
Clinical Study Protocol

Study Intervention	Tezepelumab
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**A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled
28-week Phase 3 Efficacy and Safety Study of Tezepelumab in
Reducing Oral Corticosteroid Use in Adults with Oral
Corticosteroid Dependent Asthma (SUNRISE)**

Sponsor Name: AstraZeneca AB

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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.

Version Scope: Global Version 3.0, 28 March 2023

Amendment Number: 2

CSP Local Versions:
Local CSP 3.0 Czech Republic

Study Intervention: Tezepelumab

Study Phase: 3

Brief Title: Tezepelumab Efficacy and Safety in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Acronym: SUNRISE

Study Physician Name and Contact Information will be provided separately

Study Physician is responsible for the clinical integrity of the study.

International Co-ordinating Investigator:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
<i>Global CSP v3.0 (Amendment 2)/ Local CSP 3.0 Czech Republic</i>	<i>28-Mar-2023</i>
<i>Global CSP v2.0 (Amendment 1)</i>	<i>22-Aug-2022</i>
<i>Original Protocol</i>	<i>07-Feb-2022</i>

Amendment 2 (28-March-2023)

This modification 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 and in the EU Clinical Trial Regulation Article 2, 2 (13) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the modification:

The main reasons for this amendment are to align with regulatory requirements related to Clinical Trial Transparency (CTT) language, European Union Clinical Trials Regulation (EU CTR), and CT-3 Regulation and to comply with global company requirements and the new global CSP template.

Other changes include minor non-substantial clarifications, minor formatting and editorial revisions.

Summary of Changes:

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Protocol title page	“EudraCT/EU CT Number” added to the Protocol title page.	
Protocol title page and Section 1.1 Synopsis	“Short Title” changed to “Brief Title”.	
Protocol title page	The statement “Study Physician is responsible for the clinical integrity of the study.” added to the Protocol title page.	

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.4 End-of-study Section 6.8 Treatment of Overdose and 8.4 Reporting of Overdose Section 8.3.11.1 Timelines Section 8.3.11.2 Medication Error and Appendix B 4 Medication Error, Drug Abuse, Drug Misuse Appendix A 1 Regulatory and Ethical Considerations Appendix A 1 Regulatory and Ethical Considerations Appendix A 7 Data Quality Assurance Appendix M Country-specific Requirements	“Regulatory Agency Identifier Number(s)” added to synopsis. The End of Study definition updated. Section 6.8 "Treatment of Overdose" added, section 8.4 renamed from "Overdose" to "Reporting of Overdose" and the definition of overdose moved from section 8.4 to section 6.8. “1” updated to “one calendar” in the sentence on the timelines of informing AstraZeneca representatives by the Investigator or other site personnel about a medication error, drug abuse, or drug misuse that occurs in the course of the study. Wording on medication error updated. Wording on Regulatory and Ethical Considerations updated. Wording related to requirements of regulatory reporting for Serious Breaches added. Text on Data Quality Assurance updated, including the addition of text on Quality tolerance limits (QTLs) and medical oversight and update of text on retaining records and documents, pertaining to the conduct of this study. Appendix M containing Country-specific requirements added.	To align with regulatory requirements related to Clinical Trial Transparency (CTT) language, European Union Clinical Trials Regulation (EU CTR), and CT-3 Regulation and to comply with global company requirements and the new global CSP template.
Protocol title page and Section 1.1 Synopsis	EU CT number updated from "2022-500062-96-00" to "2023-504648-33-00".	To reflect the new EU CT number assigned to the SUNRISE study.
Section 1.3 Schedule of Activities (SoA), Table 2	The visit window for Visit 6 updated from “0” to “+5” in Table 2.	To clarify that the visit window for Visit 6 is +5 days.

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA), Table 2	Footnote “k” update and added to the condition when to collect ADA/nAb samples.	To clarify that ADA/nAb samples must be collected pre-dose at dosing visits.
Section 2.2 Background, 4.1 Overall Design, 5.1 Inclusion Criteria, Appendix G Maintenance therapy equivalence table and References, Section 11 References	References to “GINA 2021” updated to “GINA 2022”.	To align with the GINA 2022 guidelines.
Section 2.3.1 Risk Assessment	Phrase “for the presence of ADA and” deleted from the text on the mitigation strategy of serious hypersensitivity reactions.	To remove not applicable information from a mitigation strategy for serious hypersensitivity reactions, as the results of the ADA testing are not available during the trial.
Section 2.3.1 Risk Assessment	The phrase “who have a history of clinically significant infection, requiring treatment with systemic antibiotics or antiviral medications finalised < 2 weeks before Visit 1 or during the run-in period or at randomisation; and participants” deleted from the text on the mitigation strategy of the Helminths infections.	To remove not applicable information from a mitigation strategy for Helminths infections as Helminths infections are not treated with systemic antibiotics or antiviral medications.
Section 5.1 Inclusion Criteria	Inclusion criteria 20 and 21 updated: The phrase “at each visit during the OCS optimisation phase (Visit 2 to Visit 5).” changed to “at Visits 3-5 during the OCS optimisation phase.”.	To clarify that the requirement for compliance described in inclusion criteria 20 and 21 pertains to Visit 3-5. The requirement for compliance at Visit 2 is already covered in inclusion criteria 17 and 18.
Section 5.1 Inclusion Criteria	The word “morning” added to the “PEF measurements” in inclusion criteria 17, 21 and 22.	Wording clarified to ensure consistency throughout the CSP.
Section 5.1 Inclusion Criteria	The words “ measurements ” replaced with “diary assessment” in inclusion criteria 17, 21 and 22.	To clarify that note on a compliant day pertains to daily diary assessment.
Section 6.1.1 Study Intervention, Table 5	Text on study intervention packaging and labelling updated.	To clarify that both syringes and cartons are labelled as per the GMP.

Section Number and Name	Description of Change	Brief Rationale
Section 8.1.6 Patient-reported outcomes Patient-reported outcomes	The phrase “study completion” updated to “the EOT visit” in the sentence on the requirements for completion of the at-home PRO assessments.	To align with Table 2 of the CSP.
Section 8.3.6 Adverse Events of Special Interest	The phrase “(including opportunistic infections)” deleted from the AESI category of serious infections.	To align with the Investigator’s Brochure edition 5.1 (dated 22 July 2022).
Section 9.4.2.2 Secondary Endpoint(s)	Text on summarising and analysing of rates for the asthma exacerbation updated.	Wording clarified to ensure consistency throughout the CSP.
Appendix K Abbreviations	New abbreviations added.	To include all abbreviations in the document.
Appendix L Protocol Amendment History	Summary of changes introduced in the CSP Version 2.0 (Amendment 1) added to the Protocol Amendment History.	To include all changes in the Protocol Amendment History.

In addition, minor formatting and editorial revisions were made throughout the protocol.

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1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Protocol Title: A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled 28-week Phase 3 Efficacy and Safety Study of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma (SUNRISE)

Brief Title: Tezepelumab Efficacy and Safety in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma

Regulatory Agency Identifier Number(s)

IND number: 103031

EudraCT number: 2021-006691-17

EU Trial number: 2023-504648-33-00

Rationale: The purpose of this global study is to demonstrate the ability of tezepelumab, compared with placebo, to reduce oral corticosteroid (OCS) use in adults with severe asthma being treated with maintenance OCS in combination with high dose inhaled corticosteroids (ICS) and long-acting β_2 agonists (LABA), with or without other asthma controller therapies, while maintaining asthma control. Oral corticosteroids are effective agents for controlling airway inflammation in asthma. However, when given for extended periods of time, OCS are associated with multiple and potentially debilitating side effects.

Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP) monoclonal antibody. A phase 2b (NCT02054130; PATHWAY) study and a phase 3 (NCT03347279; NAVIGATOR) study in participants with inadequately controlled severe asthma have both demonstrated a considerable reduction in the annualised asthma exacerbation rate (AAER) with tezepelumab treatment, irrespective of the participants' baseline biomarkers (eosinophils, fractional exhaled nitric oxide [FeNO] and immunoglobulin E [IgE]) and allergic status. These studies also showed that the use of tezepelumab resulted in improved lung function, asthma control, and health-related quality of life.

In the previously-conducted OCS-sparing phase 3 study SOURCE (NCT03406078), tezepelumab numerically reduced OCS use in participants with OCS-dependent asthma, but a statistically significant difference in the primary endpoint versus placebo was not achieved. Study design elements might have contributed to these results, and SUNRISE has therefore been designed to incorporate learnings from the SOURCE study.

Objectives and Endpoints

Objectives	Endpoints/variables
Primary	
To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	Endpoint: Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control. The categories for percent change from baseline in daily OCS dose are defined as: 1. $\geq 90\%$ to $\leq 100\%$ reduction 2. $\geq 75\%$ to $< 90\%$ reduction 3. $\geq 50\%$ to $< 75\%$ reduction 4. $> 0\%$ to $< 50\%$ reduction 5. no change or any increase.
	Population: Adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, and who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.
	Intercurrent events: • Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 will be included in the analysis (treatment policy strategy). • Initiate therapy with another biologic for treatment of asthma: final dose for analysis will be defined as the OCS dose achieved prior to initiation of another biologic for treatment of asthma, increased by one OCS dose level (composite strategy).
	Summary measure: The cumulative odds ratio at Week 28 (tezepelumab/placebo).
Key Secondary	
To evaluate the effect of tezepelumab compared with placebo on pre-bronchodilator lung function in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	Endpoint: Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV ₁) at Week 28.
	Population: Adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.
	Intercurrent events: • Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 will be included in the analysis (treatment policy strategy). • Initiation of another biologic for treatment of asthma: post intercurrent event data will be imputed assuming an unfavorable outcome (composite strategy).

Objectives	Endpoints/variables
	Summary measure: The difference in means at Week 28 (tezepelumab – placebo).
Secondary	
To evaluate the effect of tezepelumab compared with placebo on the daily dose of maintenance OCS	- Proportion of participants with 100% reduction from baseline in daily maintenance OCS dose at Week 28 - Proportion of participants with daily maintenance OCS dose ≤ 5 mg at Week 28 - Proportion of participants with $\geq 50\%$ reduction from baseline in daily maintenance OCS dose at Week 28
To evaluate the effect of tezepelumab compared with placebo on asthma exacerbations	- Annualised asthma exacerbation rate (AAER) over 28 weeks - Time to first asthma exacerbation Supportive outcome variables: - Rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit, or hospitalisation over 28 weeks - Proportion of participants who did not experience an asthma exacerbation over 28 weeks
To assess the effect of tezepelumab compared with placebo on asthma control and other asthma control metrics	Change from baseline in - Asthma Control Questionnaire 6 (ACQ-6) score at Week 28 - Weekly mean home peak expiratory flow (PEF) (morning and evening) at Week 28
To assess the effect of tezepelumab compared with placebo on asthma-related quality of life	Change from baseline in: - Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score at Week 28 - St George's Respiratory Questionnaire (SGRQ) score at Week 28
To assess the effect of tezepelumab on biomarkers	Change from baseline in fractional exhaled nitric oxide (FeNO), peripheral blood eosinophils and total serum immunoglobulin E (IgE) at Week 28
To evaluate the pharmacokinetics (PK) of tezepelumab	Tezepelumab serum trough concentrations at Week 0, 12, and 28
To evaluate the immunogenicity of tezepelumab	Incidence of anti-drug antibodies (ADAs) at Week 0, 12, 28, and 40
Safety	
To evaluate the safety and tolerability of tezepelumab	- Adverse events (AEs), serious adverse events (SAEs) - Clinical chemistry, haematology - Vital signs

For exploratory objectives and endpoints, see Section 3 of the Clinical Study Protocol (CSP).

Overall Design

This is a Phase 3, randomised, double-blind, parallel-group, placebo-controlled, multicentre study to evaluate the efficacy and safety of tezepelumab 210 mg every 4 weeks (Q4W) administered subcutaneously (SC) using an accessorised pre-filled syringe (APFS), compared with placebo in reducing OCS use in OCS-dependent adult asthma participants.

Disclosure Statement:

This is a placebo-controlled, parallel-group treatment study with 2 arms that is participant, investigator, and sponsor blinded.

Number of Randomised Participants:

Approximately 414 participants will be screened to achieve approximately 207 participants randomly assigned to study intervention.

The participants will be monitored to ensure that

- a maximum of 20% of those randomised have an eosinophil count (EOS) of < 150 cells/ μ L at Visit 1 (with an historical EOS ≥ 300 cells/ μ L within 12 months),
- and approximately 40% of those randomised have an eosinophil count of ≥ 300 cells/ μ L at Visit 1.

Intervention Groups and Duration

Approximately 207 participants will be randomised in a 2:1 ratio to receive tezepelumab 210 mg or placebo SC Q4W for a total of 7 doses of study intervention. The randomisation is on Day 1. Study intervention will be administered at weeks: 0 (Day 1), 4, 8, 12, 16, 20, and 24. Treatment allocation will be stratified by region and eosinophil count at Visit 1 (< 150 cells/ μ L, $150 < 300$ cells/ μ L, ≥ 300 cells/ μ L), to ensure that treatment assignment across regions and eosinophil subgroups is balanced.

After enrolment at Visit 1, all participants will enter a 2-week run-in period and then an 8-week OCS optimisation phase. The OCS optimisation phase is to establish participant eligibility and to determine the minimum effective dose (the optimised dose) of the participant's prescribed OCS. The OCS optimisation phase may be shortened if the optimised dose is determined earlier than 8 weeks, or it may be extended to accommodate for treatment of an asthma exacerbation and still allow for the 2-week period of the optimised OCS dose prior to randomisation.

Following the OCS optimisation phase, participants who fulfil the eligibility criteria will be randomised at Visit 6 (Week 0) and will start the 28-week treatment period.

There are 3 phases in the 28-week treatment period:

- **Induction phase** – from Visit 6 (Week 0) to Visit 7 (Week 4) during which participants should remain on their optimised OCS dose.

- **OCS reduction phase** – from Visit 7 (Week 4) to Visit 12 (Week 24) during which the OCS dose reduction should be started at Visit 7, with the possibility of dose reduction every 4 weeks.
- **Maintenance phase** – from one day after Visit 12 (Week 24) to the day of Visit 13 (Week 28), which is the End of Treatment visit. In this phase participants should remain on the stable maintenance OCS dose reached during the reduction phase or continue without OCS if the OCS dose was reduced to 0 mg during the reduction phase. No further OCS dose reduction will take place during this phase.

The End of Treatment visit will be performed at Week 28. A post-treatment safety follow-up visit will be performed at Week 40 (Visit 14).

Data Monitoring Committee: No

Independent Adjudication Committee

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

The committee will also assess whether cases of ER or urgent care visits and hospitalizations, that occur from randomisation until the end of the follow-up period, are due to a worsening of asthma. Details on the adjudication process, including the scope of adjudication and the committee membership, will be included in the Adjudication Committee Charter/Manual of Operations.

Statistical Methods

Approximately 207 participants will be assigned to study intervention using a 2:1 treatment allocation ratio (tezepelumab:placebo).

With 138 participants randomised to tezepelumab and 69 randomised to placebo it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint is approximately 90% assuming a true odds ratio of 2.5 and with the placebo assumptions based on SOURCE (NCT03406078), a previous OCS-sparing study in the tezepelumab programme, and exploratory analyses performed to assess differences in design in the current study.

Participants who meet the eligibility criteria will be randomised to receive either tezepelumab or placebo. Efficacy analyses will be performed using the full analysis set (FAS), which consists of all participants randomised who received at least one dose of study intervention. Participants will be assigned to the FAS according to their randomised treatment. All

participants in the FAS will be included in the main efficacy analyses, including participants who discontinue study intervention prior to Week 28 (for whom every attempt will be made to collect data after discontinuation of study intervention up until Week 28) or who initiate treatment with another biologic. No need is envisaged to adjust the planned number of randomised participants in order to obtain an appropriate number of evaluable participants.

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

- 1 First the superiority of tezepelumab will be tested with regard to the primary endpoint (categorised percent reduction from baseline in the daily maintenance dose at Week 28 whilst maintaining asthma control).
- 2 If superiority of tezepelumab is shown at Step 1, then the superiority of tezepelumab will be tested with regard to the key secondary endpoint (change from baseline in pre-BD FEV₁ [L] at Week 28).

The primary endpoint in the tezepelumab group will be compared to that in the placebo group using a proportional odds (ordinal logistic regression) model. The response variable in the model will be the ordered category number (1 to 5) at Week 28. Treatment and region will be included as categorical covariates, and baseline OCS dose and log baseline blood eosinophil counts will be included as continuous covariates in the model.

The key secondary endpoint will be analysed using an analysis of covariance (ANCOVA) model. The response variable in the model will be the change from baseline at Week 28. Treatment and region will be included as categorical covariates in the model, and baseline pre-BD FEV₁ and log baseline blood eosinophil counts will be included as continuous covariates in the model.

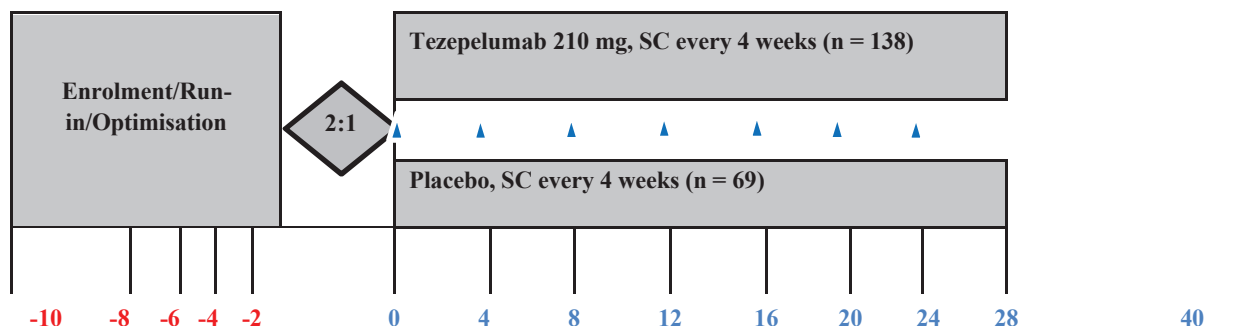
In general, all data up to Week 28 will be included in the statistical analyses, even if a participant discontinues study intervention treatment or changes background therapy (other than OCS). If a participant initiates therapy with another biologic, for treatment of asthma, the composite strategy will be applied. Missing data will be imputed using a multiple imputation (MI) approach.

In general, the safety variables will be summarised descriptively (unless otherwise stated). The safety analysis will be performed using the safety analysis set, which consists of all participants receiving at least one dose of study intervention and assigned according to their actual treatment.

1.2 Schema

Figure 1 Study Design

V1	V2-V5	V6		V7-12		V13		V14
Wk -10 to -8	Wks -8 to 0	Wk 0	Wk 0 to 4	Wk 4 to 24		Wk 24 to 28	Wk 28	Wk 28 to 40
Enrolment / Run-in	OCS Optimisation phase	Randomis ation	Treatment period				End of Treat ment	Follow- up period
			Induct ion phase	OCS reduction phase		Mainte nance phase		



V = Visit; Wk/Wks = week/weeks; n = number of participants; OCS = oral corticosteroids; SC = subcutaneous injection

▲ = Study intervention dose administration

1.3 Schedule of Activities (SoA)

Table 1 Schedule of Activities – Enrolment/Run-in and OCS Optimisation Phase

Assessment/ activity	Enrolment/ Run-in	OCS optimisation phase ^b					Details in CSP Section or Appendix
	V1 ^a	V2	V3	V4	V5		
	W -10	W -8	W -6	W -4	W -2		
	Visit window (days)						
	N/A	+3 ^c	±3	±3	±3 ^c		
Informed consent	X						Appendix A 3
Inclusion/exclusion criteria	X	X	X	X	X	X	Sections 5.1 and 5.2
Routine clinical procedures							
Demographics	X						Section 5.1
Medical, surgical, and asthma history	X						Section 5.1
COVID-19 ^d							
COVID-19 Questionnaire	X	X	X	X	X	X	Section 8.2.5.4
Safety assessments							
Complete physical examination	X						Section 8.2.1
Weight, Height	X						Section8.2.5.2
Vital Signs	X						Section 8.2.2
12-lead ECG ^e	X						Section 8.2.3
Assessments of asthma exacerbations	X	X	X	X	X	X	Section 8.1.2
Adverse events	X	X	X	X	X	X	Section 8.3
Concomitant medications ^f	X	X	X	X	X	X	Section 6.5

Table 1 **Schedule of Activities – Enrolment/Run-in and OCS Optimisation Phase**

Assessment/ activity	Enrolment/ Run-in	OCS optimisation phase ^b					Details in CSP Section or Appendix
	V1 ^a	V2	V3	V4	V5		
	W -10	W -8	W -6	W -4	W -2		
	Visit window (days)						
	N/A	+3 ^c	±3	±3	±3 ^c		
Laboratory assessments							
Safety laboratory assessments [Clinical chemistry, Lipid profile {serum sample} and haematology {blood sample}]	X						Section 8.2.4
Urine sample for urinalysis (dipstick) ^g	X						Section 8.2.4
Serum sample for serology (hepatitis BsAg, hepatitis C Ab; HIV-1; HIV-2)	X						Section 8.2.5.3
Serum sample for pregnancy (serum β-hCG) or FSH test ^h (Females WOCBP only)	X						Section 8.2.5.1
Theophylline blood concentration ⁱ	X						Section 6.5
Blood sample for EOS count ^j	X						Section 8.6.1
Patient reported outcome assessments							
Dispense ePRO device and provide instructions ^k	X						Section 8.1.6
Daily diary ^l	Completed twice daily at home on ePRO device						
ACQ-6 ^m	X	X					Section 8.1.6.2
Review ePRO assessments/compliance ⁿ		X	X	X	X	X	
Confirm a visit (ePRO) ^o	X	X	X	X	X	X	

Table 1 Schedule of Activities – Enrolment/Run-in and OCS Optimisation Phase

Assessment/ activity	Enrolment/ Run-in	OCS optimisation phase ^b					Details in CSP Section or Appendix	
	V1 ^a	V2	V3	V4	V5			
	W -10	W -8	W -6	W -4	W -2			
	Visit window (days)							
	N/A	+3 ^c	±3	±3	±3 ^c			
Lung function assessments								
Pre-BD spirometry	X	X	X	X	X		Section 8.1.3	
Post-BD spirometry (Bronchodilator responsiveness test) ^p	X	X	X				Section 8.1.3	
Home peak-flow monitor (PEF meter) training and distribution	X						Section 8.1.4	
Home assessment of PEF	Measurement every morning and evening							Section 8.1.4
Check compliance with home PEF meter		X	X	X	X	X	Section 8.1.4	
OCS optimisation								
OCS switch to prednisone or prednisolone equivalent (if required)	X						Section 8.1.1.1.1	
Review all OCS reduction criteria as per Table 8		X	X	X	X	X	Section 8.1.1.1	
OCS dose reduction			X ^q	X	X		Section 8.1.1.1	
OCS dose increase, if applicable ^r						X	Section 8.1.1.1	

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

^b The optimisation phase may be extended, in consultation with the AstraZeneca Study Physician, to account for treatment of an exacerbation to allow for

^c 2-week stable OCS dose prior to randomisation.

^d At a minimum there must be 14 days between Visit 1 and 2 and between Visit 5 and 6 (randomisation).

^e COVID-19 questionnaire must be completed for each participant prior to study visit activities. Sites should also follow local SARS-CoV-2 testing guidelines outside of CSP study assessments, if applicable.

^f To be performed locally.

