
		If serum cortisol <250 nmol/L on both samples 1 and 2, delay titration and repeat test in 3 months[b] (see 3rd test below)	Complete AI

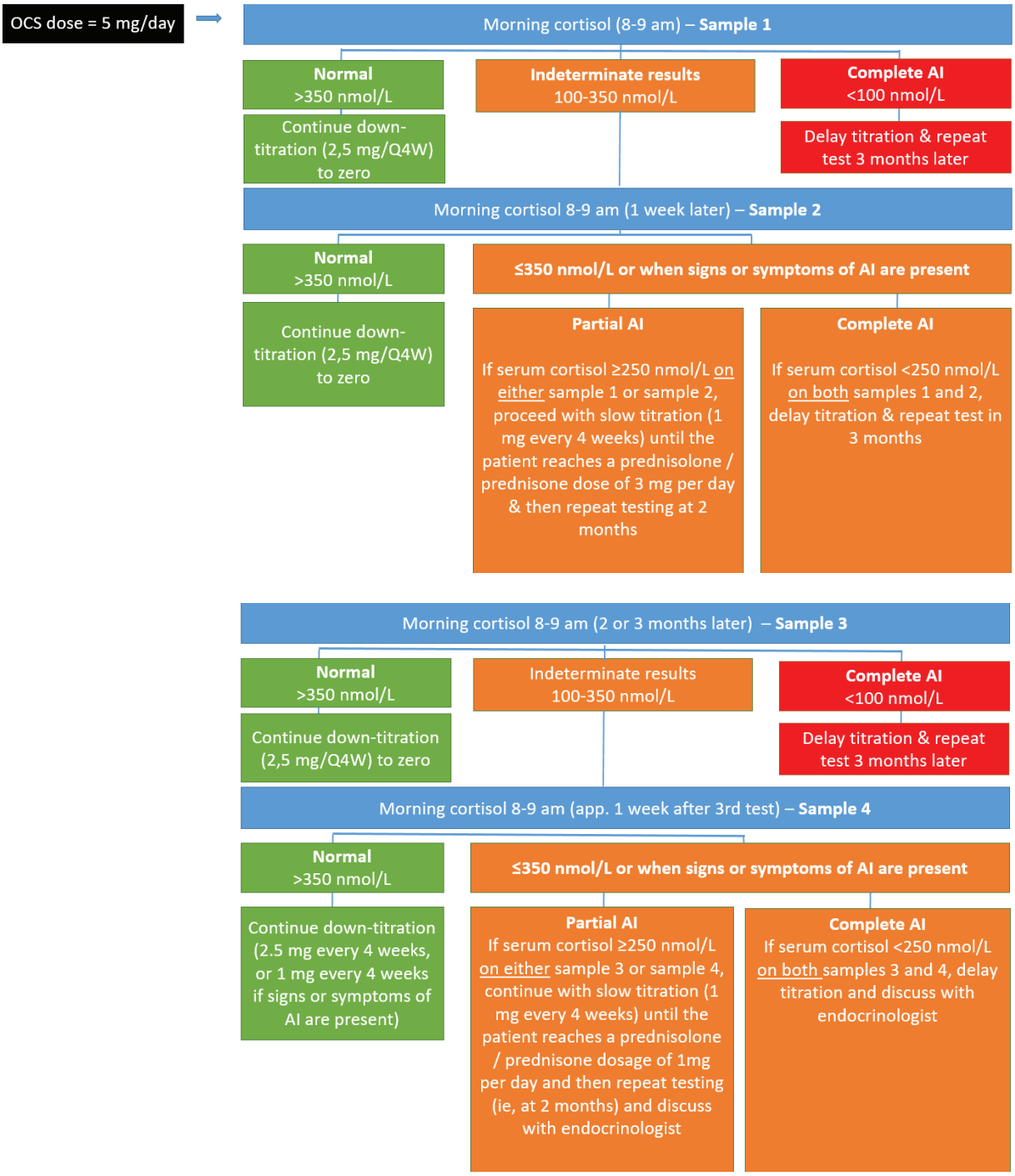
Third test - 2 or 3 months later (see Section 8.2.1)

