Clinical Study Protocol	
Study Intervention	Tezepelumab
Study Code	D5242C00001
Version	6.0
Date	17 Jan 2024
EudraCT/EU CT Number	2020-003062-39

A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Tezepelumab in Participants with Severe Chronic Rhinosinusitis with Nasal Polyposis (WAYPOINT)

Sponsor Name: AstraZeneca AB, 151 85 Södertalje, Sweden

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Regulatory Agency Identifier Number(s)

IND number: 146838
EudraCT number: 2020-003062-39
ClinicalTrials.gov Number: NCT04851964

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.

Protocol Number: Version 6.0 17-Jan-2024
Study Intervention: Tezepelumab
Study Phase: 3

Short Title: Efficacy and safety of tezepelumab in participants with Severe Chronic Rhinosinusitis with Nasal Polyposis

Acronym: WAYPOINT

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment v6.0	17-Jan-2024
Amendment v5.0	17-Oct-2022
Amendment v4.0	28-Jan-2022
Amendment v3.0	26-May-2021
Amendment v2.0	06-Apr-2021
Original Protocol v1.0	14-Sep-2020

Amendment v6.0 17-Jan-2024

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 and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

- Two key secondary objectives ‘resolution/near complete resolution of nasal polyps’, and ‘resolution/near complete resolution of nasal polyps and NPSD TSS responses’ were moved to exploratory objectives.
- Estimand for US FDA and multiplicity testing procedure for secondary endpoints were modified to align with FDA guidance.
- Mandatory modifications resulting from the release of the AstraZeneca CSP template v9.0 were implemented.
- Editorial changes were made to enhance clarity and consistency of the CSP.

The Summary of Changes tables for previous amendments to this protocol are presented in Appendix J.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title page	Updated version number, version date and removed Study Clinical Lead information	Administrative changes	Non-substantial
Section 1.1 Synopsis: Section 3 Objectives and Endpoints Section 9.1 Statistical hypotheses Section 9.4.2.2 Secondary Endpoint(s) Section 9.4.4 Other Analyses	Key secondary objective 'resolution/near complete resolution of nasal polyps (defined as maximum NPS of 1 in each nostril)' moved to exploratory objectives. Statistical analyses revised accordingly	The definition of resolution/near complete resolution of polyps is not well-defined and not agreed with health authorities	Substantial
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 9.1 Statistical hypotheses Section 9.4.2.2 Secondary endpoint(s) Section 9.4.4 Other Analyses	Key secondary objective 'resolution/near complete resolution of nasal polyps (defined as maximum NPS of 1 in each nostril) and NPSD TSS response' moved to exploratory objective. Statistical analyses revised accordingly	The definition of resolution/near complete resolution of polyps is not well-defined and not agreed with health authorities	Substantial
Section 8.3.8 Reporting of Serious Adverse Events	Additional wording added from AstraZeneca CSP template v9.0 regarding the procedure for SAE reporting when EDC is not available	Alignment with AstraZeneca CSP template v9.0. Mandatory updates according to CSP Release Notification	Non-substantial
Section 8.4.1 Reporting of Overdose Section 8.4.2 Medication Error, Drug Abuse and Drug Misuse Appendix B 4 Medication Error, Drug Abuse, and Drug Misuse	Added detailed Drug Abuse and Drug Misuse definition and examples	To align with AstraZeneca CSP template v9.0	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.1 Statistical Hypotheses: Testing strategy for confirmatory endpoints.	Text added for US FDA Primary Estimand 'For the US FDA, the described testing procedure will be applied to the US FDA primary estimand described in Section 9.4.1.2'	To align with FDA guidance and expectations	Non-substantial
Section 9.1 Statistical Hypotheses: Figure 4	Updated Holm procedure in MTP to truncated Holm. Text and Figure 4 updated accordingly	To align with FDA guidance and expectations	Non-substantial
Section 9.4.1 General Considerations	Addition of Biologic use for NP, steroids or biologic use for co-morbid conditions, and COVID-19 related events to handling of intercurrent events bulleted list	To provide additional details on intercurrent events and strategies for handling them	Non-substantial
Section 9.4.1 General Considerations	Addition of Section 9.4.1.2: US FDA Primary Estimand and corresponding text	To align with FDA guidance and expectations	Non-substantial
Section 9.4.2.1 Primary Endpoint(s)	Updates to supplementary and sensitivity analyses	To align with Health Authorities guidelines and expectations	Non-substantial
Section 9.4.2.1 Primary Endpoint	Term "seasonal" removed from the subgroup "seasonal allergic rhinitis"	To clarify that the subgroup will not be restricted to seasonal allergic rhinitis	Non-substantial
Section 9.4.2.2 Secondary Endpoint	Update to text for the analysis of change from baseline in FEV1 at Week 52 to include the use of a treatment policy for all intercurrent events described in Section 9.4.1.1	To clarify the analysis for FEV1	Non-substantial
Section 9.4.4 Other Analyses	Update to add selected exploratory endpoint analysis	To clarify that some of the exploratory analysis will be described in the exploratory SAP	Non-substantial
Appendix A 4 Data Protection	Sub-section and corresponding text on 'Personal Data Breaches' added	Alignment with AstraZeneca CSP template v9.0, mandatory update according to CSP release notification	Non-substantial.
Appendix A 6 Dissemination of Clinical Study Data	Corrected URL for the website containing the description of AstraZeneca clinical studies.	To update the URL as the previous URL was incorrect.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix A 7 Data Quality Assurance	Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations	Update required to comply with global company requirement	Non-substantial
Spelling, grammar, and formatting corrections have been made throughout the document.			