- f All asthma medications taken in the 12 months prior to Visit 1 must be recorded in the eCRF along with total daily doses and reason for treatment. All other medications taken for conditions other than asthma in the 3 months prior to Visit 1 must be recorded in the eCRF along with reason for treatment.
- g Urinalysis analysed by the central Laboratory only if positive dipstick result observed at the site.
- h Serum pregnancy (β -hCG) test only for women of childbearing potential (WOCBP). FSH test done only in women < 50 years who have been amenorrhoeic for > 12 months to confirm postmenopausal status.
- i Participants on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented before Visit 1, or if documentation not available, assessed at Visit 1. The sample can be analysed at the central or local lab as applicable.
- j Assessment of eosinophils will be based upon a separate whole blood aliquot not linked to the complete blood count safety analysis. Eosinophils may be reported in $\times 10^9/L$ or $\times 10^3/\mu L$, for example $150 \text{ cells}/\mu L$ is equivalent to $0.15 \times 10^9/L$ or $0.15 \times 10^3/\mu L$.
- k ePRO device should be dispensed after all other assessments have been performed.
- l The daily diary completion will start at home on the evening of Visit 1.
- m ACQ-6 at Visit 1 will be completed on-site. ACQ-6 for Visit 2 can be completed at home. If it has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.
- n Daily Diary: Asthma Symptom Diary (ASD), global asthma symptom score item, rescue medication use, night-time awakenings, and adherence to maintenance medications.
- o Visit can be confirmed within the ePRO device or in the ePRO study portal.
- p If Post-BD spirometry (bronchodilator responsiveness test) is not met at Visit 1, it should be verified at Visit 2 or at Visit 3. Post-BD spirometry should be performed 15-30 min after administration of 4 puffs of albuterol/salbutamol. Bronchodilator responsiveness can be documented (spirometry results) in the previous 60 months prior to Visit 1. Note: Bronchodilator responsiveness (both historical and during screening) is defined as $FEV_1 \geq 12\%$ and $\geq 200 \text{ mL}$ OCS dose reduction is mandatory at Visit 2 and will not be based on a protocol captured set of daily diary data and spirometry data. At other optimisation visits, daily diary data preceding the visits will be compared to the daily diary data derived from the interval between Visits 1 and 2 for OCS dose titration decisions. For the pre-BD FEV_1 OCS reduction criterion, the result from the given visit will be compared to the result from Visit 2 measurement.
- r If the participant does not meet the criteria for OCS dose reduction at Visits 3 or 4, the investigator should increase the OCS dose to at least one step higher (return to the last effective dose) and Visit 5 should be activated instead of Visit 3 or 4 on the same day. Participant should be maintained at the optimised dose of OCS for at least 2 weeks before randomisation. If the OCS dose increase took place prior to Visit 5 (ie, at unscheduled visit) due to asthma worsening, the OCS dose increase will not take place at Visit 5.

Table 2 **Schedule of Activities – Treatment and Follow-up Period**

Assessment/ activity	Induction Phase	Reduction Phase						Maintenance phase / phase / EOT	FU	IPD visit	UNSA	Details in CSP Section or Appendix			
	V6 W0 (Day 1)	V7	W4	W8	W12	W 16	W 20	V11	V12	V13	V14		W40		
		Visit window (days) ^b													
		+5	±5	±5	±5	±5	±5	±5	±5	±5	±5			±7	
	Verifying inclusion/ exclusion criteria	X													N/A
X		X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.5.4
X										X			X		Section 8.2.5.2
X															
X		X	X	X	X	X	X	X	X	X	X	X	X		Section 8.8
Complete physical examination	X												X		Section 8.2.1
		X	X	X	X	X	X	X	X	X	X	X			Section 8.2.1
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.2
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2
Assessments of asthma exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
	X												X		Section 8.2.3
	X														
	X														

Table 2 **Schedule of Activities – Treatment and Follow-up Period**

Assessment/ activity	Induction Phase	Reduction Phase						Maintenance phase / EOT	FU	IPD visit	UNSA	Details in CSP Section or Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14			
	W0 (Day 1)	W4	W8	W12	W 16	W 20	W 24	W 28	W40			
	Visit window (days) ^b											
	+5	±5	±5	±5	±5	±5	±5	±5	±5	±7	N/A	
Safety laboratory assessments (Clinical chemistry [serum sample] and haematology [blood sample]) ^g	X	X		X				X	X	X		Section 8.2.4
Urine sample for urinalysis (dipstick) ^h	X	X		X				X		X		Section 8.2.4
Urine sample for pregnancy test (dipstick) ⁱ	X	X	X	X	X	X	X	X		X		Section 8.2.5.1
Serum sample for specific IgE (FEIA) ^j	X											Section 8.6.1.1
Serum sample for total serum IgE ^j	X	X						X		X		Section 8.6.1.1
Serum sample PK ^k	X			X				X		X		Section 8.5.1
Serum sample for ADA/nAb testing ^k	X			X				X	X	X		Section 8.5.2
Serum for exploratory biomarker assessments ^l	X	X						X				Section 8.6.1
Blood sample for EOS count ^m	X	X							X	X		Section 8.6.1

Table 2 **Schedule of Activities – Treatment and Follow-up Period**

Assessment/ activity	Induction Phase	Reduction Phase							Maintenance phase / EOT	FU	IPD visit	UNSA	Details in CSP Section or Appendix	
	V6	V7	V8	V9	V10	V11	V12	V13	V14	N/A	N/A	N/A		
	W0 (Day 1)	W4	W8	W12	W 16	W 20	W 24	W 28	W40					
	Visit window (days) ^b													
	+5	±5	±5	±5	±5	±5	±5	±5	±7					
Blood sample for transcriptomics ^l	X							X					Section 8.6.1.2	
Genomics Initiative, exploratory genetic sample ^{ln} (Optional)	X												Section 8.7	
Daily diary ^o	Completed twice daily at home on ePRO device													
ACQ-6 ^p	X	X	X	X	X	X	X	X	X		X		Section 8.1.6.2	
AQLQ(s)+12 ^p	X	X						X			X		Section 8.1.6.3	
EQ-5D-5L ^{pq}	Completed every 2 weeks on the ePRO device													
SGRQ ^p	X								X		X		Section 8.1.6.5	
Review ePRO assessments/compliance	X	X	X	X	X	X	X	X	X				Section 8.1.6.4	
Confirm a visit (ePRO) ^r	X	X	X	X	X	X	X	X	X		X	X		
FeNO ^s	X	X						X			X		Section 8.1.5	

Table 2 Schedule of Activities – Treatment and Follow-up Period

Assessment/ activity	Induction Phase	Reduction Phase						Maintenance phase / EOT	FU	IPD visit	UNS ^a	Details in CSP Section or Appendix
	V6	V7	V8	V9	V10	V11	V12	V13	V14			
	W0 (Day 1)	W4	W8	W12	W 16	W 20	W 24	W 28	W40			
	Visit window (days) ^b											
	+5	±5	±5	±5	±5	±5	±5	±5	±7	N/A		
	N/A											
Pre-BD spirometry (X) assessments may be skipped for participants who have reached the permanent stop of the OCS reduction	X	X	X	(X)	X	(X)	(X)	X		X		Section 8.1.3
Post-BD spirometry	X							X		X		Section 8.1.3
Home assessment of PEF	Measurements every morning and evening throughout treatment period											Section 8.1.4
PEF adherence check	X	X	X	X	X	X	X	X	X			Section 8.1.4
Administration of study intervention ^t	X	X	X	X	X	X	X	X				Section 6.2
Review all OCS reduction criteria as per Table 8		X	X	X	X	X	X	X				Section 8.1.1.1
OCS dose reduction		X	X	X	X	X	X	X			X ^u	Section 8.1.1.1

^a Unscheduled visits may be initiated as needed, and additional assessments performed at these visits. At unscheduled visits for assessing an asthma exacerbation, at a minimum, these assessments need to be performed.

^b All visits are to be scheduled from the date of randomisation (Day 1), not from the date of previous visit.

^c COVID-19 questionnaire must be completed for each participant prior to study visit activities. Sites should also follow local SARS-CoV-2 testing guidelines outside of CSP study assessments, if applicable.

^d Asthma specific resource utilisation (eg, unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications).

- e Vital signs will be taken prior to administration of study intervention. Participants should be observed for a minimum of 2 hours after the first 2 study intervention administrations. For the remaining doses, participants will be observed for a minimum of one hour after study intervention administration.
- f To be performed locally at Visit 6, only if any new clinically significant ECG findings at Visit 1. To be performed locally at Visit 13 and IPD, only if the participant had a pre-existing cardiac condition, as determined at the discretion of the investigator. ECG must be collected prior to any blood draws.
- g During treatment period all laboratory samples should be obtained prior to study intervention administration. Participants should be fasting for at least 12 hours prior to blood collection. Blood eosinophil, basophil and monocyte numbers and percentages will be redacted from the central laboratory reports and blinded until primary database lock.
- h Urinalysis analysed by the central laboratory only if positive dipstick result observed at the site.
- i For WOCBP urine pregnancy test (dipstick) to be done at site at each treatment visit prior to study intervention administration. Positive urine pregnancy test must be confirmed by serum β -hCG.
- j All immunoglobulin results will be redacted from central laboratory reports and blinded until primary database lock.
- k At dosing visits, PK and ADA/nAb samples must be collected pre-dose.
- l Exploratory serum biomarkers, transcriptomics, and genetics data will be reported outside of the CSR and in a scientific manuscript or stand-alone report.
- m Assessment of eosinophils will be based upon a separate whole blood aliquot not linked to the complete blood count safety analysis.
- n Blood sample for DNA is optional and will be collected from participants who have consented to participate in the genetic analysis component of the study.
- o Daily Diary: Asthma Symptom Diary, global asthma symptom score items, rescue medication use, night-time awakenings, and adherence to maintenance medications.
- p To be completed on the ePRO device. Assessments during Visit 6, Visit 13 and IPD Visit are completed at site. All other assessments may be completed at home. If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.
- q EQ-5D-5L will be completed bi-weekly starting at Visit 6 and ending at Visit 13.
- r Visit can be confirmed within the ePRO device or in the ePRO study portal. Unscheduled visits related to asthma worsening should be confirmed.
- s FeNO test needs to be completed prior to spirometry. FeNO results will be blinded until primary database lock.
- t Study intervention should be administered after all other assessments have been completed at the visit.
- u Up-titration only.

2 INTRODUCTION

2.1 Study Rationale

Participants with uncontrolled severe asthma may require long-term daily maintenance treatment with OCS. However, OCS are associated with multiple and potentially debilitating adverse outcomes when given for extended periods of time. These include, but are not limited to, metabolic disorders such as glucose intolerance and dyslipidaemia (Gounarides et al 2008, de Oliveira et al 2011), osteoporosis (Sambrook et al 1990), adrenal axis insufficiency and excessive and abnormal fat deposition (Gounarides et al 2008). The odds for developing OCS associated side effects are dose dependently associated with long-term (≥ 6 months) OCS use starting at doses of 5 mg or even lower per day of prednisone (Dalal et al 2016). Chronic OCS dosing in patients with severe asthma is also associated with increased direct healthcare costs and resource utilisation. As such, a reduction in OCS dose in severe asthma patients requiring chronic maintenance OCS use would be of clinical relevance.

Previous randomised, controlled trials of monoclonal antibodies targeting type 2 (T2) cytokines, specifically interleukin [IL]-4/IL-13 and IL-5, or their respective receptors, have demonstrated tapering or discontinuation of the daily OCS doses in severe asthma patients requiring maintenance therapy with OCS (Bel et al 2014, Nair et al 2017, Rabe et al 2018), particularly in those with eosinophilic asthma.

In the OCS-sparing phase 3 study SOURCE (NCT03406078), tezepelumab numerically reduced OCS use in participants with OCS-dependent asthma compared to placebo, but the difference was not statistically significant. A numerically higher proportion of tezepelumab-treated participants reduced their daily OCS dose by 90–100% compared to placebo-treated participants. Post hoc analysis of the SOURCE data suggest that the lack of significance in the effect of tezepelumab on OCS dose reduction may have been due in part to study design features (Wechsler et al 2022). In addition, tezepelumab-treated participants with a baseline blood eosinophil count < 150 cells/ μL had less of an OCS-sparing effect than placebo-treated participants.

This study will evaluate the ability of tezepelumab versus placebo to reduce the daily maintenance dose of OCS in adults with asthma treated with high dose ICS plus LABA, with or without other asthma controller therapy, while maintaining asthma control.

2.2 Background

Asthma is a chronic inflammatory airway disease characterised by bronchial hyperreactivity and reversible airflow limitation that causes wheezing, shortness of breath, cough, and chest tightness. Although several treatments are available (eg, ICS, LABA, and long-acting muscarinic antagonists [LAMA]), there continues to be a clear unmet medical need among patients with severe asthma.

Biologic therapies can provide additional asthma control for patients with severe asthma. Omalizumab may be suitable for a subgroup of patients with proven reactivity to an aeroallergen and elevated serum immunoglobulin E (IgE) levels who remain inadequately controlled with ICS plus LABA (XOLAIR US PI 2019). Additional biologics, such as mepolizumab, reslizumab, benralizumab, and dupilumab, have been approved for severe asthma with an eosinophilic phenotype (NUCALA US PI 2019, CINQAIR US PI 2020, FASENRA US 2017, DUPIXENT US 2017). Biologics targeting IL-5, IgE, and IL-4 are now included in international treatment guidelines (Global Initiative for Asthma [GINA 2022]) as an add-on treatment for patients whose asthma remains uncontrolled despite high dose ICS/LABA treatment.

However, even when using currently available biologics, substantial proportions of patients continue to experience exacerbations and may benefit from agents that target different molecular pathways (Wenzel 2012, Froidure et al 2016, Swedin et al 2017). Therefore, despite these additional therapeutic options, there remains a clear unmet medical need among patients with severe asthma, independent of IgE status or eosinophil level, who are unable to gain complete asthma control using currently available therapies.

Thymic stromal lymphopoietin is an epithelial cell-derived cytokine that is produced in response to proinflammatory stimuli (eg, infectious, allergic, and environmental stimuli) and trauma. TSLP has an upstream and central role in the initiation of inflammatory responses and can activate a broad range of cell types including eosinophils, mast cells, T cells, dendritic cells, type 2 innate lymphoid cells and basophils (Tedeschi et al 2017, Watson and Gauvreau, 2014). Classically, TSLP may be a critical component in the initiation and perpetuation of the T helper 2 (Th2) response and the resulting cascade of cytokines associated with Th2 driven asthma (Kaur and Brightling 2012). Asthma is now recognised as a heterogenous disease with subsets of patients that do not exhibit Th2-associated disease (Wenzel 2012). There are emerging data that TSLP may also mediate non-allergic (non-T helper cell 2) inflammation (Tanaka et al 2009, Ziegler et al 2013). Given that TSLP is an upstream and pleiotropic cytokine, the blockade of TSLP is therefore anticipated to have broad impact on the spectrum of inflammatory responses seen in asthma.

Tezepelumab is a human monoclonal antibody (immunoglobulin [Ig]G2λ) that binds specifically to TSLP, blocking TSLP from interacting with its heterodimeric receptor (Gauvreau et al 2014).

In the PATHWAY phase 2b study (NCT02054130), tezepelumab significantly reduced exacerbations by up to 71% in adults with severe, uncontrolled asthma, irrespective of baseline disease phenotype (Corren et al 2017). In the NAVIGATOR (NCT03347279) phase 3 study tezepelumab reduced exacerbations in patients with severe, uncontrolled asthma, irrespective of baseline levels of T2 inflammatory biomarkers (blood eosinophil counts,

FeNO, and serum total IgE), allergic status, and baseline maintenance OCS use ([Menzies-Gow et al 2021](#)). In these studies, tezepelumab also improved lung function, asthma control, and patient health-related quality of life in the overall population.

Tezepelumab was well tolerated in the OCS-dependent asthma population in the SOURCE (NCT03406078) phase 3 study. In this study, 71.6 % (53/74) of tezepelumab-treated participants and 85.5% (65/76) of placebo-treated participants reported an adverse event (AE), and 14.9% (11/74) and 21.1% (16/76) reported a serious adverse event (SAE), respectively. There were no meaningful differences in the frequency and type of AEs between the tezepelumab and placebo groups.

In the NAVIGATOR phase 3 study, a total of 77.1% (407/528) of the participants in the tezepelumab group and 79.5% (422/531) of those in the placebo group reported an on-treatment AE, and 8.7% (46/528) and 13.2 (70/531) reported a SAE, respectively. At or after baseline, 4.9% (26/527) of the participants in the tezepelumab group and 8.3% (44/530) of those in the placebo group were positive for anti-drug antibodies. Neutralising antibodies were detected in 1 (0.2%) participant in each group ([Menzies-Gow et al 2021](#)).

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

2.3 Benefit/Risk Assessment

The benefit-risk assessment for tezepelumab in severe asthma based on development through Phase 3 is favourable. Benefits for tezepelumab over placebo demonstrated in exacerbation studies include a clinically meaningful reduction in AAER, clinically meaningful increases in FEV₁ and clinically meaningful improvements in asthma control metrics. In SOURCE there was a numerical benefit in OCS reduction with tezepelumab treatment.

Tezepelumab has been well tolerated in clinical trials to date. No serious allergic or anaphylactic reactions considered related to tezepelumab have been reported. To date there has been a low incidence of ADA and neutralising antibodies (nAb) reported with tezepelumab treatment in the Phase 2 or Phase 3 studies. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host 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.

Potential risks with tezepelumab will be mitigated by the selected inclusion/exclusion criteria and continuous monitoring of safety data during the study. In the present study, measures are taken to mitigate the risk for embryonal, foetal and child exposure to tezepelumab.

More detailed information about the known and expected benefits and risks of tezepelumab can be found in the IB.

2.3.1 Risk Assessment

Table 3 Risk Assessment

Important potential risks	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Serious infections are defined as infections fulfilling criteria for regulatory reporting	The mechanism of action of tezepelumab suggests potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to infection. Although there is a theoretical risk of serious infections with tezepelumab treatment, there is no data to support this potential risk. There is also no evidence for causal relationship with tezepelumab.	Vulnerable participants will be excluded based on eligibility criteria, and randomised participants will be monitored for infection with complete blood counts, including differential white cell count throughout the study; and through standard AE/SAE reporting. Participants will be excluded if they received systemic immunosuppressive or immunomodulating drugs within the last 12 weeks or 5 half-lives (whichever is longer) prior to Visit 1; <u>or</u> if they have a history of a known immunodeficiency disorder; <u>or</u> have a history of clinically significant infection requiring treatment with systemic antibiotics or antiviral medications finalised < 2 weeks before Visit 1 or during the run-in period or at randomisation; <u>or</u> who have evidence of active coronavirus disease 2019 (COVID-19) infection during the run-in period or optimisation phase; <u>or</u> have had tuberculosis requiring treatment within the 12 months prior to Visit 1. Serious infections are an AESI and participants who develop serious infection will be followed up closely throughout study.
Malignancies	Given the potential theoretical risk, the long-term treatment intended for a chronic disease and the nature of malignancy development, malignancy is included as an important potential risk. There is no evidence to suggest increase in malignancies in the data to-date in either pre-clinical or clinical studies. No	Participants with current malignancy or whose curative therapy was completed recently will be excluded from participation based on eligibility criteria. All participants will be closely followed during the study for any adverse events, including malignancies that are considered AESI.

	causal relationship with tezepelumab could be established for cases reported.	
Serious cardiac events	A numerical imbalance in cardiac disorder SAEs was observed in the DESTINATION Long Term Extension study (Investigator's Brochure) with more events in participants treated with tezepelumab versus participants treated with placebo. None of the cardiac disorder SAEs was considered causally related to tezepelumab by investigators or Independent Adjudication Committee. There is no known mechanism by which blocking TSLP would lead to cardiac pathophysiology.	Participants with cardiac disorders that are not stable in the opinion of the investigator or who present meaningful abnormal findings in examination, lab assessments or ECG will be excluded based on eligibility criteria. All participants will be closely followed during the study for any adverse events, including serious cardiac events that are considered AESI.
Potential risks	Summary of data/rationale for risk	Mitigation strategy
Study intervention		
Serious hypersensitivity reactions	Systemic reactions to large therapeutic molecules can be IgE or non-IgE-mediated and are generally characterised by signs and symptoms such as skin rash, urticaria, pruritus, local or diffuse erythema, angioedema, fever, chills, cough, dyspnoea, wheezing, bronchospasm, nausea/vomiting, diaphoresis, chest pain, tachycardia or bradycardia, and/or hypotension, which can all be severe or life-threatening. Effects typically occur during or within several hours after study intervention but may be delayed. The administration of a monoclonal antibody can result in the formation of ADA. The occurrence of ADA could result in immune complex disease (Type 3 hypersensitivity reactions) with manifestations such as serum sickness, nephritis, and vasculitis, or altered tezepelumab levels or activity.	To mitigate the potential risk of serious hypersensitivity reactions during and after administration of tezepelumab, specific requirements for observing participants for AEs/SAEs and for monitoring vital signs are included in this CSP. In addition, medical equipment to treat acute anaphylactic reactions will be immediately available and site staff will be trained to recognise and treat anaphylaxis. To mitigate the potential risk of immune complex disease participants will be monitored for confirmed immune complex disease through routine monitoring of AEs/SAEs. Participants with sensitivity to any component of the study intervention or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation will be excluded. Participants who have a history of anaphylaxis or documented immune

		complex disease following any biologic therapy will also be excluded. Serious hypersensitivity reactions are an AESI and these events will be monitored closely throughout the study.
Helminth infections	Potential inhibitory effects on immune responses mediated by Th2 cells, leading to the possibility of diminution of the host's protective response to parasitic infestation/infection.	To decrease the risk of parasitic infestation or infection participants with a helminth infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy will be excluded. Helminth infections are an AESI. Participants who develop such infections will be monitored closely throughout the study.
Study procedures		
Risk for adrenal insufficiency complication	As a result of OCS dose reduction, adrenal insufficiency (AI) may develop when participants receive daily doses below 5 mg.	To mitigate the potential risk of AI dose reductions will occur every 4 weeks which should allow for carryover effects from the previous dose to be minimised and minimise the risk for AI complications. In addition, the OCS dose will be tapered with decreasing daily dose to allow the adrenal glands to adapt to the lower dose of external corticosteroids. At each Visit in the OCS reduction phase signs and symptoms of AI will be assessed by the investigator and the assessment will contribute to the OCS titration decision (ie, AI suspicion will be a stop criterion for OCS dose reduction).

COVID-19 Pandemic, risk of COVID-19 infection	There is the risk of exposure to COVID-19 to participants during site visits	Local guidelines will be followed to mitigate risk of participant's exposure to COVID-19. To identify potential COVID-19 infection during the study a COVID-19-related questionnaire is recommended prior to every visit. Visits will be deferred if abnormalities noted. Sites are recommended to follow local severe acute respiratory coronavirus 2 (SARS-CoV-2) testing guidelines, if applicable. COVID-19 vaccination is allowed during the study (see Table 6).
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2.3.2 Benefit Assessment

Benefits for tezepelumab over placebo in reducing the participants' OCS dose in this study might include a decrease in corticosteroid toxicity through both a reduction in the OCS daily dose and overall corticosteroid load, a clinically meaningful reduction in asthma exacerbations, improvement in lung function and asthma control metrics ([Corren et al 2017](#), [Menzies-Gow et al 2021](#)). Participants in this study may benefit from the continuous monitoring of their asthma and other health conditions. In addition, participants will also be contributing to the development of therapies for severe asthma.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants enrolling in this study (see Section [2.3.1](#)), the potential risks identified associated with tezepelumab are justified by the anticipated benefits that may be afforded to participants in this study, all of whom have OCS-dependent severe asthma.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objectives	Endpoints/variables
Primary	
To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	Endpoint: Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control. The categories for percent change from baseline in daily OCS dose are defined as: 1. $\geq 90\%$ to $\leq 100\%$ reduction 2. $\geq 75\%$ to $< 90\%$ reduction 3. $\geq 50\%$ to $< 75\%$ reduction 4. $> 0\%$ to $< 50\%$ reduction 5. no change or any increase.
	Population: Adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, and who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.
	Intercurrent events: • Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 will be included in the analysis (treatment policy strategy). • Initiate therapy with another biologic for treatment of asthma: final dose for analysis will be defined as the OCS dose achieved prior to initiation of another biologic for treatment of asthma, increased by one dose level (composite strategy).
	Summary measure: The cumulative odds ratio at Week 28 (tezepelumab/placebo).
Key Secondary	
To evaluate the effect of tezepelumab compared with placebo on pre-BD lung function in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	Endpoint: Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁) at Week 28.
	Population: Adults with severe asthma who require daily or daily equivalent maintenance OCS therapy in addition to high dose ICS plus LABA, with or without other asthma controllers, who have had at least 1 asthma exacerbation in the previous 2 years and have received at least one dose of study intervention.
	Intercurrent events: • Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 will be included in the analysis (treatment policy strategy). • Initiation of another biologic for treatment of asthma: post intercurrent event data will be imputed assuming an unfavorable outcome (composite strategy).