Sample	8–9am cortisol cortisol[a]	Action	Status
3	>350 nmol/L	Continue down-titration (2.5 mg every 4 weeks to zero)	No AI
	100–350 nmol/L	Repeat 8–9am cortisol approximately 1 week later and interpret according to sample 4 below	Indeterminate
	<100 nmol/L	Delay titration and repeat test in 3 months[b]	Complete AI

Fourth test - Approximately one week after the third

Sample	8–9am cortisol cortisol[a]	Action	Status
4	>350 nmol/L	Continue down-titration (2.5 mg every 4 weeks, or 1 mg every 4 weeks if signs or symptoms of AI are present)	No AI
	≤350 nmol/L or when signs or symptoms of AI are present	If serum cortisol ≥250 nmol/L on either sample 3 or sample 4, continue with slow titration (1 mg every 4 weeks) until the participant reaches a prednisolone / prednisone dosage of 1 mg per day and then repeat testing (ie, at 2 months) and discuss with endocrinologist[b]	Partial AI
		If serum cortisol <250 nmol/L on both samples 3 and 4, delay titration and discuss with endocrinologist	Complete AI

[a] NB thresholds must be adjusted upward for women receiving oral oestrogen therapy as per existing protocol.
[b] Participants will be educated for symptom awareness of adrenal suppression and use of steroid emergency cards.


OCS dose = 5 mg/day
Morning cortisol (8-9 am) – Sample 1
Normal >350 nmol/L
Continue down-titration (2,5 mg/Q4W) to zero
Indeterminate results 100-350 nmol/L
Complete AI <100 nmol/L
Delay titration & repeat test 3 months later
Morning cortisol 8-9 am (1 week later) – Sample 2
Normal >350 nmol/L
Continue down-titration (2,5 mg/Q4W) to zero
≤350 nmol/L or when signs or symptoms of AI are present
Partial AI
If serum cortisol ≥250 nmol/L on either sample 1 or sample 2, proceed with slow titration (1 mg every 4 weeks) until the patient reaches a prednisolone / prednisone dose of 3 mg per day & then repeat testing at 2 months
Complete AI
If serum cortisol <250 nmol/L on both samples 1 and 2, delay titration & repeat test in 3 months
Morning cortisol 8-9 am (2 or 3 months later) – Sample 3
Normal >350 nmol/L
Continue down-titration (2,5 mg/Q4W) to zero
Indeterminate results 100-350 nmol/L
Complete AI <100 nmol/L
Delay titration & repeat test 3 months later
Morning cortisol 8-9 am (app. 1 week after 3rd test) – Sample 4
Normal >350 nmol/L
Continue down-titration (2.5 mg every 4 weeks, or 1 mg every 4 weeks if signs or symptoms of AI are present)
≤350 nmol/L or when signs or symptoms of AI are present
Partial AI
If serum cortisol ≥250 nmol/L on either sample 3 or sample 4, continue with slow titration (1 mg every 4 weeks) until the patient reaches a prednisolone / prednisone dosage of 1mg per day and then repeat testing (ie, at 2 months) and discuss with endocrinologist
Complete AI
If serum cortisol <250 nmol/L on both samples 3 and 4, delay titration and discuss with endocrinologist

Appendix N Abbreviations

Abbreviation or special term	Explanation
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire 6
ACTH	Adrenocorticotropic hormone
AD	Atopic dermatitis
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AI	Adrenal insufficiency
AIRQ	Asthma Impairment and Risk Questionnaire
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APFS	Accessorised pre-filled syringe
AQLQ(s)+12	Standardised Asthma Quality of Life Questionnaire for 12 years and older
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
BD	Bronchodilator
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Discontinuation of investigational product due to adverse event
DBL	Database lock
DILI	Drug Induced Liver Injury
DMP	Data Management Plan
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	Eosinophil
EOT	End of Treatment
ePRO	Electronic patient-reported outcome device
ER	Emergency room