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Tezepelumab in Participants with Severe Chronic Rhinosinusitis with Nasal Polyposis (WAYPOINT)

Short Title: Efficacy and safety of tezepelumab in participants with Severe Chronic Rhinosinusitis with Nasal Polyposis

Registry	ID
IND Number	146838
EudraCT Number	2020-003062-39
ClinicalTrials.gov Number	NCT04851964

Rationale:

The aim of the present study is to investigate the efficacy and safety of tezepelumab in participants with severe chronic rhinosinusitis with nasal polyps (CRSwNP), with or without co-morbid asthma/aspirin-exacerbated respiratory disease (AERD)/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD), whose severity is consistent with a need for surgery (total nasal polyps score (NPS) ≥ 5 (at least 2 for each nostril) despite documented treatment with systemic corticosteroid (SCS) or prior surgery for NP. The effect of tezepelumab 210 mg every 4 weeks (Q4W) on nasal polyps will be assessed on top of standard of care therapy with intranasal corticosteroids (INCS) over a 52-week treatment period and up to 24-week post-treatment follow-up period.

Objectives and Endpoints:

Primary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• Nasal polyp score (NPS)	• Co-Primary: Change from baseline in total NPS evaluated by nasal endoscopy at Week 52.
• Participant reported Nasal Congestion (NC)	• Co-Primary: Change from baseline in bi-weekly mean Nasal Congestion Score (NCS) evaluated as part of the Nasal Polyposis Symptom Diary (NPSD) at Week 52.

Key Secondary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• Loss of smell	• Change from baseline in bi-weekly mean loss of smell evaluated as part of the NPSD at Week 52.
• Nasal polyp-quality of life compared with placebo	• Change from baseline in SNOT-22 scores at Week 52.
• NP surgery and/or receiving SCS for NP	• Time to surgery decision and/or SCS for NP up to Week 52. • Time to NP surgery decision up to Week 52. • Time to SCS for NP up to Week 52.
• Sinus opacification	• Change from baseline in Lund-Mackay score (LMK) evaluated by CT at Week 52.
• NPSD total symptom score (TSS)	• Change from baseline in bi-weekly mean NPSD TSS at Week 52.
• Lung function in participants with co-morbid asthma and aspirin exacerbated respiratory disease (AERD)/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD)	• Change from baseline in pre-BD FEV1 at Week 52.
Other Secondary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• NPS	• Change from baseline over time in total NPS evaluated by nasal endoscopy through Week 52. • Proportion of participants with (i) ≥ 1 -point reduction and (ii) ≥ 2 points reduction in NPS at Week 52.
• Participant reported NC	• Change from baseline over time in bi-weekly mean NCS evaluated as part of the NPSD through Week 52.
• Loss of smell	• Change from baseline in loss of smell evaluated by UPSIT test at Week 52.
• Sinus opacification	• Change from baseline in modified LMK score evaluated by CT at Week 52. • Sinus severity score by quantitative CT assessment at Week 52.
• Systemic corticosteroid use	• Exposure of SCS over 52 Weeks.

• NPSD	• Change from baseline by domain of NPSD through Week 52.
• Nasal peak inspiratory flow (NPIF)	• Change from baseline in NPIF through Week 52.
• Asthma control in participants with co-morbid asthma and AERD/NSAID-ERD	• Change from baseline in ACQ-6 at Week 52.
• To evaluate the PK and immunogenicity of tezepelumab	• PK: Serum Concentration. • Immunogenicity: Anti-drug antibody (ADA).
Safety Objectives:	**Endpoint/variables:**
To evaluate the safety and tolerability of tezepelumab	• Adverse events (AEs)/serious adverse events (SAEs). • Clinical chemistry/haematology/urinalysis. • Vital signs. • Electrocardiograms (ECG).

For Tertiary/Exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol.

Overall Design

This is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, study designed to evaluate the efficacy and safety of tezepelumab 210 mg Q4W administered subcutaneously (SC) using the accessorised pre-filled syringe (APFS) versus placebo in participants with CRSwNP. Approximately, 400 participants will be randomised globally 1:1 to receive tezepelumab 210 mg or matching placebo.

Participants will be stratified by region, prior nasal polyp surgery and co-morbid asthma/AERD/NSAID-ERD. Randomisation will be monitored to ensure that 50%-70% of the study population will have co-morbid asthma/AERD/NSAID-ERD, and at least 50% will have had prior surgery for CRSwNP. When the target percentage of participants in a stratum in a region is reached, consideration will be given to closing the Integrated Web Response System (IWRS) randomisation for that subgroup, which may be done either overall or within a specific region. Once a subgroup is closed, participants in the screening/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed.