Table 4 Objectives and Endpoints

Objectives	Endpoints/variables
	Summary measure: The difference in means at Week 28 (tezepelumab – placebo).
Secondary	
To evaluate the effect of tezepelumab compared with placebo on the daily dose of maintenance OCS	- Proportion of participants with 100% reduction from baseline in daily maintenance OCS dose at Week 28 - Proportion of participants with daily maintenance OCS dose $\leq$ 5 mg at Week 28 - Proportion of participants with $\geq$ 50% reduction from baseline in daily maintenance OCS dose at Week 28
To evaluate the effect of tezepelumab compared with placebo on asthma exacerbations	- Annualised asthma exacerbation rate (AAER) over 28 weeks - Time to first asthma exacerbation Supportive outcome variables: - Rate of asthma exacerbations associated with emergency room (ER) visit, urgent care visit, or hospitalisation over 28 weeks - Proportion of participants who did not experience an asthma exacerbation over 28 weeks
To assess the effect of tezepelumab compared with placebo on asthma control and other asthma control metrics	Change from baseline in - Asthma Control Questionnaire 6 (ACQ-6) score at Week 28 - Weekly mean home peak expiratory flow (PEF) (morning and evening) at Week 28
To assess the effect of tezepelumab compared with placebo on asthma-related quality of life	Change from baseline in: - Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score at Week 28 - St George's Respiratory Questionnaire (SGRQ) score at Week 28
To assess the effect of tezepelumab on biomarkers	Change from baseline in fractional exhaled nitric oxide (FeNO), peripheral blood eosinophils and total serum immunoglobulin E (IgE) at Week 28
To evaluate the pharmacokinetics (PK) of tezepelumab	Tezepelumab serum trough concentrations at Week 0, 12, and 28
To evaluate the immunogenicity of tezepelumab	Incidence of anti-drug antibodies (ADAs) at Week 0, 12, 28, and 40
Safety	
To evaluate the safety and tolerability of tezepelumab	- Adverse events (AEs), serious adverse events (SAEs) - Clinical chemistry, haematology - Vital signs
Exploratory	
To explore the effect of tezepelumab compared with placebo on other pre-BD lung function measures	Including, but not limited to, the change from baseline in - pre-BD forced vital capacity (FVC) at Week 28 - forced expiratory flow over 25- 75% of the vital capacity (FEF25-75%) at Week 28

Table 4 Objectives and Endpoints

Objectives	Endpoints/variables
To explore the effect of tezepelumab compared with placebo on post-BD lung function	Including, but not limited to, the change from baseline in - post-BD forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) at Week 28 - forced expiratory flow over 25- 75% of the vital capacity (FEF25-75%) at Week 28
To assess the effect of tezepelumab compared with placebo on general health-related quality of life	Change from baseline in European Quality of Life - 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score at Week 28
To assess the effect of tezepelumab compared with placebo on health status of participants with airway obstruction disease	Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) at Week 28
To evaluate the efficacy of tezepelumab compared with placebo on health resource utilisation	Number of asthma specific resource utilisations (eg, unscheduled physician visits, unscheduled phone calls to physicians, ER/hospitalisations due to asthma, use of other asthma medications)
To evaluate the effect of tezepelumab on circulating pharmacodynamic (PD) biomarkers and relationship of baseline biomarkers with clinical response	Including, but not limited to, serum cytokines (TSLP, IL-5, and IL-13)
To evaluate the effect of tezepelumab on blood transcriptome for PD effect and associate with clinical response	Transcriptomic profiling
To evaluate the relationship of genetic variants from DNA and associate with clinical response	Genomics/genetics profiling
To evaluate the effect of tezepelumab compared with placebo on the exposure of systemic corticosteroids	Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 weeks

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the effect of tezepelumab compared to placebo on oral corticosteroid (OCS) dose reduction, whilst maintaining asthma control, in adult participants with severe, OCS-

dependent asthma. The study will also investigate the effects of tezepelumab on lung function, clinical markers of asthma control, including asthma exacerbation rate and patient-reported outcomes, along with biomarkers of asthma inflammation.

Approximately 207 participants age 18 to 80 years will be randomised to tezepelumab or placebo, in a 2:1 ratio, for a total of 7 doses.

Participants will be required to have $\text{EOS} \geq 150$ cells/ μL at Visit 1 or a documented history of $\text{EOS} \geq 300$ cells/ μL within 12 months prior to Visit 1.

Participants randomised will be monitored to ensure that a maximum of 20% have an eosinophil count of < 150 cells/ μL at Visit 1 (with a historical $\text{EOS} \geq 300$ cells/ μL within 12 months prior to Visit 1) and approximately 40% have ≥ 300 cells/ μL at Visit 1. When the target percentage of certain subgroup participants is reached, consideration will be given to closing the Interactive Response Technology (IRT)/Randomisation and Trial Supply Management (RTSM) randomisation for that subgroup, which may be done either overall or within a region/country. Once a subgroup is closed, participants in the Visit 1/run-in period in the closed subgroup will not be allowed to be randomised and will be classified as screen failures. Treatment allocation will be stratified by region and eosinophil counts at Visit 1 (< 150 cells/ μL , $150 - < 300$ cells/ μL , ≥ 300 cells/ μL) to ensure that treatment assignment across regions and eosinophil subgroups is balanced.

The study will randomise participants treated with documented OCS maintenance therapy for at least 6 months prior to Visit 1 and who are receiving a stable dose of OCS in the range ≥ 7.5 mg to ≤ 30 mg (prednisone or prednisolone) daily or daily equivalent for at least 1 month prior to Visit 1. Participants will be required to be on a medium dose (MD) or high dose (HD) ICS (as defined in [GINA 2022](#)) for at least 12 months prior to Visit 1 and on LABA with HD ICS for at least 3 months prior to Visit 1. Additional maintenance asthma controller medications are allowed according to standard of care practice. Their use must be documented for at least 3 months prior to Visit 1. Participants will remain on their entry asthma maintenance treatments (ICS/LABA, other controllers), without any changes, from Visit 1 until preferably 4 weeks after last dose of study intervention.

A schematic view of the study is shown on [Figure 1](#). After enrolment into Visit 1, all participants will enter a 2-week run-in period and then an up to 8-week OCS optimisation phase. The OCS optimisation phase is to establish participant eligibility and a minimum effective dose (the optimised dose) of prescribed OCS. The OCS optimisation phase may be shortened if an optimised OCS dose is determined earlier than 8 weeks or may be extended to allow for treatment of an asthma exacerbation and then permit the 2-week period of participants receiving a stable optimised OCS dose prior to randomisation. There are 3 phases in the treatment period following randomisation (Visit 6):

- **Induction phase** – from Visit 6 (Week 0) to Visit 7 (Week 4) during which participants should remain on their optimised OCS dose.
- **OCS reduction phase** – from Visit 7 (Week 4) to Visit 12 (Week 24) during which the OCS dose reduction should be started at Visit 7, with the possibility of dose reduction every 4 weeks.
- **Maintenance phase** – from one day after Visit 12 (Week 24) to the day of Visit 13 (Week 28), which is the End of Treatment visit. In this phase, participants should remain on the stable maintenance OCS dose reached during the reduction phase or continue without OCS if the OCS dose was reduced to 0 mg during the reduction phase. No further OCS dose reduction will take place during this phase.

Two database locks (DBLs) are planned in this study.

- 1 The primary DBL will be conducted after all participants have completed 28 weeks of treatment. All AstraZeneca personnel involved in the analysis and conduct of the study will remain blinded until the primary DBL. After the primary DBL, the treatment allocation for participants will become known to the sponsor staff and/or designated contract research organisation staff. The blind will be maintained for the investigator, investigational site staff, and for the participant until the final DBL.
- 2 The final DBL will be conducted once all participants have completed the safety follow-up visit at Week 40.

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

This guidance 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 consideration if site personnel or study participants become infected with 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 comply with the study protocol. 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 following screen failure and/or 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 AstraZeneca Study Physician. Before randomisation, the Principal Investigator (PI) must ensure that all eligibility criteria are fulfilled. The investigator should confirm with the designated AstraZeneca 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 study intervention administration: Performed by a qualified HCP. Additional information related to the visit can be obtained via telemedicine. First 3 doses of study intervention must be administered on-site (see Section 6.2.3).
- For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to [Appendix J](#).

4.2 Scientific Rationale for Study Design

In this study, tezepelumab is being compared to placebo. Both are given in addition to standard of care treatment in order that their effect can be assessed in an appropriate clinical context. This study is a randomised, parallel-group, double-blind study in which participants are stratified by region and eosinophil counts.

The OCS-dependent severe asthma population has been chosen as a reduction in the daily OCS dose will provide benefit by potentially reducing the associated multiple side effects of chronic OCS whilst potentially providing efficacy benefits.

In this study, in participants who experience an asthma exacerbation or asthma worsening, further OCS dose reduction will not be permitted (see [Table 8](#), section 8.1.1.1). A similar approach was taken in previous OCS-sparing studies with asthma biologics, ie, benralizumab (ZONDA) and dupilumab (VENTURE), ([Nair et al 2017](#), [Rabe et al 2018](#)). In contrast, in the SOURCE study ([Wechsler et al 2022](#)), multiple attempts for OCS dose reduction were allowed regardless of asthma exacerbations or failure to meet asthma control criteria.

In this study the treatment period is 28 weeks which is similar to that in the dupilumab (VENTURE) and benralizumab (ZONDA) OCS-sparing studies (24 and 28 weeks respectively), but shorter than in the SOURCE study (48 weeks).

Compared to this study, the SOURCE study had a substantially longer reduction phase (36 weeks). This offered all participants an extended opportunity to reduce their OCS dose despite having periodic loss of asthma control. The reduction phase in this study is of 20 weeks duration. This is because, in contrast to the SOURCE study, multiple attempts to reduce the dose of OCS are not permitted. Whenever a participant fails to meet the asthma control criteria for OCS dose reduction, the OCS dose will be increased at least one step higher and no further dose reduction will be allowed. This dose will then be maintained until the end of treatment (EOT) visit. The shorter duration of the OCS dose reduction phase has been shown to be sufficient in previous OCS-sparing studies with dupilumab (VENTURE) and benralizumab (ZONDA), (Rabe et al 2018, Nair et al 2017) where 16 and 20 weeks OCS dose reduction periods were implemented.

In order to further simplify the SUNRISE study design, the duration of the maintenance phase is reduced to 4 weeks compared to 8 weeks in the SOURCE study, as the additional 4 weeks did not appear to change the outcome in SOURCE.

In this study participants will be required to have $\text{EOS} \geq 150$ cells/ μL at Visit 1, or a documented history of $\text{EOS} \geq 300$ cells/ μL within 12 months prior to Visit 1, owing to the limited effect of tezepelumab in reducing maintenance OCS treatment in SOURCE in participants with a blood eosinophil count at baseline of < 150 cells/ μL .

The optimisation phase is required to ensure that study participants are OCS-dependent, and to establish the lowest OCS dose at which asthma control is maintained for baseline purposes. The duration of the induction phase is limited to 4 weeks given the dosing intervals of tezepelumab alongside the observed time to effect in previous studies (Corren et al 2017, Menzies-Gow et al 2021). The OCS reduction phase has been set at 20 weeks to reflect the learnings from SOURCE study design as mentioned above. The 4-week maintenance phase is to ensure asthma control is maintained while on the reduced or zero OCS dose. The same strict criteria will be used during the optimisation and OCS reduction phases to ensure that asthma control is assessed consistently throughout the study. In addition, the study will evaluate the effect of tezepelumab on lung function, AAER, asthma control, and safety to further characterise the benefit-risk profile of the drug and understand how best to position it in the treatment pathway.

4.3 Justification for Dose

The tezepelumab dose of 210 mg SC Q4W was selected based on the efficacy and safety results from the Phase 2b PATHWAY study. In the PATHWAY study, 210 mg tezepelumab Q4W led to numerically improved efficacy compared with 70 mg Q4W, whereas the 280 mg Q2W dose did not increase efficacy further over the 210 mg Q4W dose.

Tezepelumab was well tolerated at all 3 doses in the PATHWAY study and the safety profile was well balanced between the tezepelumab and placebo groups with no evidence of a dose relationship for AEs.

Efficacy and safety of the 210 mg SC Q4W dose was further confirmed in the pivotal Phase 3 NAVIGATOR study in adults and adolescents with severe asthma.

4.4 End of Study Definition

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

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

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

5 STUDY POPULATION

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

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 form.

Type of Participant and Disease Characteristics

2. Documented physician-diagnosed asthma for at least 12 months prior to Visit 1.
3. Participants must have received a physician-prescribed medium- or high-dose ICS (medium dose ICS corresponds to 500 µg and high dose ICS corresponds to > 500 µg fluticasone propionate dry powder formulation or equivalents) as per GINA guideline ([GINA 2022](#)) for at least 12 months prior to Visit 1.
4. Participants must have received physician-prescribed LABA and high dose ICS (total daily dose > 500µg fluticasone propionate dry powder formulation or equivalent) for at least 3 months prior to Visit 1. The ICS and LABA can be parts of a combination product or given by separate inhalers.
 - (a) Equivalent ICS doses as detailed in [Appendix G](#)
5. Additional maintenance asthma controller medications are allowed according to standard practice of care ie, leukotriene receptor antagonists (LTRAs), theophylline, long-acting muscarinic antagonists (LAMAs), and chromones. The use of these medications must be documented for at least 3 months prior to Visit 1.
6. Participants must have received OCS for the treatment of asthma for at least 6 months prior to Visit 1 and on a stable dose of between ≥ 7.5 to ≤ 30 mg (prednisone or prednisolone) daily or daily equivalent for at least one month prior to Visit 1. The OCS dose may be administered every other day (or different doses every other day); Average dose over 2 days = The daily dose.
7. Morning pre-BD FEV₁ must be < 80% predicted normal at Visit 1 or Visit 2.
8. Evidence of asthma as documented by either:
 - (a) Post-BD (albuterol/salbutamol) responsiveness test result: FEV₁ $\geq 12\%$ and ≥ 200 mL (15-30 min after administration of 4 puffs of albuterol/salbutamol), documented either in the previous 60 months prior to or at Visit 1 or at Visit 2 or at Visit 3.
OR
 - (b) Airway hyperresponsiveness (methacholine: provocative concentration that causes a positive reaction [PC20] of < 8 mg/mL) documented in the 60 months prior to Visit 1.
9. Blood eosinophils at Visit 1 ≥ 150 cells/µL ($\geq 0.15 \times 10^9/L$ or $\geq 0.15 \times 10^3/\mu l$) or documented EOS ≥ 300 cells/µL ($\geq 0.3 \times 10^9/L$ or $\geq 0.3 \times 10^3/\mu l$) within 12 months prior to Visit 1.
10. Participants must have a history of at least one asthma exacerbation event within 24 months prior to Visit 1. For the purpose of this study an asthma exacerbation is defined as a worsening of asthma that either:

- (a) required treatment with a burst of systemic corticosteroids for at least 3 consecutive days or a single depot- injectable corticosteroid dose OR
- (b) resulted in an emergency department visit (defined as evaluation and treatment for < 24 hours in an ER or urgent care centre) which required systemic corticosteroids (as per above) OR
- (c) an inpatient hospitalisation due to asthma (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)

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

The below defines acceptable documentation of an exacerbation:

- (a) Discharge summaries from a hospital, emergency room (ER), or an urgent care facility indicating that a participant was hospitalised/treated with systemic steroids for an asthma exacerbation.
- (b) Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
- (c) Participants can provide evidence of prescriptions for systemic steroids used during an exacerbation.
- (d) A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

Weight

11. Body weight ≥ 40 kg at Visit 1.

Sex

12. Male or female.
13. All women of childbearing potential must have a negative serum pregnancy test results at Visit 1 and a negative urine pregnancy test at randomisation.
14. Female participants of childbearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, from enrolment throughout the study and until at least 16 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea

method are not acceptable methods of contraception. Female condom and male condom should not be used together.

- (a) A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly.
- (b) Highly effective birth control methods include: sexual abstinence (please note: periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to Investigational Medicinal Product (IMP), and withdrawal are not acceptable methods of contraception), a vasectomised partner, Implanon®, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system, Depo-Provera™ injections, oral contraceptive, and Evra Patch™, Xulane™, or NuvaRing

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

Women not of 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 date of randomisation without an alternative medical cause. The following age-specific requirements apply:

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

Informed Consent

- 15. 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.
- 16. Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Participant must meet the following criteria at the start of optimisation phase (Visit 2):

- 17. Minimum 10 days compliance with both the morning and evening daily diary completion and morning PEF measurements during the 14 days prior to Visit 2.
A compliant day requires completion of evening diary assessment and subsequent morning diary assessment such that an ASD daily score can be calculated.

18. Minimum 10 days compliance with OCS, ICS, LABA and other asthma controller medications as captured in the daily diary during the 14 days prior to Visit 2.

Participant must meet the following criteria at the randomisation visit (Visit 6):

19. Participant must have received the optimised OCS dose for at least 2 weeks prior to randomisation.
20. Minimum 70% compliance with all asthma controller medication dosing including OCS, ICS/LABA at Visits 3-5 during the OCS optimisation phase.
21. Minimum 70% compliance with the morning and evening daily diary completion and morning PEF measurements at Visits 3-5 during the OCS optimisation phase.
- (a) A compliant day requires completion of evening diary assessment and subsequent morning diary assessment such that an ASD daily score can be calculated.
22. Minimum 10 days compliance with the morning and evening daily diary completion and morning PEF measurement during the 14 days prior to randomisation.
- A compliant day requires completion of evening diary assessment and subsequent morning diary assessment such that an ASD daily score can be calculated.
- (a) The period for this criterion is the duration from the evening of the OCS dose adjustment (defining the optimised dose) during the optimisation phase until the morning of the randomisation visit.
23. Minimum 10 days compliance with OCS, ICS, LABA and other asthma controller medications as captured in the daily diary during the 14 days prior to randomisation.
- (a) Days with missing daily diary data treated as non-compliant for this criterion
24. Acceptable inhaler, peak flow meter, and spirometry techniques as judged by the investigator.

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 (COPD), bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (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 Asthma exacerbation, requiring use of systemic corticosteroids or increase in the maintenance dose of OCS finalised within 30 days prior to Visit 1.
- 5 Clinically significant infection, including upper or lower respiratory tract infection (URTI and LRTI, respectively), requiring treatment with systemic antibiotics or antiviral medications finalised < 2 weeks before Visit 1 or during the run-in period.
- 6 Participants with evidence of active COVID-19 infection during run-in period and optimisation. Evaluation will be based on local standard of care as determined by current local guidelines.
- 7 A helminth infection diagnosed within 6 months prior to Visit 1 that has not been treated with, or has failed to respond to, standard of care therapy.
- 8 A participant who is on short-acting beta agonists (SABA) maintenance treatment within 30 days prior to Visit 1.
- 9 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.
- 10 Chronic alcohol or drug abuse within 12 months prior to Visit 1.
- 11 Tuberculosis requiring treatment within the 12 months prior to Visit 1.
- 12 A positive human immunodeficiency virus (HIV) test at Visit 1 or participant taking antiretroviral medications or history of any known immunodeficiency disorder, as determined by medical history and/or participant's verbal report.
- 13 Major surgery within 8 weeks prior to Visit 1 or planned surgical procedures requiring general anaesthesia or hospitalisation for > 1 day during the conduct of the study.

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 non-biologic agent within 30 days or 5 half-lives (whichever is longer) prior to Visit 1.

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

- 15 Treatment with the following medications within the last 12 weeks or 5 half-lives (whichever is longer) prior to Visit 1: systemic immunosuppressive/immunomodulating drugs (eg, methotrexate, cyclosporine, oral/parenteral/intra-articular corticosteroids for other use than treatment of asthma)
- 16 Receipt of immunoglobulin or blood products within 30 days prior to Visit 1.
- 17 Receipt of the T2 cytokine inhibitor Suplatast tosilate within 15 days prior to Visit 1.
- 18 Receipt of live attenuated vaccines 30 days prior to the date of randomisation and during the study including the follow-up period.
- 19 COVID-19 vaccination within 28 days prior to randomisation.
- 20 Participants who have been treated with bronchial thermoplasty within 36 months prior to Visit 1.

Prior/concurrent Clinical Study Experience

- 21 Sensitivity to any component of the study intervention formulation or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.
- 22 History of anaphylaxis or documented immune complex disease (Type III hypersensitivity reactions) following any biologic therapy.
- 23 Concurrent enrolment in another IP-related interventional clinical trial.
- 24 Participant randomised in other ongoing or previous tezepelumab studies.
- 25 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.

Diagnostic Assessments

- 26 Any clinically meaningful abnormal findings in physical examination, vital signs, electrocardiogram (ECG), haematology, clinical chemistry, or urinalysis during the run-in period, 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 entire duration of the study.
- 27 Evidence of active liver disease, including jaundice or aspartate transaminase, alanine transaminase, or alkaline phosphatase beyond twice the upper limit of normal (ULN), at Visit 1.

- 28 Positive hepatitis B surface antigen, or hepatitis C virus antibody serology at Visit 1, 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

- 29 Women who are currently pregnant (confirmed with positive pregnancy test) or breastfeeding or lactating.
- 30 Unwillingness or inability to follow the study procedures, or restrictions, in the opinion of the investigator
- 31 Previous allogeneic bone marrow transplant.
- 32 Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Exclusion Criteria at Randomisation:

- 33 During the optimisation period, asthma control reached at an OCS dose of < 7.5 mg or > 30 mg and/or 3 consecutive dose reductions after which asthma control was still obtained.
- 34 Evidence of clinically significant infection (including COVID-19) or participant receiving treatment with systemic antibiotics or antiviral medications.
- 35 Despite screening of the participant, enrolment/randomisation is stopped at the study level.

5.3 Lifestyle Considerations

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

5.3.1 Meals and Dietary Restrictions

Participants should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the study site. Participants should not eat or drink 1 hour prior to having FeNO assessment and should be fasting for at least 12 hours prior to blood collection.

5.3.2 Alcohol and Tobacco

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

Current smokers or participants with smoking history ≥ 10 pack-years at Visit 1 are not allowed. Former smokers with a smoking history of < 10 pack-years must have stopped for at least 6 months to be eligible. Smoking is not allowed throughout the course of the study. The use of e-cigarettes is also not allowed during the course of the study.

5.3.3 Activity

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

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

These participants should have the reason for study withdrawal recorded as 'Screen Failure' in the electronic Case Report Form (eCRF). This reason for study withdrawal is only valid for screen failures, and not randomised participants.