Abbreviation or special term	Explanation
FAS	Full analysis set
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
GC	Glucocorticoid
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HCP	Health Care Professional
HL	Hy's Law
HPA	Hypothalamic-pituitary-adrenal
IATA	International Airline Transportation Association
IB	Investigator brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
FEIA	Fluorescent enzyme immunoassay
IgG2λ mAb	Fully human immunoglobulin 2λ monoclonal antibody
IL-	Interleukin-
IM	Intramuscular
IMP	Investigational Medicinal Product
IP	Investigational product
IPD	Premature investigational product discontinuation
IRB	Institutional Review Board
ISF	Investigator Study File
IxRS	Interactive (voice or web) response system
IV	Intravenous
LABA	Long-acting β_2 agonist
LAMA	Long-lasting muscarinic antagonist
LRTI	Lower respiratory tract infection
LTRA	Leukotriene receptor antagonist
MCID	Minimal clinically meaningful difference
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids

Abbreviation or special term	Explanation
PHL	Potential Hy's Law
PI	Principal investigator
PRO	Patient-reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SABA	Short-acting β-agonist
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoA	Schedule of Activities
SOC	System organ class
SOP	Standard Operating Procedures
TBL	Total bilirubin
TSLP	Thymic stromal lymphopoietin
TSLPR	Thymic stromal lymphopoietin receptor
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
USADE	Unanticipated serious adverse device effect
WHO	World Health Organization
WOCBP	Women of childbearing potential

11 REFERENCES

Alves et al, 2008
Alves C, Robazzi TC, Mendonça M. Withdrawal from glucocorticosteroid therapy: clinical practice recommendations. J Pediatr (Rio J). 2008;84(3):192-202.

Alving et al, 2017
Alving K, Anolik R, Crater G, LaForce C F, Rickard K. Validation of a new portable exhaled nitric oxide analyser, NIOX VERO®: Randomized studies in asthma. Pulm Ther. 2017 Jun;3(1):207-18.

Bateman et al, 2010
Bateman ER, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, et al. Overall asthma control: The relationship between current control and future risk. J Allergy Clin Immunol. 2010;125(3):600-8.

Broersen et al, 2015
Broersen LH, Pereira AM, Jørgensen JO, Dekkers OM. Adrenal insufficiency in corticosteroids use: Systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(6):2171-80.

Chung et al, 2014
Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73.

CINQAIR US PI 2020
CINQAIR (reslizumab). Prescribing information. Teva Respiratory LLC, West Chester, PA, USA; 2020. Available at: https://www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf.

Corren et al, 2017
Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM, Van der Merwe R. Tezepelumab in adults with uncontrolled asthma. N Engl J Med. 2017;377:936-46.

Dinsen et al, 2013
Dinsen S, Baslund B, Klose M, Rasmussen AK, Friis-Hansen L, Hilsted L, Feldt-Rasmussen U. Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. Eur J Intern Med. 2013;24(8):714-20.

Doroudchi et al, 2019
Doroudchi A, Pathria M, Modena BD. Asthma biologics: Comparing trial designs, patient cohorts and study results. Ann Allergy Asthma Immunol. 2020 January;124(1):44-56.

DUPIXENT US PI 2021
DUPIXENT (dupilumab). Prescribing information. Sanofi-Aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591), USA; 2021. Available at: https://www.regeneron.com/downloads/dupixent_fpi.pdf.

FASENRA US PI 2019
FASENRA (benralizumab). US Prescribing information. AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850, USA;2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761070s005lbl.pdf.

Froidure et al, 2016
Froidure A, Mouthuy J, Durham SR, Chanez P, Sibille Y, Pilette C. Asthma phenotypes and IgE responses. Eur Resp J. 2016;47:304-19.

Gauvreau GM et al, 2014
Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. (2014). Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. N Engl J Med. 2014; 370, 2102-10.

Gauvreau GM et al, 2020
Gauvreau GM, Sehmi R, Ambrose CS, and Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. Expert Opin Ther Targets. 2020; 24, 777-792.

GINA 2017
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Updated 2017. Available from: http://www.ginasthma.org/.

GINA 2018
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2018. Available from: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention.

GINA 2020
Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2020. Available from: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf.

Hopkins et al 2009
Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clinical otolaryngology. 2009;34(5):447-45.

Graham et al 2019
Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88.

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

Johnson et al, 2014
Johnson SR, Naden RP, Fransen J, van den Hoogen F, Pope JE, Baron M, et al. Multicriteria decision analysis methods with 1000Minds for developing systemic sclerosis classification criteria. J Clin Epidemiol. 2014;67(6):706-14.