After enrolment, eligible participants will receive a standardised dose of Intranasal Mometasone Furoate Nasal Spray (MFNS) or equivalent INCS and will enter a 5-week screening/run-in period. Equivalent dose should refer to the highest approved country INCS dose for CRSwNP. Participants who meet eligibility criteria will be randomised at Week 0 (Day 0) to receive either placebo or tezepelumab 210 mg SC starting at randomisation (Week 0) and then every 4 weeks thereafter. An end of treatment (EOT) visit will be conducted at Week 52.

There will be two different follow-up periods after the 52-week treatment period. Approximately, the first 200 participants randomised will have a 24-week follow-up (FU) period without any IMP. The remaining participants will have a 12-week FU period without any IMP.

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

Number of Participants:

Approximately 890 participants are estimated to be screened/enrolled to achieve approximately 400 randomly assigned participants to study intervention.

Note: "Enrolled" means that a participant's, or their legally acceptable representative has agreed to participate in the 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 in the study are considered “screen failures” unless otherwise specified by the protocol.

Intervention Groups and Duration:

Tezepelumab 210 mg will be administered SC at randomisation (Week 0) and then every 4 weeks (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48) with an EOT at Week 52. Matching placebo will be administered SC at the same time points. In total participants may receive up to 13 doses of the investigational product. Approximately the first 200 randomised participants will be followed up for a period of 24 weeks post EOT and the remaining randomised participants will be followed up for a period of 12 weeks after EOT visit.

All participants will have their current INCS therapy standardised to Mometasone furoate (MFNS) with a total daily dose of 400 µg or equivalent dose of INCS at Visit 1 and throughout the screening and study period. Equivalent dose should refer to the highest approved country INCS dose for CRSwNP.

Independent Adjudication Committee:

An independent adjudication committee will be established to provide an external independent assessment of blinded data to confirm the diagnosis and causality of major adverse cardiac events (MACE; to be 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; please refer to Section 8.3.9.

Statistical Methods

The co-primary analysis will compare the effect of tezepelumab versus placebo in the change from baseline in NPS at Week 52 and the change from baseline in the bi-weekly mean NCS at

Week 52.

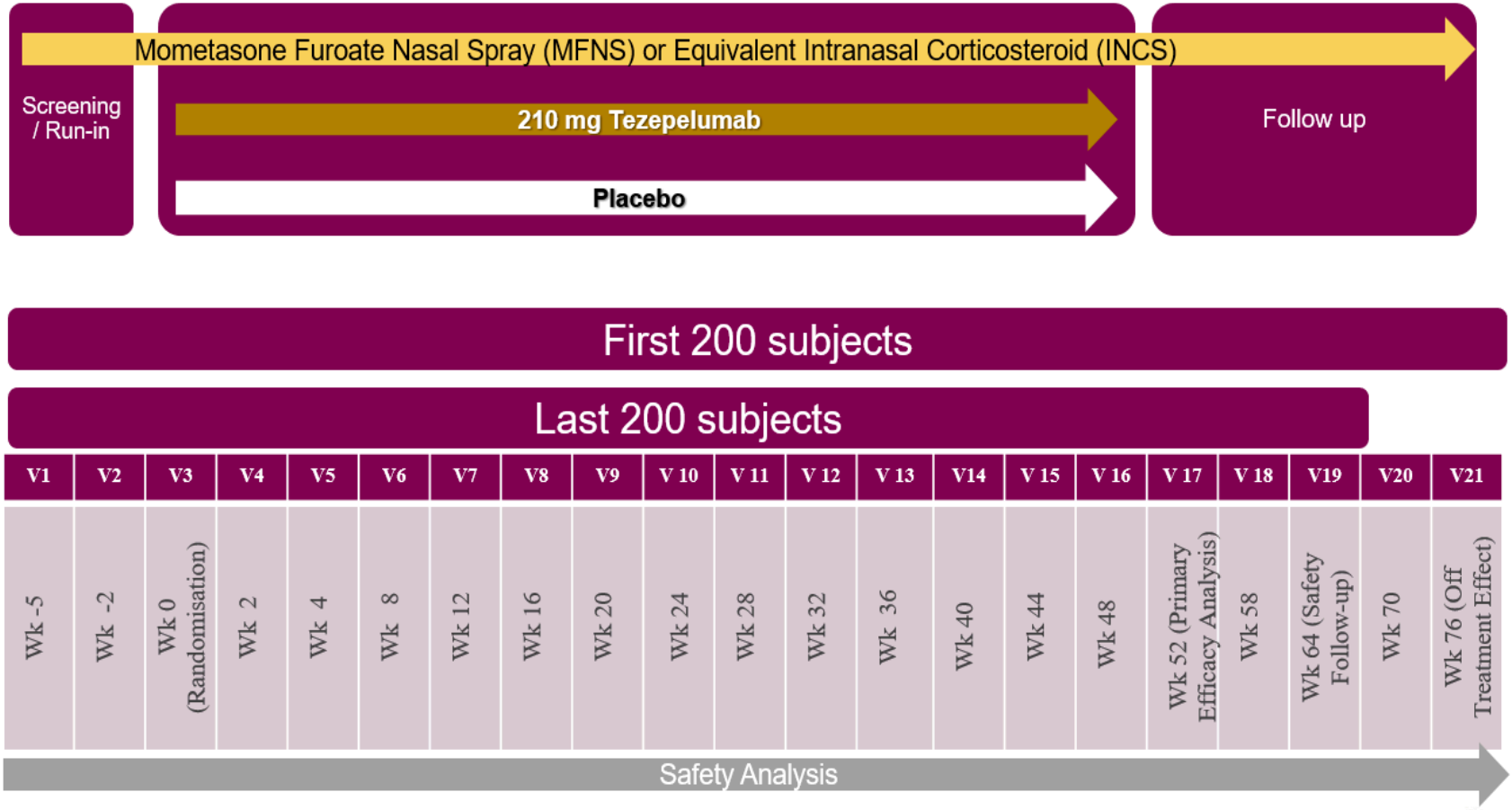
Assuming a population standard deviation (SD) of 2.25 in total NPS change from baseline and 1.22 in NCS change from baseline, the sample size of 200 participants per arm will provide at least 95% total power to detect a statistically significant difference at a 2-sided 1% level on both co-primary endpoints if the true effect of tezepelumab is -1.8 in total NPS change from baseline and -0.87 in NCS change from baseline. Two hundred participants per arm also provides at least 95% power to detect a statistically significant difference at a 2-sided 1% level in key secondary endpoints of change from baseline in loss of smell, LMK, SNOT-22, and time to SCS and/or surgery decision. In addition, this sample size provides at least 80% power to detect a difference (at a nominal 5% significance level) in the endpoint of time to surgery decision, assuming a true hazard ratio (HR) of 0.33 and a placebo rate at Week 52 of 11%.