5.4.1 Re-screening

Participants with clinically significant infection, including respiratory infections requiring systemic antibiotics or antiviral medication during run-in should be screen failed but may be re-screened 2 weeks after completion of the therapy.

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

Participants who are screen failed due to positive SARS-CoV-2 test or symptoms of COVID-19 infection may be re-evaluated after approximately 2 weeks for potential re-screening upon discussion with AstraZeneca Study Physician.

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

Any re-screened participant will be re-enrolled and reassigned their originally assigned enrolment number after signing a new ICF. All Visit 1 assessments as listed in the SoA (Section 1.3) should be re-performed with the exception of testing for HIV-1 and HIV-2, hepatitis B and C, and FSH. If the timeframe between screening and re-screening is more than 30 days, then all Visit 1 assessments should be repeated.

6 STUDY INTERVENTION

Study intervention is defined as the investigational intervention(s) or placebo intended to be administered to a study participant according to the study protocol. Study intervention in this study refers to tezepelumab or placebo.

6.1 Study Intervention(s) Administered

6.1.1 Study Interventions

Table 5 Study Treatments

Arm name	Treatment 1	Treatment 2
Intervention name	Tezepelumab	Placebo
Type	Biologic, combination product	Placebo, combination product
Dosage formulation	110 mg/mL in 10 mM acetate, 3.0% (w/v) L-proline, 0.01 % (w/v) polysorbate 80, pH 5.2	0.7% (w/v) sodium carboxy methyl cellulose in 10 mM acetate, 250 mM L-proline, 0.01% (w/v) polysorbate 80, pH 5.0
Unit dose strength(s)	210 mg	N/A
Dosage level(s)	210 mg Q4W	Placebo Q4W
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study Intervention will be provided in APFS with 1.91 mL fill volume. Each syringe and carton will be labelled in accordance with GMP and per country regulatory requirement. The labels will be translated into the local language where applicable.	Study Intervention will be provided in APFS with 1.91 mL fill volume. Each syringe and carton will be labelled in accordance with GMP and per country regulatory requirement. The labels will be translated into the local language where applicable.
Current/former name(s) or alias(es)	Formerly MEDI9929 and AMG 157	N/A

APFS, accessorised pre-filled syringe; IMP, investigational medicinal product; N/A, not applicable; NIMP, non-investigational medicinal product; Q4W, every 4 weeks; SC, subcutaneous

The APFS is a single use, disposable system that is designed to deliver the labelled dose to the SC space during one injection and automatically provide a needle 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.

6.1.2 Medical Devices

The sponsor-manufactured combination product, which includes a device constituent, is:

- Accessorised pre-filled syringe (APFS)

The medical devices manufactured by third parties and provided for use in this study are:



Instructions for medical device use are provided in device-specific Instructions for Use documents.

All medical device deficiencies (including malfunction, use error, and inadequate labelling) shall be documented and reported by the investigator throughout the study (see Section 8.3.13) and appropriately managed by the manufacturer.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation and handling

Blinded study intervention will be supplied to the site in a kit containing APFS tezepelumab or placebo. The kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the APFS within the carton).

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

All study intervention must be stored at the study site in a secure, temperature controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. Only participants enrolled in the study may receive study intervention and only authorised site staff may administer study intervention.

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, the site staff should not use the affected study intervention and should immediately contact an AstraZeneca representative for further guidance and reporting as per the Pharmacy Manual:

- Temperature excursion upon receipt or during storage at the study centre
- 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 IRT/RTSM (please refer to IRT/RTSM manual for further details).

The investigator or designee is responsible for study intervention 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 Pharmacy 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. Each APFS obtained for administration should be visually inspected prior to dose preparation. If defects are noted with the study drug device combination product, the investigator and AstraZeneca representative(s), including the Site Monitor, should be notified immediately as per the Pharmacy Manual. Refer to the Product Complaint section for further instructions (Section [6.2.4](#)).

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 IRT/RTSM. The IRT/RTSM will provide to the investigator(s) or pharmacist(s) the kit identification number to be allocated to the participant at the dispensing visit.

Dose preparation steps:

- 1 Study intervention should be at 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 APFS from the carton by holding the middle of the syringe body.
- 3 Unwrap, but do not detach, the wrap-around label attached to APFS 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 APFS 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 administration as per the site's standard operating procedures, the kit boxes must be retained for study intervention accountability.

6.2.3 Dose Administration

Prior to each study intervention administration at the study site or participant's home:

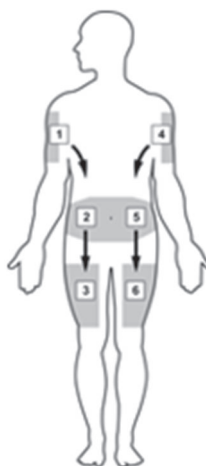
- Investigator/authorised delegate will assess injection site as per standards of medical care.
- For women of childbearing potential, urine pregnancy test will be done; study intervention will be administered only when the result of the test is negative (see Section [8.2.5.1](#)).

The administration of all study intervention should be recorded in the appropriate sections of the eCRF. The study intervention will be administered at the study site. The study intervention will be administered by the investigator/authorised delegate or qualified HCP (eg, pharmacist or study nurse) as specified in the SoA (Section [1.3](#)). Each participant will receive tezepelumab 210 mg (one 1.91 mL injection) or matching placebo administered SC Q4W for 7 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 approximately a 45-degree angle into the SC tissue. The injection site should not be rubbed after each injection. It is suggested that the site of injection of study intervention be rotated such that the participant receives study

intervention at a different anatomical site each visit. Suggested injection site rotation sequence is presented below (see [Figure 2](#)). In cases when rotation of the injection site is not favourable for the participant and/or investigator, the reason should be recorded in the source documents. The injection site must be recorded in the source documents and the eCRF at each treatment visit.

Figure 2 Suggested Scheme of Rotation of Injection Sites



Further details on study intervention administration are provided in the Study Intervention Handling Instructions. Study intervention administration must be carried out in line with the instructions provided.

Participants should be observed by the qualified HCP for a minimum of 2 hours after 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 one hour after study intervention administration for any such reaction. If any of the following occur, the investigator should reschedule the visit and the study intervention should not be administered until the rescheduled visit:

- 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 may compromise the safety of the participant in the study (eg, viral illnesses).
- The participant was febrile ($\geq 100.4^{\circ}\text{F}$; $\geq 38^{\circ}\text{C}$) 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 or based on assessment of COVID-19 symptoms.

The visit should be rescheduled within the allowed visit window and study intervention should

be administered at that rescheduled visit.

If the participant is suspected to have an active COVID-19 infection or fever ($\geq 100.4^{\circ}\text{F}$; $\geq 38^{\circ}\text{C}$) suspected due to COVID-19 infection, the visit should be rescheduled (and study intervention administration deferred) and participant should be re-assessed for symptoms of COVID-19 prior to rescheduled visit.

The AstraZeneca Study Physician should be contacted to discuss further participation in the following situations:

- The participant has been diagnosed with an active COVID-19 infection.
- The participant skips 2 consecutive study intervention administrations, regardless of the reason.

If the participant reports an injection site reaction, the investigator or qualified designee will complete the AE eCRF page.

Any change from the study intervention dosing schedule, dose interruptions, or dose discontinuations should be recorded in eCRF; study intervention dose modifications are prohibited.

6.2.4 Reporting Product Complaints

Any defects with the study intervention must be reported immediately to the Site Monitor / AstraZeneca representative, as per the Pharmacy Manual. All defects will be communicated to the sponsor and investigated further with AstraZeneca.

During the investigation of a product complaint, all study intervention 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 Site Monitor / AstraZeneca representative(s), as per the Pharmacy Manual. 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, discolouration, 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, needle bent or broke upon use.

Device malfunctions should be reported to the Site Monitor /AstraZeneca representative using the appropriate form(s), as per the Pharmacy Manual. For details, see [Section 8.3.13](#).

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 AstraZeneca Study Physician and study monitor should be notified.

If, during a home study intervention administration, 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 and follow-up of medical device AEs, SAEs, and deficiencies, please see [Appendix F](#).

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Participant Enrolment and Randomisation

The investigator(s) or designee will:

- 1 Obtain signed informed consent from the potential participant, or their guardian/legal representative, before any study specific procedures are performed.

- 2 Assign the potential participant a unique enrolment number via the IRT/RTSM.
- 3 Determine participant eligibility.
- 4 Assign the eligible participant a unique randomisation code via the IRT/RTSM.
- 5 Participants will be allocated to receive tezepelumab or placebo in a 2:1 ratio and according to the stratification factor listed in Section 4.1.
- 6 Randomisation numbers will be grouped in blocks.
- 7 If a participant withdraws from the study, then his/her enrolment/randomisation code cannot be reused.
- 8 Withdrawn participants will not be replaced.

Specific information concerning the use of the IRT/RTSM will be provided in a separate manual.

6.3.2 Procedures for Handling Incorrectly Enrolled or Randomised Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive study intervention. There can be no exceptions to this rule. Participants who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment and must be assessed as screen failures in the study. These participants are defined as screen failures.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the investigator regarding whether to continue or discontinue the participant from treatment. Study intervention must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the participant and the AstraZeneca Study Physician must ensure the decision is appropriately documented. Participants that are discontinued from treatment should be followed up according to the options described in Section 7.1.

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

6.3.3 Methods for Assigning Treatment Groups

Randomisation codes will be assigned from a central randomisation list strictly sequentially in each stratum as participants become eligible for randomisation.

The randomisation code will be assigned from a randomisation list prepared by a

computerised system provided by IRT vendor on behalf of AstraZeneca in accordance with the AstraZeneca randomization system process. All participants will be stratified at randomisation by region.

The randomisation will be monitored to ensure that a target maximum of 20% of the randomised participants have an eosinophil count of < 150 cells/ μ L at Visit 1 and a historical $\text{EOS} \geq 300$ cells/ μ L within 12 months and approximately 40% of randomised participants with the eosinophil count ≥ 300 cells/ μ L at Visit 1. When the target percentage of participants is reached, consideration will be given to closing the IRT/RTSM randomisation for that subgroup (overall or by region/country). Once a subgroup is closed, participants in the Visit 1/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed.

6.3.4 Ensuring Blinding

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

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

The following personnel will have access to the randomisation list:

- Those carrying out the packaging and labelling of study intervention
- Those generating the randomisation list
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- Bioanalytical lab analyst performing the pharmacokinetic (PK) sample analysis

No other member of the extended study team at AstraZeneca, or any Contract Research Organisation handling data, or investigators and sites will have access to the randomisation scheme during the conduct of the study until after the final DBL.

The information in the randomisation list will be kept from other personnel involved in the

conduct of the study and in a secure location until the end of the study.

Procedures to mitigate unblinding include:

- After study intervention administration at Week 0 (Visit 6) and onwards; PK, eosinophil, monocyte, and basophil counts and percentages as well as IgE and FeNO will be redacted from central laboratory reports to prevent the investigator/designee from possibly unblinding the treatment.
- If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if a haemoglobin is desired, the investigator should avoid ordering a complete blood cell count with differential.
- Site staff who are directly involved in the participant's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of outside laboratory reports. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in participant management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the participant's management and prior to filing as a source document. Similarly, eosinophil, monocyte, and basophil results must be redacted from all communications with the Independent Adjudication Committee and the sponsor.
- In cases where the investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases.

6.3.5 Methods for Unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised participant, will be available to the investigator(s) and delegate(s) at the study sites from the IRT/RTSM. Routines for this will be described in the IRT/RTSM user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator should document and report the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and until DBL after last participant completes Week 28 has been

documented.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of dose administered in the clinic will be recorded in the source documents and 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.

The study treatment provided for this study will be used only as directed in this CSP. The study intervention will be administered at the study site or home (if applicable) on-treatment visits and within visit windows as specified in the SoA (Section 1.3).

In cases where a treatment visit needs to be rescheduled, the study intervention must be administered within the visit window. The PI should make every effort to assure that no study intervention administrations are missed during the course of the study. A significant delay in conducting of treatment visit may require skipping the visit, to prevent an overdose and to keep the participant on the visit schedule established based on the date of randomisation. Those cases must be discussed with the AstraZeneca Study Physician.

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

PIs should also assure that participants are compliant and on a stable dose of the background medication during the study.

6.5 Concomitant Therapy

Information about any asthma treatment in the 12 months prior to and all other concomitant treatments 3 months prior to the date of the Visit 1 and given during the study, with reason for the treatment, will be collected by the investigator/authorised delegate at each visit and recorded in the eCRF. The treatment for any asthma exacerbation that occurred within 24 months prior to Visit 1 should be also recorded in the eCRF.

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

Medium dose ICS corresponds to 500 µg and high dose ICS corresponds to > 500 µg fluticasone propionate dry powder formulation or equivalents as outlined in [Appendix G](#). Participants may also receive other physician-prescribed asthma controller medications.

No changes are allowed to background maintenance asthma medications (except OCS) from Visit 1 to preferably 4 weeks after last dose of study intervention except during the treatment of an asthma exacerbation.

However, participants prematurely discontinuing study intervention administration should be given locally available standard of care therapy, allowing changes to background medications at the discretion of the investigator. Treatment with marketed or investigational biologics is not allowed until Week 40 even if the participant has discontinued study intervention early. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. Thus, the effects and side effects of concomitant treatment of tezepelumab and other biologics have not been evaluated. The time for elimination of tezepelumab (5 half-lives) is approximately 16 weeks. However, the duration of downstream pharmacodynamics effects of tezepelumab is unknown. For additional information regarding PK and pharmacodynamic effects of tezepelumab, reference should be made to the IB.

As theophylline has a narrow therapeutic window, please note that participants on maintenance treatment with theophylline should have blood concentration levels within therapeutic range documented before Visit 1, or if documentation not available, assessed at Visit 1. The sample can be analysed at the central or local lab as applicable. Investigators can use their clinical judgement about the therapeutic range of theophylline levels on the basis of sampling time and other factors that may impact the results.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the 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

The AstraZeneca Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

List of the restricted and prohibited medications can be found in [Table 6](#) and [Table 7](#), provided below:

Table 6 Restricted Medications

Medication/class of drug	Usage
Maintenance treatment with long-acting BDs (including ICS/LABA combinations)	No changes, in dose and regimen, are allowed (except during the treatment of an asthma exacerbation) from Visit 1, during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention. ICS/LABA should not be taken prior to scheduled spirometry, FeNO, ECG, and home lung function assessments (to be administered once assessments are completed): - Twice daily BDs should be withheld for at least 12 hours prior to the scheduled FeNO and spirometry at site. - Once daily BDs should be withheld for at least 24 hours prior to the scheduled FeNO and spirometry at site. Participants will not need to washout of their asthma medications for unscheduled visits due to asthma worsening.
Short-acting beta-agonists (SABA)	Regular scheduled use is not allowed from Visit 1, during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention. As needed use is allowed; however, attention should be paid to the following restrictions: If possible, SABA should be withheld for at least 6 hours prior to scheduled spirometry, FeNO, ECG at site and home lung function assessments. Only albuterol/salbutamol is allowed to be used as a rescue medication during the study, except during an asthma exacerbation.

Table 6 Restricted Medications

Medication/class of drug	Usage
Additional maintenance controllers	• No changes, in dose and regimen, are allowed from Visit 1, during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention. • Once daily LABA and LAMA should be withheld for at least 24 hours prior to the scheduled spirometry and FeNO. • Twice daily LABA- or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry and FeNO at site. • LTRA should be restricted for at least 24 hours prior to scheduled spirometry and FeNO at site. • Participants on theophylline should have blood concentration levels within therapeutic range documented before proceeding in the study. However, if theophylline blood concentration is out of therapeutic range after Visit 1, dose adjustments are allowed. • Twice daily theophyllines should be withheld for at least 12 hours prior to scheduled spirometry and FeNO at site. • Once daily theophyllines should be withheld for at least 24 hours prior to scheduled spirometry and FeNO at site.
Short-acting anti-cholinergics (eg, ipratropium)	Not allowed as regular scheduled use or as a rescue treatment for worsening of asthma symptoms from Visit 1, during run-in and optimisation phase, throughout study intervention treatment, and preferably 4 weeks after last dose of study intervention. May be used for managing an asthma exacerbation event.
Inactive/killed vaccinations (eg, inactive influenza vaccine)	Allowed provided they are not administered within 5 days before or after any study visit.

Table 6 Restricted Medications

Medication/class of drug	Usage
COVID-19 vaccine	COVID-19 vaccination is allowed, provided it is not administered within 28 days before and 14 days after study intervention administration. Administration timing of COVID-19 vaccination should be discussed with AstraZeneca Study Physician. If participant receives COVID-19 vaccine less than 28 days before the next scheduled dose of study intervention, the study intervention administration should be rescheduled or skipped to ensure the next study intervention dose is at least 28 days after the vaccine administration. COVID-19 vaccination schedule should follow country-specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the study intervention dosing/COVID-19 vaccination intervals are maintained. At every study visit during the treatment period, the investigator must ask if the participant has received or is planning to receive a COVID-19 vaccination. This is to ensure that the required time interval for study intervention dosing (mentioned above) is maintained. As these intervals might change, please discuss with AstraZeneca Study Physician for the most current recommended time interval prior to any vaccine dose.
Allergen immunotherapy	Allowed if on stable therapy for at least 30 days prior to Visit 1; no anticipated changes during treatment period. Should not be administered on the same day as study intervention administration.

Table 7 Prohibited Medications

Medication/class of drug	Usage
Long-acting beta-agonists as a reliever (eg, Symbicort Maintenance and Reliever Treatment)	Not allowed 15 days prior to Visit 1, during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention.
Suplatast tosilate (T2 cytokine inhibitor)	Not allowed 15 days prior to Visit 1, during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention.
Live attenuated vaccines	Not allowed 30 days prior to Visit 1; throughout study intervention treatment and preferably 4 weeks after last dose of study intervention (unless there is an absolute medical need as judged by the investigator) and follow-up period.
Any immunomodulators or immunosuppressives (corticosteroids with systemic effects such as oral, parenteral, or intra-articular administration for reasons other than asthma are not allowed. However, corticosteroid treatment of adrenal insufficiency and acute anaphylaxis is allowed.)	Not allowed 12 weeks or 5 half-lives (whichever is longer) prior to Visit 1; during run-in and optimisation phase, throughout study intervention treatment, and preferably 16 weeks after last dose of study intervention.
Blood products or immunoglobulin therapy	Not allowed 30 days prior to Visit 1; during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention (unless there is an absolute medical need as judged by the investigator).
Any marketed or investigational biologics intended for asthma (eg, benralizumab, omalizumab, mepolizumab, dupilumab, reslizumab) or any marketed or investigational biologics intended for non-asthma indications administered systemically	Not allowed within 4 months or 5 half-lives (whichever is longer) prior to Visit 1; until Week 40 even if the participant has discontinued study intervention early (unless there is an absolute medical need as judged by the investigator).
Other study interventions (including investigational use of an approved drug)	Not allowed 30 days or 5 half-lives (whichever is longer) prior to Visit 1; during run-in and optimisation phase, throughout the entire treatment period (even if the participant has discontinued study intervention) until the follow-up visit at Week 40.
Herbal remedies for the treatment of allergic, inflammatory, or respiratory diseases	Not allowed 30 days prior to Visit 1; during run-in and optimisation phase, throughout study intervention treatment and preferably 4 weeks after last dose of study intervention.
Medications not currently licensed for use in the treatment of asthma, for example medications approved for Chronic Obstructive Pulmonary Disease and not part of current standard of care	Not allowed 30 days prior to Visit 1, during run-in and optimisation phase, throughout study intervention treatment, and preferably 4 weeks after last dose of study intervention.

Table 7 Prohibited Medications

Medication/class of drug	Usage
Spironolactone	Not allowed from Visit 1, during run-in and optimisation phase, throughout the entire treatment period (even if the participant has discontinued study intervention) until the follow-up visit at Week 40.
Eplerenone	Not allowed from Visit 1, during run-in and optimisation phase, throughout the entire treatment period (even if the participant has discontinued study intervention) until the follow-up visit at Week 40.
Ephedrine (eg, in antitussives or mucolytics)	Not allowed from Visit 1, during run-in and optimisation phase, throughout the entire treatment period (even if the participant has discontinued study intervention) until the follow-up visit at Week 40.
Opiates as needed (eg, in antitussives)	Not allowed from Visit 1, during run-in and optimisation phase, throughout the entire treatment period (even if the participant has discontinued study intervention) until the follow-up visit at Week 40.

6.5.1 Other concomitant treatment

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

6.5.2 Rescue Medicine

Restrictions for the use of SABA as rescue medication are covered in the restricted medications [Table 6](#).

Prophylactic use of SABA (eg, prior to planned exercise) or any other use than to curb worsening of asthma symptoms should be documented in medical notes and entered in the eCRF. Any such use of SABA must not be recorded in the Asthma Daily Diary.

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

6.5.3 Bronchial thermoplasty

Participants must not be treated with bronchial thermoplasty during the study.

6.6 Dose Modification

No dose modification for study intervention is allowed.

6.7 Intervention After the End of the Study

At the end of the study, the participant should be given standard of care therapy, at the discretion of the investigator, per local practice.

6.8 Treatment of Overdose

For this study, any dose of study intervention greater than 700 mg within a 2-week period will be considered an overdose.

AstraZeneca does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the AstraZeneca Study physician, if possible, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.4 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose.

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 from study intervention.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

Before the discontinuation of the study intervention and IP discontinuation visit (IPD visit), the AstraZeneca Study Physician should be consulted regardless of the reason for discontinuation.

Participant may be discontinued from Study Intervention in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment

- An AE that in the opinion of the investigator, contraindicates further dosing
- Severe non-compliance with the CSP
- Risk to participant as judged by the investigator or AstraZeneca
- Pregnancy and breastfeeding
- Study intervention unblinding
- Lost to follow-up
- Development of any study specific criteria for discontinuation:
 - Anaphylactic reaction to study intervention requiring administration of epinephrine
 - Development of helminth infestations requiring hospitalisation
 - If participants become infected while receiving treatment with tezepelumab and do not respond to anti-helminth treatment, discontinue treatment with tezepelumab until infection resolves.
 - A respiratory-related event requiring intubation
 - Any malignancy, except participants who develop basal cell carcinoma or localised squamous cell carcinoma of the skin, provided that the malignancy has been excised and determined to have clean margins.
- Development of one or more of the following:
 - Confirmed alanine aminotransferase/transaminase (ALT) or aspartate aminotransferase/transaminase (AST) increase of $\geq 8 \times \text{ULN}$
 - Confirmed ALT or AST increase of $\geq 5 \times \text{ULN}$ for more than 2 weeks
 - Confirmed ALT or AST increase of $\geq 3 \times \text{ULN}$ and total bilirubin (TBL) of $\geq 2 \times \text{ULN}$
 - ALT or AST of $\geq 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($\geq 5\%$)

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

7.1.1 Procedures for Discontinuation of Study Intervention

Participants are free to discontinue Study Intervention or withdraw from the study at any time without prejudice to further treatment. Procedures to follow for study withdrawal are detailed below.

A participant that decides to discontinue study intervention should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing and the date of last study intervention administration should be recorded in the eCRF. Participants permanently

discontinuing study intervention administration should be given locally available standard of care therapy, at the discretion of the investigator. However, treatment with marketed or investigational biologics is not allowed until Week 40 even if the participant has discontinued study intervention. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been conducted. For additional information regarding PK and pharmacodynamic effects of tezepelumab, reference should be made to the IB.