Jones et al, 1991
Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med. 1991;85(Suppl B):25-31.

Jones 2005
Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2(1):75-9.

Jones et al, 2009
Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.

Joseph et al, 2016
Joseph RM, Hunter AL, Ray DW, Dixon WG. Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Semin Arthritis Rheum. 2016;46(1):133-41.

Juniper et al, 1999
Juniper E, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a Standardized Version of the Asthma Quality of Life Questionnaire. Chest Journal. 1999. 115(5):1265-70.

Juniper et al, 2005
Juniper EF, Svensson K, Mörk AC, Stähl E. Modification of the Asthma Quality of Life Questionnaire (standardised) in patients 12 years and older. Health and Quality of Life Outcomes. 2005, 3:58.

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

Lieberman et al, 2010
Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010 Sep;126(3):477-80.e1-42.

Masoli et al, 2004
Masoli M, Holt S, Weatherall M, Beasley R. The dose-response relationship of inhaled corticosteroids in asthma. Curr Allergy Asthma Rep. 2004;4(2):144-8.

Menzies-Gow et al, 2019
Menzies-Gow A, Corren J, Bel EH, Maspero J, Heaney LG, Gurnell M, et al. Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE Trial. ERJ Open Res 2019; 5: 00009-2019.

Menzies-Gow et al, 2021
Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, Brightling CE, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021; 384, 1800-1809.

Miloslavsky et al, 2017
Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis. 2017;76(3):543-6.

Moore et al, 2007
Moore WC, Bleecker ER, Curran-Everett D, Erzurum SC, Ameredes BT, Bacharier L, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(2):405-13.

NAEPP 2020
National Asthma Education and Prevention Program. 2020 Guideline update. Available from: https://www.atsjournals.org/doi/pdf/10.1164/rccm.202011-4236ED.

Nair et al, 2017
Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, ZONDA Trial Investigators, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376(25):2448-58.

Neogi et al, 2010
Neogi T, Aletaha D, Silman AJ, Naden RL, Felson DT, Aggarwal R, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: Phase 2 methodological report. Arthritis Rheum. 2010;62(9):2582-91.

Nicholas et al, 2018
Nicholas MN, Li SK, Dytoc M. An approach to minimising risk of adrenal insufficiency when discontinuing oral glucocorticoids. J Cutan Med Surg. 2018;22(2):175-81.

NUCALA US PI 2020
NUCALA (mepolizumab). US Prescribing information. GlaxoSmithKline, Research Triangle Park, NC, USA;2020. Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF.

Pham et al, 2019
PhamTH, Ren P, Parnes J, and Griffiths JM. Tezepelumab reduces multiple key inflammatory biomarkers in patients with severe, uncontrolled asthma in the phase 2b PATHWAY study. 2019; In B21. Severe asthma: Clinical and mechanistic studies (American Thoracic Society), pp. A2677–A2677.

Piccirillo et al 2002
Piccirillo JF, Merritt MG, Richards ML. Psychometric and clinimetric validity of the 20 item Sino-Nasal Outcome Test (SNOT-20). Otolaryngology-Head and Neck Surgery. 2002; 126(1);41-47.

Sampson et al, 2006
Sampson H.A, A. Munoz-Furlong, R.L. Campbell, N.F. Adkinson Jr., S.A. Bock, A. Branum, et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 117 (2006), pp. 391-7.

Shaw et al, 2015
Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J. 2015;46(5):1308-21.

Swedin et al, 2017
Swedin L, Saarne T, Rehnberg M, Glader P, Niedzielska M, Johansson G, et al. Patient stratification and the unmet need in asthma. Pharmacol Ther. 2017;169:13-34.

Sweeney et al, 2016
Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. Thorax 2016;71(4):339-46.

Wechsler et al, 2021
Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S, Welte T, et al. Oral corticosteroid-sparing effect of tezepelumab in adults with severe asthma. Oral communication at ATS 2021 International Conference, May 14-19, 2021.

Wenzel 2016
Wenzel SE. Emergence of biomolecular pathways to define novel asthma phenotypes. Type-2 immunity and beyond. Am J Respir Cell Mol Molec Biol. 2016;55:1-4.

XOLAIR US PI 2021
XOLAIR (omalizumab). Prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 2021. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf.

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