Efficacy analyses will be based on the full analysis set (FAS) according to the randomised treatments. Both co-primary efficacy endpoints will be analysed using an analysis of covariance (ANCOVA) model. Difference in LS means and the corresponding 95% confidence intervals (CIs) will be provided along with the p-values. The participants who have SCS for NP and/or a decision to undergo surgery would be considered a poor outcome. Data collected for participants who did not have rescue therapy are used regardless of whether treatment discontinuation occurs.

Both primary endpoints will be tested at 2-sided 5% level. If both are significant at 5%, then testing will proceed to the key secondary endpoints. The type I error across primary and key secondary endpoints will be controlled at 5%. The co-primary and key secondary endpoints will also be tested at the 1% level.

1.2 Schema

Figure 1 Study Design



1.3 Schedule of Activities

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
General Procedures																							
Informed consent	X																						Section 5.1, Appendix A 3
Inclusion and exclusion criteria	X	X	X																				Section 5.1, 5.2
Demography	X																						Section 5.1
Medical/ surgical history, including respiratory and nasal polyp history	X																						Section 5.1

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Healthcare Resource Utilisation (HRU) Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.8
COVID-19/SARS-CoV-2 Assessments[f]																							
COVID-19 Entry Screening Questionnaire	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	Section 8.2.4.1
SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test)	X																						Section 8.2.4.2
SARS-CoV-2 serology test			X																				Section 8.2.4.2
Safety Assessments																							
Past and current medical conditions	X																						Section 5.1

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Complete physical examination	X																X						Section 8.2.1
Brief physical exam			X				X			X			X						X		X	X	Section 8.2.1
Weight	X		X				X			X			X				X		X		X	X	Section 8.2.5.1
Height	X																						Section 8.2.5.1
ECG	X																X		X		X	X	Section 8.2.3
Vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	Section 8.2.2
Adverse Events (AE)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.4
Efficacy and Participant Reported Outcome Assessments																							
Distribute ePRO device	X																						Section 8.1.2

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
ePRO device training	X	X																					Section 8.1.2
NPSSA	X																						Section 8.1.2.1
NPSD		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.2.1
SNOT-22	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Section 8.1.2.2
SF-36v2 (standard recall)		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X						Section 8.1.2.4
EQ-5D-5L		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X						Section 8.1.2.3
PGI-S			X		X	X	X	X	X	X	X	X	X	X	X	X	X						Section 8.1.2.7
PGI-C					X	X	X	X	X	X	X	X	X	X	X	X	X						Section 8.1.2.7
WPAI			X							X							X						Section 8.1.2.8
UPSIT Smell Test[g]			X		X		X			X			X				X		X		X		Section 8.1.2.6

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Nasal peak inspiratory flow (NPIF)	X		X				X			X			X				X		X		X		Section 8.1.7
Asthma/AERD/NSAID-ERD Participants Only																							
Spirometry (FEV1, FEF 25-75% and FVC)			X							X							X		X		X		Section 8.1.5
FeNO[h]			X							X							X		X		X		Section 8.1.6
ACQ-6			X							X							X		X		X		Section 8.1.2.5
Nasal Polyposis Assessment																							
Nasal endoscopy/ NPS		X			X		X			X			X				X		X		X		Section 8.1.1
CT Scan[i,t]		X															X						Section 8.1.3
Assess decision for nasal surgery and/or SCS use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[u]	X	X	X	X	X	Section 8.1.4