All participants who prematurely discontinue study intervention at minimum should return to the site and complete the following 2 Visits:

- **The IP Discontinuation (IPD) Visit at 4 weeks (+/-5 days) post last study intervention administration**
- **The Follow-Up Visit at 16 weeks post last study intervention administration (+/-7 days) (refer to the [Schedule of Activities \(SoA\)](#), Visit 14 – Week 40).**

Participants who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments as per SoA (Section [1.3](#)).

At the IPD visit the participant will be given 3 options as to how they will be followed as follows:

- **Option 1:** The participant should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding study intervention administration) until the EOT visit at Week 28 (+/-5 days).
- **Option 2:** The participant will be offered follow-up on a monthly basis via telephone calls until the participant attends the EOT visit at Week 28 (+/-5 days) at the site. The participant will be completing the daily diary, performing PEF measurements and all questionnaires on the handheld device at home.
- **Option 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 daily diary), the investigator will contact via telephone the participant at 28 weeks post-randomisation (at EOT visit) to collect AEs/SAEs, changes in concomitant medication, including OCS dose, health care utilisation, and asthma exacerbation information.

If the participant chooses option 1, all assessments will be completed as per the SoA (Section [1.3](#)). If the participant chooses option 2, the key information will be collected during the telephone visits as per SoA (Section [1.3](#)).

For participants in option 1 and 2, protocol-specified OCS dose reductions will follow the SoA (Section [1.3](#)) and Asthma Control Criteria for OCS dose reduction, as specified in [Table 8](#).

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, participant initially choosing option 1 can continue with options 2 or 3; participants initially choosing option 2 can continue with option 3).

The EOT visit will be completed immediately in the case of early withdrawal from the study. Participants who do not wish to have any follow-up contacts, will be discontinued from the study. All discontinued participants must return the ePRO and ePEF devices 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, the EOT visit should be conducted, as shown in the SoA (Section 1.3). See the SoA for data to be collected at the time of study withdrawal.
- 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.

If the participant decides to withdraw consent, then the reason for this must be recorded in the eCRF.

7.2.1 Withdrawal due to recruitment completion in a subgroup

When a specific subgroup is full, the enrolled participants in the completed subgroup will not be randomised and will be screen failures in the study. The reason of the withdrawal should be documented in the source and eCRF. As with screen failures, no further study-related follow-up of these participants is required.

7.2.2 Withdrawal due to Recruitment Completion

When the required number of participants are randomised in the study, ongoing participants in screening will not be randomised and will be screen failures in the study. The reason of the withdrawal should be documented in the source and eCRF. As with screen failures, no further study-related follow-up of these participants is required.

7.2.3 Discontinuation or Suspension of Entire Study and Site Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/Independent Ethics Committee (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

Discontinuation of specific sites or of the study as a whole are handled as part of [Appendix A](#).

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or 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.
- Efforts to reach the participant should continue until the end of the study. Should the participant be unreachable at the end of the study, the participant should be considered lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). 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 (Section 1.3), 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 (Section 1.3).

8.1 Efficacy Assessments

8.1.1 General Overview of OCS dose management

The OCS optimisation phase (Visit 2 to Visit 5) occurs prior to randomisation. The goal of the OCS optimisation phase is to identify the lowest OCS dose (ie, optimised OCS dose) at which asthma control is maintained. During this phase, entry OCS dose will be reduced in line with [Table 9](#) at 2 weekly intervals provided all the criteria for OCS reduction are met (except for the reduction at Visit 2). Refer to [Table 8](#) and Section 8.1.1.1 for more details on criteria used for OCS dose reduction.

Once the optimised dose is determined, the participant must be able to remain on the optimised dose for 2 consecutive weeks prior to randomisation at Visit 6. The OCS dose at Visit 6 is considered as the baseline OCS dose.

The induction phase will start at Week 0 (Visit 6) after the first dose of study intervention and continue until Week 4 (Visit 7). No adjustments should be made to the OCS dose during this phase.

The OCS dose reduction phase will commence at Visit 7 (Week 4) and continue at 4-week intervals up to and including Visit 12 in accordance with the OCS dose reduction schedule described in [Table 10](#). During the OCS reduction phase, a minimum stable OCS dose or complete elimination of requirement for OCS should be reached for each participant. Participants who experience an asthma exacerbation or those who do not meet the criteria for OCS dose reduction ([Table 8](#)) will not be allowed to further reduce the OCS dose (permanent stop of the OCS dose reduction).

The maintenance phase will start after the last OCS dose reduction at Visit 12 (Week 24) and will continue until Visit 13 (Week 28, End of Treatment). No adjustments should be made to the OCS dose during this phase.

8.1.1.1 Asthma Control Criteria for OCS dose reduction

The OCS dose reduction will follow the same approach for both the optimisation and the reduction phase.

The dose of OCS must be reduced if the participant meets all of the pre-specified asthma control criteria as described in [Table 8](#).

Table 8 Asthma Control Criteria for OCS Reduction

Criteria	Definition of asthma control
1	Mean ^a Morning PEF $\geq$ 80% of baseline ^b
2	An increase of no more than 2 nights with asthma-related awakenings (requiring rescue medication) over a 7-day period compared with baseline ^{b,c}
3	Mean ^a SABA rescue medication use no more than 4 inhalations /day above the baseline ^{b,d}
4	Pre-BD FEV ₁ $\geq$ 80% of baseline ^e
5	No requirement to increase the dose of systemic corticosteroids for asthma symptoms/exacerbations since the last visit ^f
6	Non-asthma criterion: No signs or symptoms of Adrenal Insufficiency ^g

^a Mean values are calculated from completed daily diary records of a minimum of 10 out of 14 days prior to the visit.

^b Baseline values for optimisation phase are calculated from completed daily diary records of a minimum of 10 out of 14 days before Visit 2. Baseline values for the reduction phase are calculated from a minimum of 10 out of 14 days before randomisation Visit 6.

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

^d Each nebulisation used is counted as 2 inhalations.

^e Pre-BD FEV₁ baseline for optimisation phase will be collected at Visit 2 and baseline for dose reduction phase will be collected at Visit 6.

^f Investigator will provide, in the eCRF, details on asthma symptoms/exacerbations requiring systemic corticosteroids dose increase since last visit.

^g Investigator will provide, in the eCRF, detailed description of the signs/symptoms of AI leading to not reducing the OCS dose according to the schedule.

If the participant fails to meet at least one of the asthma control criteria for OCS dose reduction listed in [Table 8](#), the investigator should increase the OCS dose at least one step higher (return to the last effective dose, see [Table 10](#)). Further OCS dose reductions will not be allowed.

If pre-BD FEV₁ or morning PEF is not available e.g.: restrictions due to COVID-19 pandemic, IP discontinuation option 2 (see section [7.1.1](#)) one of them that is available can be used for the assessment of the asthma control together with remaining criteria (as per [Table 8](#)).

For OCS dose reductions at each visit participants should have a minimum compliance of 10 of the last 14 days before the visit with the daily diary completion and morning PEF measurement.

In the case of a lower compliance to the daily diary and/or morning PEF, the scheduled OCS dose reduction visit should be delayed allowing for 10 of the last 14 days compliance (using

the visit window period as per SoA [Section 1.3]). During the reduction phase, if compliance is still not met despite delaying the visit, a participant should come to a clinic within the visit window for the study intervention administration and all other assessments as per SoA (Section 1.3, Table 1). AstraZeneca Study Physician should be contacted to discuss the issue. Additional remote visit for OCS titration should be scheduled within a maximum of 7 days to allow for daily diary and/or morning PEF compliance. However, if despite allowing additional 7 days, compliance to daily diary and/or morning PEF measurement is still not met, AstraZeneca Study Physician should be contacted to discuss OCS dose change based on available criteria.

If the lower compliance to the daily diary and/or PEF measurements is due to technical issues OCS reduction can be attempted on the investigator discretion.

8.1.1.1.1 Details of OCS dose management in the optimisation phase

At Visit 1 participants will continue with or be switched from their usual OCS maintenance dose to an equivalent dose of prednisone/prednisolone. For participants not previously receiving prednisone/prednisolone as OCS, the conversion table shown in Appendix G should be used to calculate the equivalent prednisone/prednisolone dose in the study.

In the OCS dose optimisation phase, OCS dose reduction should begin at Visit 2. Visit 2 is the only visit during the optimisation phase where OCS reduction is not based upon criteria defined in Table 8. Participants who are considered by Investigators not to be candidates for starting OCS dose reduction in the optimisation phase, based upon asthma symptoms or other clinical reasons or participant's unwillingness to withdraw maintenance OCS treatment should be screen failed. Similarly, if the participant is non-compliant to daily diary completion, PEF measurements, and/ or non-complaint with prescribed OCS, ICS/LABA or other asthma controller treatment then the participants should be screen failed (see Section 5.1).

For participants entering the optimisation phase, the baseline values, related to daily diary and PEF measurements, for OCS dose reduction are:

- The mean of measures for morning PEFs and SABA use collected daily for 14 days prior to Visit 2.
- Number of nights with awakenings due to asthma requiring rescue medication are counted from the most recent 7 days of available data.

At a minimum, 10 days of completed daily diary assessments and morning PEF measurements must be available prior to Visit 2 to establish the baseline for the OCS reduction criteria for the optimisation phase.

For FEV₁ criterion, the pre-BD value obtained at Visit 2 is used as baseline.

At Visit 3 and 4, the OCS dose reduction must take place only when all the asthma control criteria for OCS dose reduction are met (as per [Table 8](#)). If all the criteria continue to be met at Visit 5 the participant should be screen failed (due to 3 consecutive OCS dose reductions with no asthma control worsening). If any of the dose reduction criteria (per [Table 8](#)) is not met at Visit 5, the OCS dose should be up-titrated as per SoA (Section 1.3) unless the dose increase already took place prior to Visit 5 (ie, at an unscheduled visit) due to asthma worsening.

In cases when criteria for OCS dose reduction are not met at Visit 3 or 4, the OCS dose should be returned to one level higher (see [Table 9](#)) and Visit 5 should be activated on the same day. This should be considered as the optimised OCS dose and no further OCS dose reductions are allowed during the optimisation phase. Participants should remain on the stable optimised OCS dose until Visit 6 (randomisation).

OCS dose reductions should occur at 2-week intervals and the reduction schedule ([Table 9](#)) should be followed. For daily doses > 10 to 30 mg prednisone or prednisolone, the change in daily dose is 5 mg, whereas for daily doses 7.5 to 10 mg, the corresponding reduction is 2.5 mg.

Table 9 OCS dose reduction schedule during the optimisation phase

Regiment	Starting dose of OCS (mg/day) at each visit of optimisation phase	Change by (mg/day) ^a
Daily regimen	> 10-30	5.0
	7.5-10	2.5

^a During the Optimisation phase the reductions should occur at 2-week intervals

The optimisation phase may be extended, in consultation with the AstraZeneca Study Physician, to account for treatment of an exacerbation to allow for 2-week stable OCS dose prior to randomisation. For exacerbation management during the optimisation phase, see Section [8.1.2.2](#).

If a participant maintains asthma control at an OCS dose of < 7.5 mg during this phase, or after 3 consecutive OCS dose reductions, then the participant should be screen failed. Re-screening of participant who was able to reduce the OCS dose by 3 steps is allowed provided participant's daily dose is ≥ 7.5 mg.

8.1.1.1.2 Details of OCS dose management in the treatment period

Induction phase

The induction phase will start at Week 0 (Visit 6) after the first dose of study intervention and continue until Week 4 (Visit 7). No adjustments should be made to the OCS dose during this

phase. The induction phase may be extended, in consultation with the AstraZeneca Study Physician, to account for treatment of an exacerbation to allow for 2-week stable OCS dose prior to initiating the first OCS down titration in the reduction phase. For exacerbation management during the induction phase, see section 8.1.2.3.

Reduction phase

In the OCS reduction phase, OCS dose reduction should start at Visit 7. OCS step down is mandatory at Visit 7 and this is the only visit during the OCS reduction phase, where the dose reduction is not based upon criteria defined in Table 8 as the participant is already on an optimised OCS dose. At all other visits in the reduction phase, the OCS dose reduction must take place only when all the asthma control criteria for OCS dose reduction are met (per Table 8). If at Visits 8, 9, 10, 11, or 12, any of these criteria listed in Table 8 is not met the OCS dose should be returned to at least one step higher (return to the last effective dose, Table 10) and no further OCS dose reductions are allowed (permanent stop of OCS reduction). This dose should be maintained until the EOT (Visit 13).

Dose reductions that begin at Visit 7 and continue at 4-week intervals up until and including Visit 12 should follow the OCS dose reduction schedule described in Table 10. For daily doses > 10 to 30 mg prednisone or prednisolone, the change in daily dose is 5 mg, whereas for daily doses 2.5 to 10 mg, the corresponding reduction is 2.5 mg.

Table 10 OCS Dose Reduction Schedule During the Reduction Phase (Visit 7-Visit 12)

Optimised dose at V6 Wk0	V7 Wk4	V8 Wk8	V9 Wk12	V10 Wk16	V11 Wk20	V12 Wk24
30 ^a	25	20	15	10	7.5	5
25	20	15	10	7.5	5	2.5
20	15	10	7.5	5	2.5	0
15	10	7.5	5	2.5	0	0
12.5	7.5	5	2.5	0	0	0
10	7.5	5	2.5	0	0	0
7.5	5	2.5	0	0	0	0

^a All doses expressed in mg/day of Prednisone/Prednisolone.

The OCS dose may be administered every other day (or different doses every other day). Average dose over 2 days = The daily dose.

For participants entering the reduction phase, the baseline values related to daily diary and PEF measurements, for OCS dose reduction are:

- The mean of measures for morning PEFs and SABA use collected daily for 14 days prior to randomisation (Visit 6).
- Number of nights with awakenings due to asthma requiring rescue medication are counted from the most recent 7 days of available data collected daily for 14 days prior to randomisation (Visit 6).

At a minimum, 10 days of completed morning and evening daily diary assessments should be available prior to randomisation (Visit 6) to consider the mean as baseline for the OCS reduction phase (see Section 5.1).

For FEV₁ criterion, the pre-BD value obtained at randomisation (Visit 6) is used as baseline.

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

Note: consideration should be given to evaluate when OCS dose is reduced to below 5 mg/day to differentiate signs /symptoms of AI which may potentially be masked by asthma worsening.

For doses below 5 mg, if the exact dose strength is not available in the country, the daily dose to be administered could be achieved by dosing every other day. Daily dose is the average of 2 days. See [Appendix H](#) for dosing < 5 mg in relation to tablet strength.

8.1.2 Asthma exacerbations - Assessment and management

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

- A temporary bolus/burst of systemic corticosteroids 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.

Note: Per protocol up titration of maintenance OCS dose to 1 level higher (as described in Table 9 and Table 10) is not considered an exacerbation event.

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

For the purpose of the protocol, worsening of asthma is defined as new or increased symptoms and/or signs identified by physical examination/participant interview or by the participant daily diary and/or PEF measurements.

The ePRO device will be programmed to alert the study centre and participant when certain pre-specified worsening thresholds mentioned in Table 11 are crossed. The purpose of the alerts is to trigger a contact between the site and participant for further evaluation if deemed necessary by the investigator.

Table 11 Asthma Worsening Alert Criteria

Criteria ^{a, b}	Definition
1	Decrease in morning peak expiratory flow $\geq 20\%$ on at least 2 consecutive days compared with the average at baseline
2	An increase in rescue medication use of ≥ 5 puffs/day on at least 2 consecutive days compared with the average use during baseline
3	An additional nebulised β_2 agonist use on at least 2 consecutive days compared with the average use during baseline
4	An increase of 3 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period ^c compared with baseline
5	An increase in global asthma symptom score of at least 2 units above the baseline average or the highest possible score (daily score of 6), on at least 2 consecutive days

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

^b Baseline values for alerts will be calculated from the most recent 7 days of available data prior to Visit 2 for the optimisation phase and prior to randomisation Visit 6 for the treatment period.

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

If an exacerbation event is not associated with deterioration in asthma defined as (at least 1 of the 3 elements of worsening listed below):

- Worsening of asthma signs/symptoms
- Increased use of 'as needed' reliever medication
- Deterioration of lung function (eg, peak expiratory flow, pre-BD FEV₁)

the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any of the pre-specified deterioration in asthma (as above) will be deemed not to be a protocol-defined exacerbation.

For the protocol, the worsening/onset of signs/symptoms include at least one of the following:

- shortness of breath
- wheezing
- chest tightness
- cough
- sputum
- night-time awakening due to asthma
- activity limitation due to asthma
- abnormal physical exam finding

For the protocol, the start of an exacerbation is defined as the start date of additional systemic corticosteroids, date of ER or urgent care visits requiring additional systemic corticosteroids, or date of hospital admission due to asthma or death due to asthma, whichever occurs earlier.

The end date of an exacerbation is defined as the last date of additional systemic corticosteroids (a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids) or of a temporary increase in a stable OCS background dose, date of ER or urgent care visit, or date of hospital discharge, whichever occurs later.

Reasonable attempts should be made by the investigator to bring the participant into the study site for evaluation of asthma worsening indicated by a diary alert or participant initiated contact due to asthma worsening, particularly when it results in additional treatment being prescribed. Study site evaluations for asthma worsening may occur as an unscheduled (UNS) visit or as part of an ordinary site visit if the worsening happens to be coincident with a

scheduled visit window. A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (eg, by the primary care HCP or at an ER/urgent care centre /hospital) and details entered into the specific eCRF module in a timely fashion. Changes in concomitant medication due to exacerbation must be recorded in the appropriate module of the eCRF.

8.1.2.1 Exacerbation management during the run-in period

Participants who experience an asthma exacerbation during the run-in period may remain in the study. After the treatment of exacerbation, the new maintenance OCS dose should be at least one step higher than the dose prior to exacerbation. They should be on a stable OCS dose for a period of 2-weeks before beginning the optimisation phase.

8.1.2.2 Exacerbation management during the optimisation phase

If a participant experiences an asthma exacerbation during the optimisation phase, OCS dose reduction should stop. After the treatment of exacerbation, the participant should be placed on an OCS dose at least one step (or more if considered necessary by the investigator) higher than the dose they were on when the exacerbation occurred. The optimisation phase could be extended to allow for the participant to be on a stable OCS dose for 2 weeks prior to randomisation.

8.1.2.3 Exacerbation management during the treatment period

Induction phase

If a participant experiences an exacerbation during the induction phase, they will undergo treatment as per investigator discretion. **After the systemic corticosteroids bolus/burst to treat an exacerbation is complete, the participant should be returned to at least one step (or more if considered necessary by the investigator) higher than the OCS dose they were on when the exacerbation occurred or the investigator may decide to maintain the same OCS dose.** Once they return to the maintenance OCS dose, they need to remain on this stable dose for 14 days prior to initiation of OCS dose reduction at Visit 7. If the 14-day stable dose is not met by Visit 7, they cannot undergo mandatory OCS reduction at this visit. However, once the treatment for the asthma exacerbation is complete and the maintenance dose is stable for 14 days, they should initiate OCS dose reduction at Visit 8 as per [Table 10](#).

Reduction phase

If a participant experiences an exacerbation during the reduction phase, after the systemic corticosteroids bolus/burst is complete, the participant should be returned to at least one step (or more if considered necessary by the investigator) higher than the OCS dose they were on when the exacerbation occurred, and no further OCS dose reduction should be performed. This dose should be maintained until the EOT (Visit 13, Week 28).

Maintenance phase

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

8.1.3 Spirometry

8.1.3.1 General requirements

Lung function (FEV₁; FEF 25 to 75% and forced vital capacity [FVC]) will be measured by spirometry at the study site using equipment provided by a central vendor. Spirometry will be performed by the investigator or authorised delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines ([Graham et al 2019](#)).

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

Participants should be instructed to follow the required restrictions for performing spirometry as described in Section 6.5 and Table 6. If the required restrictions have not been adhered to, the investigator should reschedule the visit to the earliest opportunity within the allowed visit window.

Spirometry testing must be performed according to the schedule provided in SoA (Section 1.3). All post-randomisation spirometry assessments should be performed within $\pm$ 1.5 hours of the time that the baseline (Visit 6) Pre-BD spirometry was performed. Maximum number of efforts for spirometry measurement is 8.

8.1.3.2 Spirometry technique

Detailed procedure for performing spirometry will be described in a separate instruction manual. Details regarding assessment of the quality of spirometry and the best test report (BTR) process will also be detailed in the manual. A signed and dated copy of the spirogram printout must be kept at the study site for source data verification.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the predicted normal values (PNV) and are pre-programmed into the spirometer ([Quanjer et al 2012](#)).

FEV₁, expressed as percent of the PNV, will be calculated as follows:

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

8.1.3.3 Post-BD spirometry and bronchodilator responsiveness test

Post-BD spirometry procedures will be performed according to the SoA (Section 1.3) and will be described in a separate spirometry procedure manual. Bronchodilatation can be induced using albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) up to a maximum of 4 inhalations. In rare cases where a 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. Nebuliser 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.

If bronchodilator responsiveness has not been documented in the previous 60 months prior to or at Visit 1, further assessments to meet the bronchodilator responsiveness criteria may be performed at Visit 2 and Visit 3. It is acceptable to stop further bronchodilator responsiveness tests once the criteria for responsiveness are met.

The highest pre- and post-BD FEV_1 will be used to determine bronchodilator responsiveness.

Bronchodilator responsiveness is calculated as follows:

$$\% \text{ Bronchodilator responsiveness} = (\text{post-BD } FEV_1 - \text{pre-BD } FEV_1) \times 100 / \text{pre-BD } FEV_1$$

8.1.4 Home PEF testing

An electronic, handheld spirometer to measure PEF (ePEF meter) will be provided to the participant at Visit 1.

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

Home PEF testing will be performed by the participant in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Recording of home PEF should start from the evening of Visit 1 until the morning of Visit 13 (Week 28).

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

The investigator/authorised delegate will check participant's adherence to use of the PEF meter as shown in the SoA (Section 1.3).

8.1.5 Fractional exhaled nitric oxide

Airway inflammation will be evaluated using a standardised single-breath FeNO test in accordance with the SoA (Section 1.3). The single exhalation technique recommended by the manufacturer will be followed (Alving et al 2017).

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

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

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

All FeNO measurements after randomisation will be blinded for sites, participants, and sponsor throughout the study.

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

8.1.6 Patient-reported outcomes

Patient-reported outcomes (PRO) data will be captured electronically using a handheld device. The handheld device (or web-based back-up) will be the only accepted source of PRO data in this protocol. Paper printouts of questionnaires and patient responses on paper questionnaires are not allowed; all data from paper questionnaires will be discarded and not part of the database. Appropriately trained site staff and Investigators will dispense the ePRO device to each patient at Visit 1 and ensure that patients are properly trained on the ePRO device and the importance of completing assessments as scheduled. The participant will also be asked to verify completion of training on the ePRO device. The site staff will set assessment reminder alarms on the device. At-home PRO assessment will start the evening of Visit 1 and continue thereafter until the EOT visit as per the SoA (Section 1.3). Participants will be asked to bring the device back at each study visit. Available ePRO questionnaires may be completed at home prior to the site visit except for Visit 1, Visit 6, Visit 13 and IPD visit when assessments should

be completed at the site. If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures. The investigator/authorised delegate should check ePRO compliance at each visit and even in between as shown in SoA (Section 1.3).

8.1.6.1 Asthma Daily Diary

The daily diary will be completed each day from the evening of Visit 1 to the morning of Visit 13. The morning diary will include: Asthma Symptom Diary (ASD) morning items, global asthma symptom item, questions about rescue medication, night-time awakening, and use of maintenance medications. The evening diary will include: ASD evening items, global asthma symptom item, questions about rescue medications, and OCS use. Upon completion of the morning and evening questions, the participant will complete the peak expiratory flow assessment.