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Laboratory Assessments																							
Clinical Chemistry	X		X		X		X			X			X				X		X		X		Section 8.2.4
Haematology[j]	X		X		X		X			X			X				X		X		X		Section 8.2.4
Urinalysis	X		X				X			X			X				X		X		X		Section 8.2.4
Urine dipstick pregnancy test (WOCBP only)			X		X	X	X	X	X	X	X	X	X	X	X	X							Section 8.2.4.3
Serum pregnancy test (WOCBP only)	X																X		X		X		Section 8.2.4.3
FSH[k]	X																						Section 8.2.4.3
Serology (HepB, HepC, HIV1, HIV2)	X																						Section 8.2.4.4
Exploratory Assessments																							
Tezepelumab PK[l]			X		X		X			X			X				X		X				Section 8.5.1

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Tezepelumab ADA/nAb[m]			X		X		X			X			X				X		X				Section 8.5.2
Total IgE			X							X							X		X				Section 8.6.1
IgE FEIA			X																				Section 8.6.1
Blood for serum and plasma biomarkers			X				X			X			X				X		X				Section 8.6.1
Blood for RNA transcriptomic profiling			X				X			X			X				X		X				Section 8.6.1
Nasal epithelial lining fluid for PK and Exploratory biomarkers		X[o]	X				X			X							X[n]		X				Section 8.6.1
Staph A Nasal Culture			X							X							X						Section 8.6.1

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
Staph A enterotoxin Specific IgE status **(only participants in the sub-study)**[o]			X														X						Section 8.6.1
Nasal biopsy - tissue for histology and RNA transcriptomics **(only participants in the sub-study)**[o]		X[p]															X						Section 8.6.1
Genomics Initiative optional, exploratory genetic sample[q]			X																				Section 8.7; Appendix D
Randomisation, Investigational Product Administration and INCS Management																							
Randomisation			X																				Section 4.1

Table 1 Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up

Assessment / Activity	Screening	Run-in	Randomisation	Treatment Period													EOT/ IPD	FU all[d]		Additional FU 1st 200 participants[c]		UNS[e]	Details in CSP section or Appendix
Visit	**V1**	**V2**	**V3**	**V4** ☎ [b]	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18** ☎ [b]	**V19**	**V20** ☎ [b]	**V21**		
Week	**-5**	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**58**	**64**	**70**	**76**		
Visit window (days)[a]	**N/A**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±7**	**±7**	**±7**	**±7**	**N/A**	**N/A**
IP Administration[r]			X		X	X	X	X	X	X	X	X	X	X	X	X							Section 6.1
Home IP Administration by HCP (optional)[s]								X	X		X	X		X	X	X							Section 6.2.3
INCS Distribution[v]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	Section 6.4.1

[a] All visits to be scheduled from the date of randomisation, not from the date of previous visit.

[b] Visits 4, 18 and 20 is a phone/remote visit (').

[c] Approximately, the first 200 participants randomised will have a 24-week follow-up period post EOT: V18 (Week 58), V19 (Week 64), V20 (Week 70) and V21 (Week 76). If for any reason a participant in the first set of randomised participants as described, is not willing to participant for a full 24-week FU period and would like to terminate participation in the study, the follow-up discontinuation (FUD) visit should be performed at V19 (Week 64).

[d] The remaining, approximately 200 participants randomised will have a 12 -week Follow-up period post EOT: V18 (Week 58) and V19 (Week 64).

[e] Unscheduled visits may be initiated as needed, and additional assessments may be performed at these visits as indicated.

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

[g] UPSIT smell test will be performed in all countries participating in the study except in countries in which an UPSIT version is unavailable in the applicable native language.

[h] The subjects, sites and sponsor will be unblinded to the FENO values prior to randomisation and blinded to the FeNO values post randomisation.

[i] Referral for CT scan should be provided at V2 (Week -2) and must be performed after nasal biopsy procedure (if applicable) at V2 only if the participant has met all eligibility criteria at V2. CT should be performed between V2 and V3 after the participant meets the inclusion/exclusion criteria and receive a confirmation from central readers that the inclusion criteria of NPS score is met.

[j] The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (V1 and V2), any repeat testing that is performed during the screening period prior to Investigational Product (IP) administration at V3.

[k] FSH test done only for female participants to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for > 12 month.

[l] At dosing visits, PK samples must be collected pre-dose.

[m] Neutralising antibody (nAb) testing will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

[n] For IPD, participants should only have nasal epithelial lining fluid collected if the time between randomisation and IPD Visit is ?24 weeks.

[o] The nasal biopsy sub-study will be performed at selected sites (Approximately total of 60 participants). Collection of nasal lining fluid at V2 is applicable to participants of the nasal biopsy sub-study only and should be performed before nasal biopsy to avoid potential blood contamination. If nasal biopsy cannot be collected at V2, then the participant should be withdrawn from nasal biopsy sub-study and can continue on the main study. In this event, NLF collection at Visit 2 and Staph A enterotoxin-specific IgE sample collection at Visit 3 should not be performed as well. Please note that CT scans are done after nasal biopsy at baseline, while at EOT/IPD, the CT scan will be done before nasal biopsy. Moreover, Collection of NLF at V3, V7, V10, V17/EOT/IPD, and V19 is required for all study participants,.

[p] The PI has the ability to postpone endoscopy within 3 days of V2 if nasal biopsy results in bleeding, making NPS assessment difficult.

[q] Samples can be collected at any time from V3 (Week 0) after genetic consent form is obtained.

[r] IP administration should be the last activity of the visit. All visit procedures should be done prior to dosing.

[s] Optional home dosing by HCP: The participant must complete at least 3 IP administration visits on-site dosing before IP administration at home by HCP is possible.

[t] The procedures for the EOT/IPD visit should be followed and a CT scan should be done prior to the first post-randomisation NP surgery. If SCS is used for treatment of NP, a CT scan should be performed before starting the first course of SCS, if possible, and at the EOT visit. Note, the CT scan should only be performed prior to the first initiation of NP surgery or first course of SCS for NP. If IP discontinuation occurs for other reasons, a CT scan should be performed at the IPD visit and at Week 52, if the participant opts for follow-up option 1 or 2 per section 7.1.1 of the CSP. For IPD (for any reason), only do CT if at least 12 weeks since the V2 CT scan.

[u] For participants who undergo or are planned for surgery for NP during the treatment period, the Investigator may decide to continue IP up to the time of surgery or the EOT/IPD visit; whichever date comes first. A nasal endoscopy assessment of NPS and PROs should be available for analysis prior to the NP surgery. If no such assessment is available, a visit should be scheduled to obtain those assessments. At the time of surgery, participants will be permanently discontinued from IP and assessed as soon as possible per the EOT/IPD visit described in the SoA. If SCS is used for treatment of NP, PROs, and a nasal endoscopy assessment of NPS should be performed before starting treatment with SCS. If no such assessment is available, a visit should be scheduled to obtain those assessments.

[v] Refer to the study Pharmacy Manual for detailed instructions regarding dispensation and accountability procedures.

Order of Assessments

- At Visit 1, the suggested order of assessments should be followed as: ePRO, Vital Signs, ECG, Blood Draws, and the SARS-CoV-2 nasopharyngeal swab test or COVID-19 rapid test. At Visit 2, the suggested order of assessments should be: ePRO, Vital Signs, Nasal epithelial lining fluid collection, Nasal biopsy (if applicable), Nasal endoscopy, and CT scan (referral at Visit 2).
- At Visit 3, the suggested order of assessments should be followed: ePRO, UPSIT, Vital Signs, FeNO (asthma/AERD/NSAID-ERD participants), Spirometry (asthma/AERD/NSAID-ERD participants), NPIF, Blood Draws including SARS-CoV-2 serology test, Staph A nasal culture, Nasal epithelial lining fluid collection, IP administration.
- Based on investigator's judgement and site resources, EOT assessments (V17) will be performed over more than one day, within a 5-day window. At EOT/IPD visit, the suggested order of assessments should be followed: CT scan, ePRO, UPSIT, Vital Signs, ECG, FeNO (asthma/AERD/NSAID-ERD participants), Spirometry (asthma/AERD/NSAID-ERD participants), NPIF, Blood Draws, Staph A nasal culture, Nasal epithelial lining fluid collection, Nasal endoscopy, Nasal biopsy (if applicable). **Note:** At EOT/IPD, for participants in the nasal biopsy sub-study, the CT scan should be completed before the nasal biopsy procedure.

ACQ-6 - Asthma Control Questionnaire-6; ADA - Anti-drug antibodies; ClinRO - Clinician-reported outcome; COVID-19 – Coronavirus Disease 2019; CT- Computed tomography; EOT - End of treatment; FU - Follow-up; FUD - Follow-up discontinuation; HCP – Health Care Professional; HRU - Healthcare resource utilisation; IgE - Immunoglobulin E; INCS - Intranasal corticosteroids; IPD - Investigational product discontinuation; nAb - Neutralising antibody; NP - Nasal polyposis; PK - Pharmacokinetics; PRO - Participant reported outcome; SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2; SCS - Systemic corticosteroids; SF-36v2- Short-Form 36-item Health Survey, Version 2; SNOT-22 - SinoNasal Outcome Test, 22 item; UNS - Unscheduled; UPSIT - University of Pennsylvania Smell Identification Test; WOCBP – Women of Child Bearing Potential

2 INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is strongly linked with asthma by epidemiological, pathophysiological, and clinical evidence, supporting an "united airway" concept to chronic inflammatory diseases of the upper and lower airways. Both diseases are co-morbid conditions (Håkansson K et al 2015). Compared to non-asthmatic patients, asthmatic patients have a higher prevalence of chronic rhinosinusitis (CRS) and CRSwNP and greater severity of rhinosinusitis (Jarvis D et al 2012, Seybt MW et al 2007, Pearlman AN et al 2009, Tint D et al 2016, Settipane GA and Chafee FH 1977). Furthermore, asthmatic subjects with CRSwNP may have more poorly controlled asthma, increased airway obstruction, and greater lower airway inflammation than those without CRSwNP (Bilodeau L et al 2010). Co-existing asthma in CRSwNP patients is associated with lower quality of life (Alobid I et al 2005, Ehnhage A et al 2009). Mechanistically, both nasal polyps (NP) and severe eosinophilic asthma are considered Type-2 (T2) driven diseases and the inflammatory profile is similar between the upper airway in NP and the lower airway in asthma (Fokkens et al 2020, Chaaban MR et al 2013). Like asthma, the role of eosinophils is considered important to the pathology of NP in a high proportion of patients.