Asthma Symptom Diary

Asthma symptoms will be recorded using the ASD ([Globe et al 2015](#)). The ASD comprises 10 items (5 items in the morning; 5 items in the evening). The morning items assess night-time symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and the frequency of night-time awakening. The evening items assess symptom severity in relation to wheezing, shortness of breath, cough, and chest tightness, and activity limitation since waking. Items are scored from “0” (no symptom, no night-time awakening, or no activity limitation) to “4” (very severe symptom, unable to sleep, or extreme activity limitation). A daily ASD score is the mean of the 10 items. Responses for all 10 items are required to calculate the daily ASD score; otherwise, it is treated as missing. Calculation of a daily ASD score requires data from the evening diary assessment and the subsequent morning diary assessment. For the 7-day average asthma symptom score, scoring is done with no imputation using the mean of at least 4 of the 7 daily ASD scores as a mean weekly item score. The 7-day average ASD score ranges from 0 to 4.

Global asthma symptom items

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

Rescue medication

The number of rescue medication inhalations (puffs) and nebuliser treatments taken will be recorded by the participant in the diary twice daily (ie, in the morning and evening) beginning the evening of Visit 1 until the morning of Visit 13. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and the morning will be recorded in the

morning.

Night-time awakenings

Night-time awakenings due to asthma symptoms will be recorded by the participant in the diary each morning, beginning in the morning after Visit 1 until the morning of Visit 13, by answering the question whether he/she woke up during the night due to asthma symptoms and was required to take rescue medication with a “yes” or “no” response.

Compliance to maintenance asthma medication

Maintenance medication compliance will be recorded in the diary once daily in the morning, beginning in the morning after Visit 1 until the morning of Visit 13. There will be separate questions for checking compliance with OCS. For participants who were able to withdraw OCS the question will confirm that they did not take OCS.

Participants continued compliance with prescribed OCS dose and background asthma medications is of utmost importance and will be monitored via diary. Alerts will be sent to the sites/investigators and participants in case of non-compliance for the OCS and background asthma medications.

8.1.6.2 Asthma Control Questionnaire (ACQ-6)

The ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and short-acting β_2 -agonist use via participant-report.

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

ACQ-6 will be completed according to the SoA (Section 1.3).

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

The AQLQ(S)+12 is a questionnaire that measures the health-related quality of life experienced by asthma participants. 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 (symptoms, activity limitations, emotional function, and environmental stimuli) are the means of the responses to the questions in each of the domains. The responder definition for AQLQ(s)+12 is 0.5-point improvement from baseline.

The AQLQ(s)+12 will be completed according to the SoA (Section 1.3).

8.1.6.4 St George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 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. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with a minimum clinically important difference (MCID). Specific details on the scoring algorithms are provided by the developer in a user manual (Jones et al 2009).

SGRQ will be completed according to the SoA (Section 1.3).

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

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

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

The EQ-5D-5L will be completed according to the SoA (Section 1.3).

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

Investigators should pay special attention to clinical signs related to previous serious illnesses as new or worsening abnormalities may qualify as AEs, see Section 8.3.5 for details.

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator, will be reported as an AE as described in Section 8.3.

- A complete physical examination will be performed and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the general appearance, abdomen, cardiovascular, and respiratory system.
- Physical examination will be performed at time points as specified in the SoA (Section 1.3).

8.2.2 Vital Signs

Vital signs (ie, pulse, blood pressure, respiration rate, and body temperature) will be performed at timelines as specified in the SoA (Section 1.3).

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

Participants should be observed by the qualified HCP for a minimum of 2 hours after 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 one hour after study intervention administration for any such reaction.

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

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

Pulse rate will be obtained before blood pressure, if the manual measurement technique is used.

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

Body temperature will be measured and recorded in Celsius or Fahrenheit, prior to study intervention administration, in accordance with local standards.

8.2.3 Electrocardiograms

An ECG will be performed as specified in the SoA (Section 1.3).

A 12-lead ECG will be taken in supine position after resting for at least 15 minutes, prior to blood draw, FeNO, spirometry, BD administration, and study intervention administration.

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

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

8.2.4 Clinical Safety Laboratory Assessments

See Table 12 for the list of clinical safety laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments, as defined in the Table 12, must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3). Participants should be fasting for at least 12 hours before blood draw.

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3). The date and results, if applicable, will be recorded on the appropriate eCRF.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

The clinical chemistry, haematology, and urinalysis (except for a dipstick urinalysis) will be performed at a central laboratory.

Additional (repeated or unscheduled) safety samples may be collected if clinically indicated at the discretion of the investigator, for safety reasons or for technical issues with the samples.

The investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables.

The following laboratory variables will be measured

Table 12 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin (Hb)	S-Alkaline phosphatase
B-Leukocyte count	S-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count) ^a	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Haematocrit	S-Blood urea nitrogen
B-Mean corpuscular volume	S-Calcium, total ^b
B-Red blood cell (RBC) count	S-Chloride ^b
B-HbA1C ^b	S-Creatinine
	S-Creatinine kinase (CK)
Urinalysis (dipstick in urine)	S-Gamma-glutamyl transpeptidase (GGT)
U-Blood	S-Glucose
U-Protein	S-Phosphorus ^b
U-Glucose	S-Potassium ^b
U-Microscopy and culture as required ^c	S-Sodium ^b
	S-Lipid profile ^{b d}

^a The sponsor personnel involved in the analysis and conduct of the study and site will be blinded to the eosinophil, basophil and monocyte absolute, and percentage values from the central laboratory reports except screening Visit 1, any repeat testing that is performed during the screening period and prior to study intervention administration at Visit 6.

^b To be done at screening Visit 1 only.

^c Urine samples will be first analysed locally using dipstick and sent to the central laboratory only for analysis when a positive dipstick result for any parameter is observed.

^d Lipid profile consists of the following tests: Direct high-density lipoprotein cholesterol (HDL-C) 4th Generation, Triglycerides, Cholesterol, Low-density lipoprotein (LDL) cholesterol Friedewald 4th (calculation), Very-low-density lipoprotein (VLDL) cholesterol Friedewald (calculation).

In case a participant shows an AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN please refer to [Appendix E](#) 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' (HL), for further instructions.

8.2.5 Other Safety Assessments

8.2.5.1 Pregnancy Test

The following tests are applicable to female participants only (WOCBP) and will be conducted at the time points specified in SoA (Section 1.3).

- Serum β -hCG or FSH test: To be done at screening Visit 1 only, for women of childbearing potential (analysed at central laboratory).
- Urine pregnancy test: To be performed at the study site for women of childbearing potential at each treatment visit (before study intervention administration on Visit 6 to

Visit 13) using a dipstick. A positive urine test result must be confirmed with serum β -hCG (analysed at central laboratory).

8.2.5.2 Weight and Height

Weight and height will be measured, and body mass index calculated in accordance with SoA (Section 1.3).

The participant's weight will be recorded in kilograms; height will be recorded in centimetres. Weight and height measurements will be performed in light clothing and with shoes off.

8.2.5.3 Serology

- Hepatitis B surface antigen and hepatitis C antibody

To be done at screening Visit 1 only (SoA, Section 1.3); test to be performed at central laboratory.

- HIV-1 and HIV-2 antibodies

To be done at screening Visit 1 only (SoA Section 1.3); test to be performed at central laboratory.

Instructions for sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the study centres.

8.2.5.4 COVID-19 Questionnaire

A COVID-19 questionnaire (see example below), must be completed prior to every study visit. Participant COVID-19 screening should include:

- Symptom history
- Exposure to someone diagnosed with COVID-19 in the past 14 days
- Recent travel including to countries with Centers for Disease Control and Prevention (CDC) Level 2 or higher travel warning or equivalent or known COVID-19 hot spots
- Unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat and/or new loss of taste or smell within the past 14 days

This questionnaire is to be conducted at minimum and local regulation and guidance should be followed.

Example of questionnaire:

- 1 Have you experienced unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the past 14 days?

- 2 Have you been in contact with anyone who is sick or with symptoms (refer to question 1) in the last 14 days?
- 3 Have you been exposed to someone diagnosed with COVID-19 in the last 14 days?
- 4 Have you been practicing social distancing over the last 14 days? (refer to region/city/country regulations)
- 5 Have you travelled in the last 14 days, if so, where? (recent travel including to countries/regions with CDC Level 2 or higher travel warning or equivalent or known COVID-19 hot spots)
- 6 Have you been in isolation or quarantine for any reason in the past 14 days?
- 7 Have you been diagnosed with COVID-19 at any time, if so, where and when?

Sites may use their own version of questionnaire per local guidance. Responses are not considered as part of clinical trial data and are not recorded in eCRF. The site will determine the appropriate course of action based on the responses to questionnaire. Participants who report symptoms should be referred for further evaluation as per investigator judgement. Visit should be cancelled or rescheduled, if needed as judged by investigator.

8.2.5.5 SARS-CoV-2 Diagnostic Test

Sites should follow local SARS-CoV-2 testing guidelines to evaluate potential COVID-19 infection.

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](#).

The definitions of medical device-related safety events can be found in [Appendix F](#). Medical device deficiencies are covered in Section [8.3.13](#).

AEs 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.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from time of signature of the ICF throughout the treatment period and including the follow-up period.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention 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.

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

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the participant is lost to follow-up.

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the 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 each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Study intervention(s) (yes or no)
- Action taken with regard to Study intervention(s)
- 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(s)

8.3.3 Causality Collection

The investigator should assess causal relationship between Study intervention and each AE and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

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

A guide to the interpretation of the causality question is found in [Appendix B](#).

For medical devices, including device constituent part of a combination product, a guide to the interpretation of the causality can be found in [Appendix F](#).

8.3.4 Adverse Events Based on Signs and Symptoms

All 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. 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

The results from the CSP mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the investigator (which may include, but be not limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign

will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (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.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

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

- The sign or symptom is serious according to definitions, see [Appendix B](#)
- The participant discontinues study intervention due to the sign or symptom
- The sign or symptom is new to the participant or not consistent with the participant's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

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

8.3.6 Adverse Events of Special Interest

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

- Serious hypersensitivity reaction
- Serious infections
- Helminth infections
- Guillain-Barré Syndrome
- Malignancy
- Serious cardiac events
- Adrenal crisis

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further

evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to [Appendix E](#) for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.8 Disease Under Study

Symptoms of Disease Under Study are those which might be expected to occur as a direct result of asthma. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the study intervention.

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

- The sign or symptom is serious according to definitions, see [Appendix B](#)
- The participant discontinues the study intervention due to the sign or symptom.
- The sign or symptom is new to the participant or not consistent with the participant's pre-existing asthma history (defined as within one year of Visit 1) as judged by the investigator.

Asthma exacerbation should be recorded as an AE or SAE only if it fulfils any of the above criteria. All asthma exacerbations should be recorded in the eCRF as per Section [8.1.2](#).

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, 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 or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one 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 one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the eCRF, an automated email alert is sent to the designated AstraZeneca representative.

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

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

For further guidance on the definition of a SAE, see [Appendix B](#) of the CSP.

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

8.3.10 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 intervention

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs.

8.3.10.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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 or she becomes aware of it.

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

8.3.10.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly), occurring from the date of the first dose until 16 weeks (5 half-lives) after the last administration of study intervention, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 Special Situations of Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

If an event of medication error, drug abuse, or drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (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, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other events.

8.3.11.2 Medication Error

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

The full definition and examples of Medication Error can be found in Appendix [B 4](#).

8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca non-investigational medicinal product (AZ NIMP) for a perceived reward or desired non-therapeutic effect.

The full definition and examples of Drug Abuse can be found in Appendix [B 4](#).

8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AZ NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AZ NIMPs study interventions, outside the intended use as specified in the CSP and includes deliberate administration of the product by the wrong route.

The full definition and examples of Drug Misuse can be found in [Appendix B 4](#).

8.3.12 Management of IP-related reactions

Appropriate drugs (eg, epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available. Site staff must be trained to recognise and treat anaphylaxis ([Kroger et al 2011](#), [Lieberman et al 2010](#)). Management of anaphylaxis must be in accordance with current standard of care and clinical guidelines. Details on anaphylaxis management are provided in [Appendix I](#).

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

- 1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise; or b) reduced blood pressure or symptoms of end-organ dysfunction.
- 2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms.
- 3 Reduced blood pressure after exposure.

Participants will have a pre-assessment (ie, vital signs and lung function) prior to study intervention administration). At Visits 6 and 7 participants should be observed after study intervention administration for a minimum of 2 hours for the appearance of any acute drug reactions. For the remaining visits involving study intervention administration, participants will be observed for a minimum of one hour after study intervention administration for any such reaction.

In order to help understand the potential drug-relatedness of any acute reaction, a blood sample should be drawn as close as possible to the event for possible additional ADA testing (if not already scheduled for this visit). Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the investigator as soon as possible after the event, at 60 minutes $\pm$ 30 minutes after the event, and at discharge for analysis of serum tryptase.

8.3.13 Medical Device Deficiencies

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

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

Device deficiencies will not be presented in the CSR, but where required by local regulations, device deficiencies will be summarised in the relevant periodic report. The definition of a medical device deficiency or deficiency in the device constituent of a combination product is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

NOTE: Additional guidance, including expanded definitions, can be found in [Appendix F](#) of the protocol and Pharmacy Manual.

- Device constituent part of the study drug combination product
 - AstraZeneca report form(s) will be used to collect the information on deficiency as per the Pharmacy Manual and CSP Section [8.3.13.3](#).
- Third Party Medical Devices
 - The deficiency will be reported directly by the site to the manufacturer's or distributor's helpdesk, as applicable.

8.3.13.1 Time Period for Detecting Medical Device Deficiencies

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

The method of documenting Medical Device Deficiency is provided in [Appendix F](#) and the Pharmacy Manual.

8.3.13.2 Follow-up of Medical Device Deficiencies

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

8.3.13.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Only deficiencies associated with study drug combination product should be reported to the AstraZeneca representative.

Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

- The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be sent to AstraZeneca by email, as per the Pharmacy Manual.
- 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](#).
- The sponsor will be the contact for the receipt of study drug - medical device combination product deficiency reports.

8.3.13.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (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 definitions, see [Appendix F](#) of the CSP.

8.3.14 Independent Adjudication Committee

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

The committee will also assess whether cases of ER or urgent care visits and hospitalizations, that occur from randomisation until the end of the follow-up period, are due to a worsening of asthma. Details on the adjudication process, including the scope of adjudication and the committee membership, will be included in the Adjudication Committee Charter/Manual of Operations.

8.4 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one 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 C](#).

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

- PK samples may be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
 - PK samples with future use consent may be anonymised by pooling.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years from the last participant last visit. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the

assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of tezepelumab as specified in SoA (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of objectives or trough matrix concentrations) to ensure appropriate monitoring.
- Samples collected for analyses of tezepelumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5.1.1 Determination of Drug Concentration

Samples for determination of tezepelumab concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded (see Section 6.3.4 for maintaining the study blind).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, may be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA and neutralising antibodies in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report. A summary of the immunogenicity analysis results will be presented in the CSR.

ADA samples may also be further tested for characterisation of the ADA response.

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

8.5.2.1 Anti-drug antibodies

Serum samples for analysis of ADA will be collected at selected visits as per SoA (Section 1.3).

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods. Tiered analysis will be performed to include screening, confirmatory, and titre assay components, and positive-negative cut points statistically determined from drug-naïve samples will be employed.

8.5.2.2 Neutralising antibodies

Samples confirmed positive for ADA will be further evaluated for the presence or absence of neutralising antibodies (nAb) using a validated bioanalytical method. Samples that are ADA negative will not be tested for nAb.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters will be evaluated using biomarkers (Section 8.6)

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of mandatory samples for biomarker analysis

- Mandatory collection of samples for exploratory biomarker research is also part of this study. Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Section 1.3).
- Biomarker analysis will be performed to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to asthma, type 2 (T2) high and T2 low inflammation, TSLP pathway, and OCS dose reduction. Biomarkers will also be used to explore for potential pharmacodynamic (PD) biomarkers of response or exposure to tezepelumab.
- Biomarker analysis may include (but is not limited to) serum cytokines (TSLP, IL-5, and IL-13), blood eosinophils, FeNO (Section 8.1.5), aeroallergen-specific serum IgE (FEIA), total serum IgE (Section 8.6.1.1), and blood transcriptomics (Section 8.6.1.2).
- Samples will be tested to evaluate pharmacodynamic (PD) effects of tezepelumab and associate with clinical response.
- Assessment of eosinophils will be based upon a separate whole blood aliquot not linked to the complete blood count (CBC) safety analysis (see SoA[Section 1.3]).

8.6.1.1 Serum immunoglobulins

The levels of total IgE with seasonal and perennial aeroallergen-specific IgE (FEIA) will be evaluated by a central laboratory in accordance with SoA (Section 1.3). Instruction for sample

collection, processing, storage, and shipment will be provided in a separate laboratory manual.

8.6.1.2 Transcriptomics

Blood samples will be collected for transcriptomics analysis. RNA may be evaluated for gene expression and stored for future analyses. Instructions for sample collection, processing, storage, and shipment will be provided in a separate laboratory manual.

8.6.1.3 Storage, re-use, and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the last participant's last visit (end of study is defined in Section 4.4), after which they will be destroyed. The results of this biomarker research may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

Guidance regarding handling, transport, and destruction of human biological samples is provided in [Appendix C](#).

8.7 Optional Genomics Initiative Sample Collection

Collection of optional blood samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the ICF addendum.

A blood sample for deoxyribonucleic acid (DNA) extraction will be collected from participants who have consented to participate in the genetics analysis component of the study as per SoA (Section 1.3). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See [Appendix D](#) for Information regarding the Genomics Initiative DNA sample.

For storage and destruction of genetic samples see [Appendix D](#).

8.8 Healthcare Resource Utilisation

Medical resource utilisation and health economics data, associated with medical encounters will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

At randomisation, HRU information will be collected with a 'one year' recall period. All the subsequent visits will collect HRU information with a recall period of 'since the last scheduled visit'. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, other selected procedures (inpatient and outpatient), and physician visits or telephone consultations

- Duration of hospitalisation (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or ER visits, tests and procedures, and medications).

Use of systemic corticosteroids (oral, parenteral) for at least 3 days, an ER/urgent care visit with use of systemic corticosteroids or hospitalisation due to asthma should be recorded in the corresponding eCRFs.

Any hospitalisations for more than 24 hours should be reported as an SAE. Refer to Appendix B 2 for reporting hospitalisation.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

To strongly control type I error at 5%, the following 2-sided hypotheses will be evaluated sequentially in this trial at the 0.05 significance level. All other hypothesis testing in this study will be considered exploratory.

The following 2-sided hypotheses will be evaluated in the trial:

Endpoint	Null Hypotheses	Alternative Hypotheses	Direction of superiority of tezepelumab is indicated by
Primary endpoint	H01: Cumulative odds ratio of percentage reduction category from baseline in daily maintenance OCS dose at 28 weeks whilst maintaining asthma control (tezepelumab/placebo) = 1	H11: Cumulative odds ratio of percentage reduction category from baseline in daily maintenance OCS dose at 28 weeks whilst maintaining asthma control (tezepelumab/placebo) $\neq$ 1	An odds ratio greater than 1
Key secondary endpoint	H02: The difference in mean change from baseline in pre-BD FEV ₁ (L) at Week 28 (tezepelumab – placebo) = 0	H12: The difference in mean change from baseline in pre-BD FEV ₁ (L) at Week 28 (tezepelumab – placebo) $\neq$ 0	A difference greater than 0

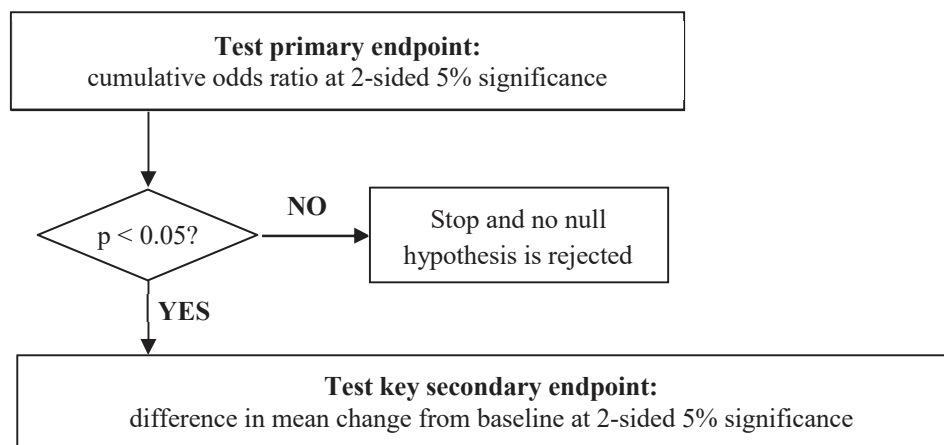
Multiple Testing Procedure

To account for multiplicity when testing the primary and key secondary objectives, the following hierarchical testing procedure will be applied, with the hypotheses tested defined above:

- 1 First the null hypothesis H01 will be tested at a 2-sided 5% significance level with regard to the primary endpoint (categorised percent reduction from baseline in the daily maintenance dose at Week 28 whilst maintaining asthma control).
- 2 If H01 is rejected, then the null hypothesis H02 will be tested at a 2-sided 5% significance level with regard to the key secondary endpoint (change from baseline in pre-BD FEV₁ (L) at Week 28).

The multiple testing strategy is presented at [Figure 3](#).

Figure 3 Multiple Testing Strategy



9.2 Sample Size Determination

Approximately 414 participants will be enrolled to achieve approximately 207 participants randomly assigned to study intervention using a 2:1 treatment allocation ratio (tezepelumab:placebo). Since the primary analysis of the primary endpoint will include all randomised participants as far as possible, no need is envisaged to adjust the number of participants planned to be randomised in order to obtain a number of evaluable participants.

With 138 participants randomised to tezepelumab and 69 randomised to placebo it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint is approximately 90% assuming a true odds ratio of 2.5 and with the placebo assumptions as per [Table 13](#). The assumption of 2.5, as well as the placebo reduction assumptions, is chosen based on a previous OCS-sparing study in the tezepelumab programme, and exploratory analyses performed to assess impact of differences in design ([Wechsler et al 2022](#)). The minimal odds ratio still being significant with the above assumptions is ~1.7.

For the key secondary endpoint, change from baseline in pre-BD FEV₁, the nominal power is approximately 90% using a t-test for 2 independent groups and a nominal 2-sided significance level of 5%, assuming a standard deviation of 0.4L and a true difference in means of 0.2L.

Table 13 Power by Different Assumed Effects in the Placebo Arm, True OR = 2.5, N = 207

Assumed percent participants in placebo achieving the different reduction categories	Scenario A	Scenario B	Scenario C
≥ 90% to ≤ 100% reduction	46.1%	28.9%	21.1%
≥ 75% to < 90% reduction	5.3%	13.2%	3.9%
≥ 50% to < 75% reduction	18.4%	19.7%	17.1%
≥ 0% to < 50% reduction	11.8%	13.2%	15.8%
No change or any increase	18.4%	25.0%	42.1%
Power	89.4	93.6	93.7
Minimal OR still being significant ^a	1.72	1.67	1.67

^a Refers to the smallest odds ratio that would yield a significant result ($p < 0.05$) under the respective assumptions.

Scenario A, B and C corresponds to placebo response from (A) the primary analysis in a previous OCS reduction study, (B) post hoc analysis of the same study assessing the effect at Week 20 in the case of permanent stop in OCS reduction after 2 exacerbations, and (C) post hoc analysis assessing the effect at Week 20 if permanent stop in OCS reduction after first exacerbation or failure to meet asthma control criteria ([Wechsler et al 2022](#))

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 randomly assigned/assigned in the study, are considered” screen failures”, unless otherwise specified by the protocol.