Nasal polyposis represents an area of significant unmet medical need, especially for a subset of patients with NP who have exhausted current treatment options, which include medical interventions (intranasal corticosteroids (INCS), systemic corticosteroids (SCS), and antibiotics) and surgical interventions. Patients and healthcare professionals both point to a greater need for new therapies that reduce the need for repeated courses of SCS or surgery for all patients with NP. Surgery to remove polyps remains a consideration in patients whose symptoms are not controlled with corticosteroids, but rates of recurrence are high (approximately 40%, 12 months after surgery) and repeated surgical interventions are often needed. Although INCS are continued after surgery, a proportion of patients will nevertheless experience post-surgical recurrence despite treatment with currently available therapies, and these participants carry an even higher risk of recurrence if they undergo further surgery (Fokkens et al 2020, Orlandi RR et al 2013, Agarwal et al 2019, van der Veen et al 2017).

2.1 Study Rationale

Chronic rhinosinusitis with nasal polyps is a chronic heterogenous inflammatory condition of the nasal and paranasal mucosa (Fokkens et al 2020). The underlying pathogenesis of the disease is currently undefined but in recent years type 2 (T2) driven inflammation has been shown to be a dominant process in CRSwNP and therapeutics targeting T2 inflammation have demonstrated efficacy in CRSwNP (Gevaert et al 2011, Bachert et al 2016, Bachert et al 2017, Bachert et al 2019, Gevaert et al 2020). Thymic stromal lymphopoietin (TSLP) is an epithelial cytokine released in response to airborne environmental triggers. TSLP can drive T2 cytokine release from Th2 and ILC2 cells as well as have effects on other immune cells present in NP tissue. TSLP levels are elevated in nasal polyp tissue from patients with CRSwNP compared

with healthy sinus tissue or that from patients with CRS without NP (Kimura S et al 2011, Nagarkar DR et al 2013). TSLP may therefore play a role in the initiation and persistence of CRSwNP and blockade is predicted to be beneficial to patients.

Tezepelumab is a fully human immunoglobulin G (IgG) 2λ monoclonal antibody (mAb) directed against thymic stromal lymphopoietin (TSLP). It binds to human TSLP and prevents its interaction with heterodimeric TSLP receptor and is currently being evaluated for bronchial asthma, COPD, atopic dermatitis and severe CRSwNP.

Currently available biological treatment for NP is limited to an approximately 40% to 60% success rate (Gevaert et al 2011, Bachert et al 2016, Bachert et al 2017, Bachert et al 2019, Gevaert et al 2020). There are two possible explanations for the lack of complete response with biologics. First is that when polyps become large enough to be symptomatic, reduction of inflammatory cells and/or inflammation may limit and reduce new growth but may not be able to substantially reduce polyp size in the face of persistent tissue fibrosis (Stevens et al 2016). TSLP contribution to extracellular matrix (ECM) deposition may be indirect, as an initiator of the inflammatory processes driving fibrosis, or direct, since TSLP has been shown to have effects on or to be produced by lung fibroblasts (reviewed in Gauvreau et al 2020). Furthermore, in CRSwNP TSLP has been shown to indirectly stimulate fibroblasts via CST-1 (Kato et al 2019) inducing periostin; a matricellular signalling protein demonstrated to regulate ECM structure and organisation through its ability to bind ECM and promote collagen fibrillogenesis and crosslinking. This suggests that in addition to its anti-inflammatory MoA treatment with tezepelumab may potentially have an anti-fibrotic effect which could result in improvement of CRSwNP. The kinetics of ECM turnover is known to be slow therefore the 52-week treatment period proposed is required if sufficient time is to be given for changes in ECM to occur. Continued improvement in NPS score beyond Week 24 may be expected based on this potential anti-fibrotic MOA for tezepelumab.

Second, there is a subset of CRSwNP patients who do not have T2 mediated disease. Analysis of subgroups in the tezepelumab Phase 2b study and Phase 3 studies (PATHWAY and NAVIGATOR) in asthma patients showed that tezepelumab benefited participants with low and high baseline eosinophil counts and a low and high baseline T2 profile. These analyses suggest that tezepelumab, unlike other currently available biologics on the market used to treat severe asthma, is effective in patients with T2 high and T2 low airway inflammation and might be effective in T2 low as well as T2 high CRSwNP. It is assumed that tezepelumab reduces the AAER in asthma by acting as an airway anti-inflammatory. However, information directly supporting this assumption in CRSwNP is currently not available, and this study will investigate the role of tezepelumab as an anti-inflammatory in CRSwNP.

Asthma and CRSwNP share a similar pathophysiology and are common comorbidities. A post-hoc analysis of patients with co-morbid nasal polyps in the PATHWAY population

revealed that 15.2% of the subjects had co-morbid CRSwNP. Asthma patients with NP treated with tezepelumab demonstrated improvement in AERR, FEV1 and ACQ-6 and T2 inflammatory biomarkers relative to placebo to an equivalent extent as non-NP asthma patients. These finding support the rationale of a broad effect of tezepelumab in asthma and potential efficacy in CRSwNP. (Emson C et al 2020; Emson C et al 2020 ; Emson C et al 2021).