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Randomly assigned to study intervention	All participants randomised to study treatment (irrespective of whether treatment is subsequently taken).
Full Analysis Set	All participants randomised to study treatment who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study.
Safety Analysis Set	All participants who received at least one dose of study intervention.
Pharmacokinetic analysis set	All participants in the full analysis set who received tezepelumab; including PK blood samples that are assumed not to be affected by factors such as protocol deviations (eg, disallowed medication or incorrect study medication received).

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

Safety and ADA presentations will be based on the safety analysis set, with participants assigned according to their actual treatment. Further details of how actual treatment will be determined for analysis in the event of treatment dispensing errors etc will be specified in the Statistical Analysis Plan (SAP). Any important deviations from the randomised treatment assignment, and any participants that have received study intervention without being randomised will be listed and considered when interpreting the safety data.

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

9.4 Statistical Analyses

There will be 2 DBLs in this study. The primary DBL will be conducted after last participant completes Week 28, and the final DBL will be conducted once all participants have completed the last safety follow-up visit (Week 40). All analyses of the primary and secondary objectives will be performed based on the primary DBL data. Following the final DBL, data summaries created will be presented as an addendum to the CSR.

All personnel involved in the analysis and conduct of the study will remain blinded until primary DBL and important protocol deviations identified. After primary DBL, treatment allocation for participants will become known to the sponsor staff and/or designated CRO. The blinding will be maintained for the investigator, investigational site staff, and for the participant.

The SAP will be finalised prior to primary DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. Any deviations from this plan will be reported in the CSR.

Analyses will be performed by AstraZeneca or its representatives.

9.4.1 General Considerations

In general, the last measurement at or prior to randomisation (efficacy)/first dose of study intervention (safety) will serve as the baseline measurement. If there is no value at or prior to randomisation/first dose of study intervention, then the baseline value will be set to missing.

The baseline OCS dose is derived as the most recent prescribed, daily maintenance OCS dose prior to randomisation (Visit 6) ie, the daily dose regimen that a participant is prescribed at the

time of randomisation. If the OCS dose is administered every other day, the total OCS dose over the 2 days will be summed and averaged.

For weekly means derived from participant diaries, baseline is defined as the mean of the available data in the most recent week prior to randomisation. If more than 3 days within that period is missing, then the baseline will be considered to be missing. Note the derivation of baseline values required for reduction of the OCS dose in optimisation and reduction phase are described in Section 8.1.

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 study intervention will be presented. Participants who prematurely discontinue the study intervention 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 by treatment group using frequency and percentages (for categorical variables) and n, mean, standard deviation, minimum, median and maximum (for continuous variables) using the full analysis set. Relevant medical history/current medical conditions will be summarised by treatment group, system organ class and preferred term of the MedDRA dictionary using frequency and percentage of participants for each treatment group.

Prior and concomitant medications, categorised according to the WHO Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system, will be summarised by treatment group as frequency and percentage of participants reporting usage. Prior medications are defined as those which stopped before first dose of study intervention. Concomitant medications are defined as those which either started or continued after first dose of study intervention. Important protocol deviations will be defined prior to unblinding and summarised by treatment group. Participants will not be excluded from the Full or the Safety analysis sets on the basis of any important protocol deviations. The definitions of each category of important protocol deviation will be fully specified in the SAP and may include (but not necessarily limited to): participants who were randomised to study treatment without fulfilling key entry criteria; participants who received prohibited or restricted concomitant medications while on study intervention, participants who received the incorrect study treatment or study dose at any time during the 28-week double-blind treatment period.

Estimates will be presented together with 95% confidence intervals. P-values will be presented for the primary analyses of the primary and key secondary endpoints included in the multiple testing procedure described in Section 9.1.

In general, all data up to Week 28 will be included in the statistical analysis, even if a participant discontinues treatment or changes background therapy (other than OCS). If a participant initiates therapy with another biologic for treatment of asthma, the composite strategy will be applied. Missing data will be imputed using a multiple imputation (MI) approach.

In the case of death, given the expectation that very few deaths (if any) would be observed in this study, the impact is expected to be minimal and as such, the data after death will be imputed assuming an unfavorable outcome, and for the primary endpoint, the category 5 (no change or any increase) will be used. The efficacy analyses will be based on planned treatment period, and the safety analyses based on-treatment and/or on-study period.

Planned treatment period starts on the date of randomisation and ends on the date of the Week 28 visit or earlier study withdrawal date. On-treatment period starts on the date of randomisation (efficacy)/date of first dose of study intervention (safety) and ends on earliest (date of last dose of study intervention + 33 days, date of death, date of study withdrawal). On-study period (planned treatment and follow-up): starts on the date of randomisation (efficacy)/date of first dose of study intervention (safety) and ends on the study completion or withdrawal date. Further details will be specified in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary endpoint is the percentage reduction from baseline in daily maintenance OCS dose at Week 28 whilst maintaining asthma control (as per Table 8), by ordered categories defined as follows:

- Category 1: $\geq 90\%$ to 100% reduction
- Category 2: $\geq 75\%$ to $< 90\%$ reduction
- Category 3: $\geq 50\%$ to $< 75\%$ reduction
- Category 4: $> 0\%$ to $< 50\%$ reduction
- Category 5: no change or any increase

The percent change from baseline is defined as $\{(final\ dose - baseline\ dose) / baseline\ dose\} * 100\%$.

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. 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 15. Further details may be specified in the SAP.

Note: In the case of death, the category 5 (no change or any increase) will be assigned regardless of the observed percentage reduction.

Table 15 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 for treatment of asthma and increased by one dose level.
Premature withdrawal from the study prior to Week 28	Last reported OCS dose ^a received by participant with asthma stability verified ^b at the time of study withdrawal, increased by one dose level.
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.

The primary endpoint in the tezepelumab group will be compared to that in the placebo group using a proportional odds (ordinal logistic regression) model. This model will be used to perform the statistical test specified in Section 9.1, and to estimate the treatment effect and its 95% confidence interval. The response variable in the model will be the ordered category number (1 to 5 at Week 28 as defined in Section 9.1). Treatment and region will be included as categorical covariates and baseline OCS dose and log baseline blood eosinophil counts will be included as continuous covariates in the model. For 5 ordered categories, there are 4 possible cumulative odds for each treatment group, corresponding to the 4 different possible binary splits, which are defined as follows:

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

An underlying assumption of proportional odds model is that the 4 possible odds ratios between the 2 treatments as defined above are the same. An investigation into the proportional odds assumption will be done, and if necessary further analyses which make fewer restrictions with regards to this assumption and/or analyses using different response category definitions

will be performed.

Frequency tables of the number and proportion of participants in each of the response categories will be presented.

The treatment effect across baseline biomarkers and demographic variables will be evaluated similarly as the primary endpoint. The statistical model will include additional factors for the relevant subgroup and the treatment-by-subgroup interaction. The subgroups include (but are not limited to):

- Baseline EOS group: < 300 cells/ μ L, ≥ 300 cells/ μ L
- Baseline EOS group: < 150 cells/ μ L, ≥ 150 cells/ μ L
- Baseline FeNO group: < 25 ppb, ≥ 25 ppb
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA

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

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

- Describing and comparing categorised percent reduction from baseline in daily maintenance OCS dose between treatments using a non-parametric Wilcoxon rank sum test stratified by region (van Elteren test).
- Controlled multiple imputation analyses will be performed which allow for different underlying assumptions about missing data to be used (MAR - missing at random, MNAR - missing-not-at-random).

Supplementary analyses for the primary endpoint will be described in the SAP.

9.4.2.2 Secondary Endpoint(s)

Key secondary endpoint

Pre-BD FEV₁ will be determined by spirometry at the clinic visit. Only the assessments collected at scheduled, mandatory visits for all participants (Visits 6, 7, 8, 10, 13 and IPD), will be used in the statistical analyses. Change from baseline will be calculated as defined in Section 9.4.1.

For participants who initiate another biologic for the treatment of asthma data points after the initiation will be imputed assuming an unfavorable outcome. Details on the imputation

approach to account for this composite strategy will be provided in the SAP, prior to unblinding of the study. For other intercurrent events, a treatment policy strategy will be applied utilizing all available data including data collected post the intercurrent events, with missing data assumed to be missing at random. Other missing data (i.e., not following ICE) at the mandatory post randomisation visits will be imputed using a multiple imputation (MI) approach assuming missing at random. Details on the missing data imputation will be provided in the SAP.

Following the imputation steps, each of the imputed datasets will be analysed using an analysis of covariance (ANCOVA) model. The response variable will be the change from baseline in pre-BD FEV₁. Treatment and region will be included as categorical covariates and baseline pre-BD FEV₁ and log baseline blood eosinophil counts will be included as continuous covariates in the model. Rubin's rule will be applied to combine analysis results (point estimates and standard errors) from the imputed datasets. The adjusted mean changes from baseline for each treatment arm together with its 95% confidence interval will be estimated from this model, as well as the mean difference with 95% confidence interval (CI). In addition, descriptive statistics will be provided for each time point.

The treatment effect across baseline biomarkers and demographic variables will be evaluated similarly as the primary endpoint. The statistical model will include additional factors for the relevant subgroups and the treatment-by-subgroup interaction. The subgroups include (but are not limited to):

- Baseline EOS group: < 300 cells/ μ L, $\geq$ 300 cells/ μ L
- Baseline EOS group: < 150 cells/ μ L, $\geq$ 150 cells/ μ L
- Baseline FeNO group: < 25ppb, $\geq$ 25ppb
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA

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

To explore the robustness of inferences from the main analysis of key secondary endpoint, sensitivity analyses will be performed. These may include, but are not limited to, the controlled multiple imputation analyses allowing for different underlying assumptions about missing data to be used.

Supplementary analyses for the key secondary endpoint will be described in the SAP.

Other secondary endpoints

Binary endpoints related to OCS dose reduction will be summarised using frequency tables.

The odds ratio (tezepelumab/placebo) and its 95% confidence interval will be estimated for each endpoint from a logistic regression model with treatment and region included as categorical covariates and baseline OCS dose and log baseline blood eosinophil counts included as continuous covariates.

Annualised asthma exacerbation rate in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to estimate the annual exacerbation rate for each treatment arm together with its 95% CI as well as the rate ratio and its 95% CI. The response variable in the model will be the number of asthma exacerbations experienced by a participant over the 28-week treatment period (or shorter duration if not followed up for the full 28 weeks). Treatment, region, and history of exacerbations (≤ 2 or > 2 in previous 24 months) will be included as categorical covariates and log baseline blood eosinophil counts will be included as a continuous covariate in the model. The logarithm of the time at risk for exacerbation in the study will be used as an offset variable in the model, to adjust for participants having different follow-up times during which the events occur. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, will not be included in the calculation of time at risk for exacerbation. Descriptive summaries of the AAER will also be presented.

Rates for the exacerbation related to ER or urgent care visits due to asthma that required additional systemic corticosteroids, or a temporary increase in a stable OCS background dose, or hospitalisation due to asthma will be summarised and analysed similarly as described above.

Time to first asthma exacerbation will be summarised graphically using Kaplan-Meier estimates, and analysed using a Cox proportional hazards model with treatment, region, history of exacerbations (≤ 2 or > 2 in previous 24 months) as categorical covariates and log baseline blood eosinophil counts as a continuous covariate.

Proportion of participants who did not experience an asthma exacerbation over 28 weeks will be summarised and analysed similarly to other binary endpoints. The analyses will be adjusted for treatment, region, history of exacerbations (≤ 2 or > 2 in previous 24 months) and log baseline blood eosinophil counts.

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.

Change from baseline in other continuous secondary endpoints will be summarised and analysed similarly as the key secondary endpoint.

9.4.2.3 Exploratory Endpoint(s)

Details regarding the analyses of exploratory endpoints will be specified in the SAP. Note that any analyses of exploratory objectives may be reported separately from the CSR.

The statistical analyses of exploratory endpoints will be described in detail in the SAP.

9.4.3 Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in force at the primary DBL. They will be presented based on on-treatment and/or on-study period as described in Section 9.4.1.

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

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

Adverse events of special interest (AESIs) will also be summarised descriptively by treatment group.

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

Vital signs data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital signs abnormalities will be summarised.

9.4.4 Other Analyses

Analysis of pharmacokinetics variables will be described in the SAP.

The prevalence and incidence of ADA will be reported by treatment group. Anti-drug antibody data will be summarised using descriptive statistics at each visit by treatment group. Samples

confirmed positive for ADA will be tested for neutralising antibodies (nAb), and the nAb status will be summarised by treatment group. The potential effects of ADA status and ADA titre on PKs of tezepelumab will be evaluated. The potential association of ADA status, ADA titre, and nAb status with efficacy will be evaluated. The potential association of ADA status with safety may be evaluated.

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

9.5 Interim Analyses

No interim analyses are planned in this trial.

9.6 Data Monitoring Committee

A data safety monitoring board will not be utilised for this study.

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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
 - Applicable International Council for 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 IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study 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 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European MDR 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

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

- European MDR 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

- A ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one 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 or his/her legally authorised representative 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 or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the 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.
- Participants who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

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 data safety monitoring board will not be utilised for this study.

A 6 Dissemination of Clinical Study Data

Due to scientific reasons, results, both technical and lay summaries for this trial, will be disclosed to European Union Clinical Trials Information System within a year from global End of Trial Date in all participating countries, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on:

- <http://astrazenecagrouptrials.pharmacm.com>
- <http://www.clinicaltrials.gov>
- www.clinicaltrialsregister.eu

as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded in the 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 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.
- Quality tolerance limits (QTLs) will be predefined in the Integrated Quality Risk Management Plan (IQRMP) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.
- 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 non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Medical oversight details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight 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, Contract Research Organisations).
- 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 25 years after study archiving according to the AstraZeneca Global Retention and Disposal (GRAD) schedule, 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 when the first participant consents to take part in the study 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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

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 between the sponsor and external parties.
- Authorship will be determined by mutual agreement between the sponsor and external parties 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 adverse event is the development of any untoward medical occurrence in a participant 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 serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient 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 (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, 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 a serious AE, 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 serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 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, Drug Abuse, Drug Misuse

Medication Error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and 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
- Drug not stored as instructed eg, kept at room temperature when it should be kept in the refrigerator.
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - 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)
- Accidental overdose (will be captured as an overdose)

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

Drug abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of the IMP or AZ NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)

Drug misuse

Drug misuse is the intentional and inappropriate use (by a study participant) IMP or AZ NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AZ NIMPs, outside the intended use as specified in the Clinical Study Protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include, but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used with the connotation to cause an effect or facilitate assault in another person
- The drug is deliberately administered by the wrong route
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator at each centre 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 whilst 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.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

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.

C 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 subject 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 D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetics research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetics research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetics research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetics analyses may be reported outside of the CSR and in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetics Research Population

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

Inclusion Criteria

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

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
 - Previous allogeneic bone marrow transplant
 - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetics Research

- Participants may withdraw from this genetics research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetics Research

- The blood sample for this genetics research will be obtained from the participants at randomisation Visit 6. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 6, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in [Appendix A](#).

Informed Consent

- The genetics research component of this study is optional and the participant may participate in other components of the main study without participating in this genetics research component. To participate in the genetics research component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The PI is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdraw the informed consent from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, or any general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetics data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetics data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Study Physician or an investigator might know a participant's identity and also have access to his or her genetics data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetics files would remain physically separate.

Data management

- Any genetics data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetics research with other researchers, such as hospitals, academic organisations, or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summarised results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetics data in a suitable secure environment separate from the clinical database.

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

E 1 Introduction

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

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 TBL from a local laboratory.

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

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. 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 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.

E 2 Definitions

Potential Hy's Law

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3 \times$ Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ 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.

E 3 Identification of Potential Hy's Law Cases

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

- $ALT \geq 3 \times ULN$
- $AST \geq 3 \times ULN$
- $TBL \geq 2 \times ULN$

Central Laboratories Being Used:

When a 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 Section [E 2](#) for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the 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 Clinical Study Protocol.

E 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 one 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 study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The AstraZeneca 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. Completes follow-up SAE Form as required.
 - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the AstraZeneca Study Physician. This includes deciding which the tests available in the HL lab 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 AstraZeneca Study Physician if there is any uncertainty.

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

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

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

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

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE 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 'HL') 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 'HL 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.

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

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

^a HBV DNA is only recommended when IgG anti-HBc is positive.

^b HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.

Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device/Device Constituent Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up

This appendix supports the activities described in Section [8.3.13](#)

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

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

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section [6.1.2](#) for the list of sponsor medical devices.

For simplicity, medical device term is used in this appendix to cover device constituent parts of combination product and the medical devices manufactured by third parties provided for use in this study whether investigational or approved.

F 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

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

F 2 Definition of Medical Device SAE, SADE, and USADE

A Medical Device SAE is any medical device adverse event that:

- 1 Led to death
- 2 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).
- 3 Led to fetal distress, fetal death, or a congenital anomaly or birth defect

A Medical Device SADE definition is:

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

F 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

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

F 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/device deficiency reported during the study and assign it to one of the following categories:

- 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)

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 judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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 recognised follow-up period, the investigator will provide sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
The investigator will submit any updated SAE data to sponsor within 24 hours of receipt of the information.

Appendix G Maintenance therapy equivalence table

Table G1 Estimated daily doses for inhaled corticosteroids

Asthma Therapy	Total Daily Dose (µg/day)
Inhaled Corticosteroid	High
Beclomethasone dipropionate (pMDI, standard particle HFA)	> 1000
Beclomethasone dipropionate (pMDI or DPI extrafine particle, HFA)	> 400
Ciclesonide (pMDI, extrafine particle, HFA)	> 320
Fluticasone furoate (DPI) eg, Arnuity® Ellipta®	200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	> 500
Budesonide (DPI, or pMDI, standard particle HFA)	> 800
Mometasone furoate (pMDI, standard particle, HFA)	> 440
Mometasone furoate (DPI)	Depends on DPI device- see product information
Inhaled Corticosteroid in ICS/LABA combination^a	High
Beclomethasone dipropionate (eg, Fostair®)	> 400
Fluticasone propionate HFA (eg, Seretide®, Advair®)	> 500
Fluticasone furoate (eg, Relvar® Ellipta®, Breo® Ellipta®)	184 - 200
Budesonide, if as delivered dose (eg, Symbicort®)	> 640
Mometasone Furoate (eg, Dulera®)	> 400

^a The ICS doses for the ICS/LABA combinations were derived from [GINA 2022](#) and using prescribing information.

Table G2 Estimated OCS dose therapy equivalence

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

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

Table H1 Prednisone/Prednisolone doses < 5 mg in relation to available tablet strengths (scored tablets)^a

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

^a If available, oral solution is allowed to achieve Prednisone/Prednisolone doses <5 mg

Appendix I Anaphylaxis: Signs and Symptoms, Management

I 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorised anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex mediated]) and nonimmunologic ([Johansson et al 2004](#)). The clinical criteria for defining anaphylaxis for this study are listed in Appendix I 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix I 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 $\pm$ 30 minutes after the event, and at discharge for analysis of serum tryptase.

I 2 Clinical Criteria for Defining Anaphylaxis

Anaphylaxis

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, 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 PEF, hypoxemia).
 - b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a 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, hypoxemia).
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).

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

I 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all 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:

- 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

I 4 Management of Acute Anaphylaxis

Immediate intervention

- 1 Assessment of airway, breathing, circulation, and adequacy of mentation
- 2 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:

- 1 Place participant in recumbent position and elevate lower extremities.
- 2 Establish and maintain airway.
- 3 Administer oxygen.
- 4 Establish venous access.
- 5 Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate:

- 1 Consider epinephrine infusion.
- 2 Consider H1 and H2 antihistamines.
- 3 Consider nebulised β_2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine.
- 4 Consider systemic corticosteroids.
- 5 Consider vasopressor (eg, dopamine).
- 6 Consider glucagon for participant taking β -blocker.
- 7 Consider atropine for symptomatic bradycardia.
- 8 Consider transportation to an emergency department or an intensive care facility.
- 9 For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Adapted from: [Kemp et al 2008](#).

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

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. Instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca Medical Monitor.

J 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 J 2 through J 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.

J 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 AstraZeneca 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 study intervention. If this delay is outside the screening window specified in SoA (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 5.4.

J 3 Home or Remote Location 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 Standard Operating Procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP. Study assessments, where possible to be performed at home, should be conducted according to the SoA (Section 1.3). At minimum, during home or remote location visit the qualified HCP is expected to:

- Collect information on asthma-related healthcare resources utilisation
- Perform a physical examination
- Collect vital signs
- Collect adverse events
- Collect information on asthma exacerbation
- Review concomitant medications
- If possible, collect blood and urine sample according to the SoA (Section 1.3)
- Conduct urine pregnancy test (dipstick), prior to study intervention administration, if applicable
- Daily diary and PEF data review/completion
- Evaluation of OCS dose (done by investigator, can be done remotely after relevant data are reviewed)
- Administer study intervention
- Observe the participant for one hour after study intervention administrations for the signs or symptoms of any acute drug reactions
- Document the visit

J 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.

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 adverse events, concomitant medication, asthma exacerbations, healthcare resource utilisation, ePRO, and the assessment and adjustment of OCS dose based on available sources of information (see J 6) at the discretion of the PI to be collected and entered on the source documents.

J 5 At-home or Remote Location Study Intervention Administration Instructions

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

NOTE: Before initiating consent for home study intervention 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 study intervention administrations at the site.

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

J 5.1 At-home or Remote Location Study Intervention Administration by a Qualified HCP

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

J 6 OCS Reduction and Data Capture During Telemedicine

J 6.1 OCS Reduction during Telemedicine/Remote Visits

Decision on OCS dose can be based on remote interview of participant, data from ePRO and ePEF devices, and if applicable, home visit physical examination and vital signs, as per the investigator's judgement.

J 6.2 Data Capture During Telemedicine or Home/Remote Location Visits

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

Appendix K Abbreviations

Abbreviation or special term	Explanation
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-Drug Antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AI	adrenal insufficiency
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
APFS	accessorised pre-filled syringe
AQLQ(s)+12	Standardised Asthma Quality of Life Questionnaire for 12 years and older
ASD	Asthma Symptom Diary
AST	aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
AZ	AstraZeneca
BD	Bronchodilator
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
BTR	best test report
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CK	creatinine kinase
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CTR	Clinical Trials Regulation
CTT	Clinical Trial Transparency
DBL	database lock
DILI	Drug Induced Liver Injury

Abbreviation or special term	Explanation
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOS	eosinophil count
EOT	end of treatment
ER	Emergency Room
EQ-5D-5L	European Quality of Life-5 dimensions-5 levels
EU	European Union
FAS	full analysis set
FeNO	Fractional exhaled nitric oxide
FEV ₁	Forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GRAD	Global Retention and Disposal
Hb	hemoglobin
HCP	Health Care Professional
HD	high dose
HDL-C	high-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HL	Hy's Law
HRU	health resource utilisation
IAC	Independent Adjudication Committee
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	Investigational Medicinal Product

Abbreviation or special term	Explanation
IPD	Investigational product discontinuation visit
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Study File
LABA	long-acting β_2 agonists
LAMA	Long-acting muscarinic antagonist
LDL	low-density lipoprotein
LTRA	leukotriene receptor antagonists
MACE	Major Adverse Cardiac Events
MAR	missing at random
MCID	minimum clinically important difference
MD	medium dose
MDR	Medical Device Regulation
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing-not-at-random
nAb	neutralizing antibodies
NIMP	non-investigational medicinal product
OCS	Oral Corticosteroids
PEF	peak expiratory flow
PHL	Potential Hy's Law
PI	Principal investigator
PK	pharmacokinetic(s)
PNV	predicted normal values
QTL	quality tolerance limit
Q4W	every 4 weeks
RBC	red blood cell
RTSM	Randomisation and Trial Supply Management
SABA	Short-acting beta agonists
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory coronavirus 2
SC	subcutaneous

Abbreviation or special term	Explanation
SGRQ	St George's Respiratory Questionnaire
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TSLP	thymic stromal lymphopoietin
UNS	unscheduled
ULN	upper limit of normal
USADE	unanticipated serious adverse device effect
V	visit
VLDL	very-low-density lipoprotein
Wk	week
Wks	weeks
WOCBP	women of childbearing potential

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 (22-August-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The main reasons for this amendment include:

- a) Adding assessment of the pre-specified events by the Independent Adjudication Committee to the study design,
- b) Removing the requirement of pre-BD FEV₁ spirometry for participants who achieve a permanent stop of OCS dose reduction, except for the mandatory spirometry at visits 6, 7, 8, 10, 13 regardless of OCS dose reduction status and revising statistical analyses for secondary endpoints,
- c) Revising restrictions for COVID-19 vaccination,
- d) Adding important potential risks and adverse event of special interest (serious cardiac events),
- e) Revising the estimand for the intercurrent events related to the initiation of other biologic for treatment of asthma.

Other reasons include updating wording of the asthma exacerbation definition, as well as, adding clinical chemistry test of blood lipid panel at Visit 1 and 12-lead ECG assessment at Visit 13 and IPD.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Protocol title and Section 1.1 Synopsis	“40” updated to “28” in the protocol title.	Correction of an error: The study treatment duration to replace the duration of combined study treatment and safety follow-up phases.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis, Section 3 Objectives and Endpoints and Section 9.4 Statistical Analyses	The phrase “for treatment of asthma” added to “Initiate therapy with another biologic”.	To clarify that the intercurrent event is related to the initiation of other biologic for treatment of asthma.	Non-substantial
Section 1.1 Synopsis, Section 3 Objectives and Endpoints and Section 9.4 Statistical Analyses	The strategy for handling the intercurrent event of “initiate therapy with another biologic” is updated from “hypothetical strategy” to “composite strategy”.	Consistency of handling intercurrent events across primary and key secondary objectives.	Non-substantial
Section 1.1 Synopsis and Section 3 Objectives and Endpoints	Timepoint has been specified in the summary measure for primary and key secondary endpoints.	To clarify that, the summary measure is presented at Week 28.	Non-substantial
Section 1.1 Synopsis, Section 6.3.4 Ensuring Blinding and Section 8.3.14 Independent Adjudication Committee	Language regarding Independent Adjudication Committee added.	To clarify that assessment of the pre-specified events by the Independent Adjudication Committee was added to the study design.	Substantial
Section 1.1 Synopsis and Section 9.4.2.2 Secondary Endpoint(s)	Statistical analyses for secondary endpoints updated.	To accommodate the analyses to the composite strategy of handling data after initiation of another biologic for treatment of asthma and reduction of spirometry assessments.	Non-substantial
Section 1.1 Synopsis	Information added that the actual treatment assignment will be used in the analysis of safety variables.	To clarify treatment assignment in analyses of safety variables.	Non-substantial
Section 1.3 Schedule of Activities, Table 1	The phrase “women of childbearing potential” added to footnote “h”.	To clarify the meaning of the “WOCBP” abbreviation.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 Schedule of Activities, Table 1 and Table 2	Schedule of Activities updated, to clarify that visits can be confirmed within the ePRO device or in the ePRO study portal and only unscheduled visits related to asthma worsening should be confirmed.	To clarify the visit confirmation process and that OCS reduction criteria are based not only on ePRO data.	Non-substantial
Section 1.3 Schedule of Activities, Table 1, Section 5.1 Inclusion Criteria and Section 8.1.3.3 Post-BD spirometry and FEV ₁ responsiveness testing	“Reversibility assessment” updated to “bronchodilator responsiveness testing”.	To align wording with the ATS/ERS 2019 guidelines.	Non-substantial
Section 1.3 Schedule of Activities, Table 1 and Section 5.1 Inclusion Criteria	Units for eosinophil count updated from “GI/L” to “x10 ⁹ /L”.	To reflect eosinophil count units for the results obtained from the contracted laboratory vendor.	Non-substantial
Section 1.3 Schedule of Activities, Table 1 and Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	“Total cholesterol” replaced with “Lipid profile” as a laboratory safety variable. List of tests, included in the Lipid Profile, added to footnote “d” of Table 12.	To assess participant lipid profile for a better understanding of participant's risk for cardiovascular disorder.	Substantial
Section 1.3 Schedule of Activities, Table 2	Added 12-lead ECG at Visit 13 and IPD and text to footnote “f” on the requirement for 12-lead ECG at Visit 13 and IPD.	To implement a local 12-lead ECG assessment at Visit 13 and IPD for participants who had a pre-existing cardiac condition to document any potential changes during the study.	Substantial
Section 1.3 Schedule of Activities, Table 2	Footnote “k” added on condition when to collect PK samples.	To clarify that PK samples must be collected pre-dose at dosing visits.	Non-substantial
Section 1.3 Schedule of Activities, Table 2	Schedule of Activities updated to clarify the	To reduce participant burden.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	reduced requirement for pre-BD spirometry at Visits 9, 11 and 12 after the permanent stop of the OCS dose reduction.		
Section 1.3 Schedule of Activities, Table 2 and Section 8.1.6 Patient-reported outcomes	Wording on completion of available ePRO questionnaire at Visit 6, Visit 13 and IPD at the site added to the footnote “p” of Table 2 and section 8.1.6. Text on EQ-5D-5L in footnote “p” moved to footnote “q”.	To clarify that ePRO assessments at Visits 6, 13 and IPD are completed at the site. For clarity, footnote “q” on the EQ-5D-5L questionnaire created.	Non-substantial
Section 2.3.1 Risk Assessment	New category of “Important potential risks” including serious infections, malignancies and serious cardiac events added, “Potential risks of clinical significance” updated to “Potential risks” and text on risk of serious infections and serious hypersensitivity reactions updated.	To align with the Investigator’s Brochure edition 5.1 (dated 22 July 2022).	Substantial
Section 2.3.1 Risk Assessment, Section 5.2 Exclusion Criteria and Section 5.4.1 Re-screening	The word “systemic” was added to “antibiotics or antiviral”.	To specify that usage of systemic antibiotics or antiviral medications finalised < 2 weeks before Visit 1 or during the run-in period or at randomisation is exclusionary.	Non-substantial
Section 4.1 Overall Design and Section 6.5 Concomitant Therapy	Sentences on changes of asthma maintenance treatments updated to indicate that the treatment should not be changed until preferably 4 weeks	To be aligned with Table 6 of the CSP.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	after the last dose of study intervention instead until the end of the study.		
Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	“2” was updated to “3” in the sentence on the number of doses of study intervention that must be administered on-site before initiation of at-home study intervention administration.	To be aligned across CSP.	Non-substantial
Section 5.2 Exclusion Criteria and Section 6.5 Concomitant Therapy, Table 6	COVID-19 vaccination restriction updated from 7 days to 28 days before and 14 days after study intervention administration	To align with the Investigator’s Brochure edition 5.1 (dated 22 July 2022).	Substantial
Section 5.4 Screen Failures	The text on the screen failures updated.	To clarify that the screen failures are participants who are not subsequently randomly assigned to study intervention because of not meeting required inclusion/exclusion criteria.	Non-substantial
Section 6.1.2 Medical Devices, Section 6.2.4 Reporting Product Complaints, Section 6.2.5 Reporting Product Defects, Section 6.2.6 Single Use APFS device malfunction, Section 8.3.13 Medical Device Deficiencies, 8.3.13.3 Prompt Reporting of Medical Device Deficiencies to Sponsor and Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical	The text regarding the medical device, medical device deficiencies definitions and reporting requirements updated.	To be aligned with International Organization for Standardization 14155 and European Medical Device Regulation.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Device/Device Constituent Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up			
Section 6.2.3 Dose Administration	Removed “and an additional eCRF page with questions about the injection site reaction”.	To indicate that no completion of an additional eCRF page is required for injection site reaction.	Non-substantial
Section 6.3.4 Ensuring Blinding	Removed “immunoglobulins (IgA, IgG, IgM)” in the sentence on redaction of the results from central laboratory reports.	Immunoglobulins (IgA, IgG, IgM) are not tested during the trial and will not be present in the central laboratory report.	Non-substantial
Section 6.5 Concomitant Therapy	“12” was updated to “24” in the sentence on the timeframe of recording the treatment for the asthma exacerbation in the eCRF.	To be aligned across CSP.	Non-substantial
Section 8.1.1.1 Asthma Control Criteria for OCS dose reduction, Table 8	“OCS” updated to “systemic corticosteroids” in the Asthma Control criterion 5 for OCS reduction.	To clarify that asthma control is maintained when no increase in the dose of systemic corticosteroids for asthma symptoms/exacerbations since the last visit occurred.	Non-substantial
Section 8.1.1.1 Asthma Control Criteria for OCS dose reduction, Table 8	The words “baseline” added to the sentence on when pre-BD FEV ₁ for optimisation phase and for dose reduction phase is collected.	To clarify that the pre-BD FEV ₁ baseline for the optimisation phase and for the dose reduction phase is collected at Visit 2 and 6 respectively.	Non-substantial
Section 8.1.1.1.2 Details of OCS dose	Reference to “Table 8” changed to “Table 10”	To provide the correct reference to the OCS	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
management in the treatment period	and moved to the part of the sentence on the returning of the OCS dose at least one step higher.	dose reduction schedule during the reduction phase.	
Section 8.1.2 Asthma exacerbations - Assessment and management	The phrase “increase in systemic corticosteroids dose by dose greater than one dose level (Table 9, Table 10)” replaced with “bolus/burst of systemic corticosteroids or a temporary increase in stable OCS background dose” in the definition of the asthma exacerbation and word “maintenance” added to the note on exacerbation event.	To align with AstraZeneca standards related to asthma exacerbations.	Substantial
Section 8.1.2 Asthma exacerbations - Assessment and management and Section 9.4.2 Efficacy	Statement on relapse of the prior asthma exacerbation updated and moved from the section on the Asthma exacerbations - Assessment and management to the Efficacy section of the CSP.	To be aligned with AstraZeneca standards related to asthma exacerbations.	Non-substantial
Section 8.1.2.3 Exacerbation management during the treatment period	“OCS” updated to “systemic corticosteroids” in the sentences on the OCS dose management after completion of asthma exacerbation treatment.	To be aligned across CSP.	Non-substantial
Section 8.1.2.3 Exacerbation management during the treatment period	The word “can” updated to “should” and reference to Table 8 removed in the sentence on OCS dose reduction at Visit 8.	To clarify, if the participant cannot undergo mandatory OCS reduction at Visit 7, OCS reduction will be mandatory at Visit 8.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.3 Spirometry	Added statement “Maximum number of efforts for spirometry measurement is 8.”	To clarify the maximum number of efforts for spirometry.	Non-substantial
Section 8.1.6 Patient-reported outcomes	Text on the patient-reported outcomes (PRO) data collection updated.	To clarify that PRO data will be captured electronically not on paper and that at home PRO assessment will continue until study completion as per SoA.	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	Footnote “a” linked to B-Leukocyte differential count (absolute count) instead of B-Red blood cell (RBC) count.	Correction of reference in table footnote.	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments, Table 12	Phrase “personnel involved in the analysis and conduct of the study” added to the sentence on the blinding of the eosinophil, basophil and monocyte absolute, and percentage values from the central laboratory reports.	To clarify that the study personnel will be blinded to the eosinophil, basophil and monocyte absolute, and percentage values from the central laboratory reports.	Non-substantial
Section 8.3.5 Adverse Events Based on Examinations and Tests and Section 8.3.8 Disease Under Study	Sentence on the recording of all asthma exacerbations updated and moved to section 8.3.8.	For clarity, to have information on capturing asthma symptoms in correct section, aligned to the CSP.	Non-substantial
Section 8.3.6 Adverse Events of Special Interest	Serious cardiac events added as an AESI.	To align with the Investigator’s Brochure edition 5.1 (dated 22 July 2022).	Substantial
Section 8.3.8 Disease Under Study	Word “intervention” added to the sentence “The participant discontinues the study due to the sign or symptom.”	Correction of the error: To clarify, if the participant discontinues the study intervention due to the sign or	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		symptom of asthma, it will be recorded as AE.	
Section 8.3.9 Reporting of Serious Adverse Events	The phrase “EDC system” replaced with “eCRF” in the sentences on the SAE collection.	To be aligned across CSP.	Non-substantial
Section 8.5 Human Biological Samples, Section 8.6.1.3 Storage, re-use, and destruction of biomarker samples and Appendix D 2 Genetic Research Plan and Procedures	The phrase “25 years from the date of the issue of the CSR” updated to “15 years from the last participant last visit” in the sentences on the ADA and PK samples management.	To be aligned with AstraZeneca standards related to human biological sample handling and lifecycle management.	Non-substantial
Section 8.5.1.1 Determination of Drug Concentration	The word "will" replaced with "may" in the sentence on the reporting of the drug concentration evaluation results.	Correction of the error: To clarify that the drug concentration evaluation results may be reported in separate Bioanalytical Report.	Non-substantial
Section 9.4.1 General consideration	Reference to the first dose of study intervention was removed from the planned treatment analysis.	Planned treatment period applies only to efficacy analyses with baseline value defined by means of randomisation date.	Non-substantial
Section 9.4.1 General consideration	Post death data will be imputed using unfavourable outcome.	To be consistent with handling data post initiation of another biologic for treatment of asthma.	Non-substantial
Appendix B 2 Definition of Serious Adverse Events	The phrase "in-participant" replaced with "in-patient" in the sentence on SAE criteria of hospitalisation or prolongation of existing hospitalisation.	Correction of the error: To clarify that in-patient hospitalisation or prolongation of existing hospitalisation is a criterion for SAE.	Non-substantial
Appendix B 4 Medication Error, Drug Abuse, Drug Misuse	Text updated.	For clarity, examples of a medication error, drug abuse and drug misuse	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		not applicable to the investigational product deleted.	
Appendix H Prednisone/Prednisolone doses < 5 mg in relation to available tablet strengths (scored tablets), table H1	Footnote “a” added.	To clarify that if available, oral solutions can be used to achieve Prednisone/Prednisolone doses <5 mg.	Non-substantial
Appendix K Abbreviations	New abbreviations added.	To include all abbreviations in the document.	Non-substantial
Appendix L Protocol Amendment History	Appendix L added.	To include information about protocol amendment history.	Non-substantial

Appendix M Country-specific Requirements

Local CSP 3.0 Czech Republic

Overall Rationale for the local Amendment

Based on the Regulatory Authority requirement in the Czech Republic, the following changes were performed:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.3 Schedule of Activities, Table 1	QuantiFERON-TB test added as mandatory local test for all participants at Visit 1, in line with the local public health practice and guidelines.	Czech Health Authority requirement. To align with local requirements regarding treatment with biologics.	Substantial
1.3 Schedule of Activities, Table 2	Local ECG testing for all participants implemented at the End of Study visit and IPD	Czech Health Authority requirement. To document any potential changes in the ECG during the study.	Substantial
5.1 Inclusion criteria	The inclusion criterion no.16 has been reworded: "ONLY applicable to the participants who agree to take part in the Optional Genomics Initiative"	Czech Health Authority requirement. To clarify that participation in genetic research is voluntary.	Substantial
5.2 Exclusion criteria	Exclusion criterion no.11: information on the need to perform QuantiFERON TB local test for all patients, in line with the local public health practice and guidelines added	Czech Health Authority requirement. To align with local requirements regarding treatment with biologics.	Substantial
4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or	Delete information about administration of study intervention at participant's home	Czech Health Authority requirement. This study intervention is unregistered biological product and home administration will not be permitted in the Czech Republic.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Public Health Crisis 6.2.3 Dose administration 6.2.6 Single Use APFS device malfunction 6.4 Study Intervention Compliance			
7.1 Discontinuation of Study Intervention	Revision of the sentence: "the AstraZeneca Study Physician should be informed regardless of the reason for discontinuation."	To align with the GCP (ICH GCP 4.3.1) - all medical decisions regarding the patient are the responsibility of the investigating physician, including the decision to remove the patient from the study or from the use of study intervention.	Substantial
7.1 Discontinuation of Study Intervention	Revision of the sentence: "Participant must be discontinued from Study Intervention in the following situations"	Czech Health Authority requirement - with regard to patient safety	Substantial
7.1 Discontinuation of Study Intervention	Addition "by investigator" in the line: "Study intervention unblinding by investigator".	To clarify that in the scenario specified study intervention discontinuation is a must.	Substantial
Appendix J3 Home or Remote Location Visit to replace On-site Visit	Delete information about administration of study intervention at participant's home	Czech health Authority requirement - This study intervention is unregistered biological product with a potential risk of reaction in injection site and allergic reaction.	Substantial
Appendix J5 At-Home or remote Location Study Intervention Administration Instructions	All section of Appendix J5 removed.	Czech Health Authority requirement - This study intervention is unregistered biological product and home administration will not be permitted in the Czech Republic.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Appendix J6 OCS Reduction and Data Capture During Telemedicine	Renamed to Appendix J5	Deletion of previous Appendix section J5	Non-substantial

11 REFERENCES

Alving et al 2017

Alving K, Anolik R, Crater G, LaForce C F, Rickard K. Validation of a New Portable Exhaled Nitric Oxide Analyzer, NIOX VERO®: Randomised Studies in Asthma. *Pulm Ther*. 2017e;3(1):207-18.

Bel et al 2014

Bel EH, Wenzel S, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *N Engl J Med*. 2014;371:1189-1197.

CINQAIR US PI 2020

CINQAIR (reslizumab). Prescribing information. Teva Respiratory LLC, West Chester, PA, USA; Revised February 2020. Available at: <https://www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf>. Accessed 28 Sep 2021.

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 Sep 7;377(10):936-46. doi: 10.1056/NEJMoa1704064. PMID: 28877011.

Dalal et al 2016

Dalal AA, Sheng M, Gozalo L, Robitaille M, Albers F, Yancey S, et al. Dose-Response Relationship between Long-Term Systemic Corticosteroid Use and Related Complications in Patients with Severe Asthma. *J Manag. Care Spec Pharm*. 2016;22:833-47.

de Oliveira et al 2011

de Oliveira C, de Mattos ABM, Biz C, Oyama LM, Ribeiro EB, do Nascimento CMO. High-fat diet and glucocorticoid treatment cause hyperglycemia associated with adiponectin receptor alterations. *Lipids Health Dis*. 2011;10:11.

DUPIXENT US 2017

DUPIXENT (dupilumab). Prescribing information. Sanofi-Aventis US LLC, Bridgewater, NJ, USA and Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA; Revised December 2021. Available at: https://www.regeneron.com/downloads/dupixent_fpi.pdf. Accessed 28 Sep 2021.

FASENRA US 2017

FASENRA (benralizumab). Prescribing information. AstraZeneca AB Södertälje, Sweden; Revised February 2021. Available at: <https://www.azpicentral.com/pi.html?product=fasenra>. Accessed 28 Sep 2021

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 et al 2014

Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et. al. Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses. *N Engl J Med*. 2014; 370:2102-10.

GINA 2022

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Updated 2022. Available from: <https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf>.

Globe et al 2015

Globe G, Martin M, Schatz M, Wiklund I, Lin J, von Maltzahn R, et al. Symptoms and markers of symptom severity in asthma—content validity of the asthma symptom diary. *Health Qual Life Outcomes*. 2015;13-21.

Gounarides et al 2008

Gounarides JS, Korach-André M, Killary K, Argentieri G, Turner O, Laurent D. Effect of dexamethasone on glucose tolerance and fat metabolism in a diet-induced obesity mouse model. *Endocrinology*. 2008;149(2):758–66.

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. doi:10.1164/rccm.201908-1590ST.

Johansson et al 2004

Johansson SGO, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004; 113(5): 832-6.

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 et al 2009

Jones PW, Harding G, Berry P, Wiklund I, Chen W-H, Leidy NK. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009, 34: 648–654.

Juniper et al 2006

Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100: 616-21.

Kaur and Brightling 2012

Kaur D, Brightling C. OX40/OX40 ligand interactions in T-cell regulation and asthma. *Chest*. 2012;141: 494-9.

Kemp et al 2008

Kemp SF, Lockey RF, Simons FER; 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.

Kroger et al 2011

Kroger AT, Sumay CV, Pickering LK, Atkinson WL, Baker C, Chilton L; National Center for immunization and Respiratory Diseases. General recommendations on immunization: Recommendations of the Advisory Committee on Immunizations Practices (ACIP). *MMWR*. 2011;60(2):1-64.

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;126(3):477-80.e1-42.

Menzies-Gow et al 2021

Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *N Engl J Med*. 2021;384(19):1800-1809.

Nair et al 2017

Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al; ZONDA Trial Investigators. Oral Corticosteroid-Sparing Effect of Benralizumab in Severe Asthma. *N Engl J Med*. 2017 Jun 22;376(25):2448-58. doi: 10.1056/NEJMoa1703501. PMID: 28530840. Epub 2017 May 22.

NUCALA US PI 2019

NUCALA (mepolizumab). US Prescribing information. GlaxoSmithKline, Research Triangle Park, NC, USA; Revised September 2020. Available at: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed 28 Sep 2021.

Rabe et al 2018

Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma *N Engl J Med*. 2018;378:2475-85.

Quanjer et al 2012

Quanjer PH, Stanojevic S, Cole TJ, Baur X, L Hall GL, Culver B, et al; ERS Global Lung Function Initiative. Multi ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-43. doi: 10.1183/09031936.00080312.

Sambrook et al 1990

Sambrook P, Birmingham J, Kempler S, Kelly P, Eberl S, Pocock N, et al. Corticosteroid effects on proximal femur bone loss. *J Bone Miner Res*. 1990;5(12):1211-16.

Simpson et al 2006

Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology*. 2006;11(1):54-61.

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.

Tanaka et al 2009

Tanaka J, Watanabe N, Kido M, Saga K, Akamatsu T, Nishio A, et al. Human TSLP and TLR3 ligands promote differentiation of Th17 cells with a central memory phenotype under Th2-polarizing conditions. *Clin Exp Allergy*. 2009 Jan;39(1):89-100.

Tedeschi et al 2017

Tedeschi SK, Johnson SR, Boumpas D, Daikh D, Dörner T, Jayne D, et al. Developing and Refining New Candidate Criteria for SLE Classification: An International Collaboration. *Arthritis Care Res (Hoboken)*. 2018 Apr;70(4):571-81. doi: 10.1002/acr.23317. Epub ahead of print 2018 Feb 22.

Watson and Gauvreau, 2014

Watson B, Gauvreau GM. Thymic stromal lymphopoietin: a central regulator of allergic asthma. *Expert Opin Ther Targets*. 2014;18:771-85.

Wechsler et al 2020

Wechsler ME, Colice G, Griffiths JM, Almqvist G, Skärby T, Piechowiak T, et al. SOURCE: a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma *Respir Res*. 2020;21:264.

Wechsler et al 2022

Wechsler ME, Menzies-Gow A, Brightling C E et al. SOURCE: a randomised, placebo-controlled, phase 3 study to evaluate the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma. *Lancet Respir Med* Forthcoming 2022.

Wenzel 2012

Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18:716-25.

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 2019

XOLAIR (omalizumab). Prescribing information. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; revised July 2021. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed 28 Sep 2021.

Ziegler et al 2013

Ziegler SF, Roan F, Bell BD, Stoklasek TA, Kitajima M, Han H. The biology of thymic stromal lymphopoietin (TSLP). *Adv Pharmacol.* 2013;66:129-55.