2.2 Background

Nasal polyposis is recognised to be a consequence of chronic inflammatory disease of the nasal mucosa. The presence of polyps can cause long-term symptoms such as prominent nasal obstruction, post-nasal drip and nasal discharge, loss of smell, and facial pain. These symptoms can greatly impact a patient's quality of life. Patients with CRSwNP have been observed to have worse symptoms (as evidenced by higher Sino-Nasal Outcome Test [SNOT]-22 scores), more severe disease by imaging (as demonstrated by Lund-Mackay and modified LMK score computed tomography [CT] scores), and require more frequent revision surgery than patients with CRSsNP (Hull and Chandra 2017; Fokkens et al 2020).

The aetiology of NP is still considered unclear, but allergy, asthma, infection and aspirin sensitivity (AERD) have all been associated with this complex refractory disease in adults (Hull and Chandra 2017). Both NP and asthma are T2-driven disease processes that are characterised by an eosinophilic infiltrate in affected tissue, either the polyps or the airways. The inflammatory profile observed in asthma shares many features and similarities with the inflammation seen in patients with NP where eosinophils are the primary effector cell in the pathophysiology of both upper airway sinusitis and lower airway asthma (Håkansson K et al 2015; Ediger et al 2005).

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

2.3 Benefit/Risk Assessment

Nasal polyposis represents an area of significant unmet medical need, especially for a subset of patients with NP who have exhausted current treatment options, which include medical interventions (INCS, SCS and antibiotics) and surgical interventions.

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

2.3.1 Risk Assessment

Table 2 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 by safety blood work 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; or if they have a history of a known immunodeficiency disorder; or 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; or who have evidence of active coronavirus disease 2019 (COVID-19) infection during the run-in period or optimisation phase; or 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 nonclinical or clinical studies. No causal relationship with tezepelumab could be established for cases reported.	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/serious adverse events, including malignancies that are considered AESI.

Table 2 Risk Assessment

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.

Table 2 Risk Assessment

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.	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		
Computed tomography (CT):	The use of CT involves ionising radiation that increases the risk of radiogenic tumours in participants	A dose constraint for the CT scan, based on the as low as reasonably achievable principle, is applied for this study.
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 5).

2.3.2 Benefit Assessment

Treatment with tezepelumab may significantly improve nasal congestion and reduce the size of nasal polyps, thus reducing the need for the use of systemic corticosteroids or the performance of additional surgical procedures.

2.3.3 Overall Benefit: Risk Conclusion

Use of tezepelumab has been demonstrated to show an important benefit in asthma in a phase 2b and phase 3 study. Because of the similar pathogenesis of CRSwNP and asthma, it is expected that tezepelumab will improve outcomes in CRSwNP. Tezepelumab has been well tolerated with an acceptable safety profile and no confirmed safety signals in subjects with

severe, uncontrolled asthma identified in the completed studies to date. No serious allergic reactions or anaphylactic reactions considered related to tezepelumab were reported in the Phase 3 programme. A numerical imbalance in serious cardiac events in the tezepelumab arm was observed in a single study in severe asthma, but none of the events were considered to be causally related to tezepelumab. Although TSLP suppression could theoretically have unanticipated immune-related side effects impairing host defense against certain infections and malignancies, there is no clear nonclinical or clinical evidence supporting such a role, and no safety signals related to either severe infections, parasitic infections or malignancy have been detected in the completed studies to date.

The benefit/risk assessment for tezepelumab in CRSwNP is considered favourable.

Risk minimisation measures for important potential risks will be in place during the conduct of this study, in conjunction with the performance of the AstraZeneca's routine pharmacovigilance activities.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Primary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• Nasal polyp score (NPS)	• Co-Primary: Change from baseline in total NPS evaluated by nasal endoscopy at Week 52.
• Participant reported Nasal Congestion (NC)	• Co-Primary: Change from baseline in bi-weekly mean Nasal Congestion Score (NCS) evaluated as part of the Nasal Polyposis Symptom Diary (NPSD) at Week 52.
Key Secondary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• Loss of smell	• Change from baseline in bi-weekly mean loss of smell evaluated as part of the NPSD at Week 52.
• Nasal polyp-quality of life compared with placebo	• Change from baseline in SNOT-22 scores at Week 52.
• NP surgery and/or receiving SCS for NP	• Time to surgery decision and/or SCS for NP up to Week 52. • Time to NP surgery decision up to Week 52. • Time to SCS for NP up to Week 52.

• Sinus opacification	• Change from baseline in Lund-Mackay score (LMK) evaluated by CT at Week 52.
• NPSD total symptom score (TSS)	• Change from baseline in bi-weekly mean NPSD TSS at Week 52.
• Lung function in participants with co-morbid asthma and aspirin exacerbated respiratory disease (AERD)/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD)	• Change from baseline in pre-BD FEV1 at Week 52.
Other Secondary Objectives:	**Endpoint/variables:**
To evaluate the effect of tezepelumab on:	
• NPS	• Change from baseline over time in NPS evaluated by nasal endoscopy through Week 52. • Proportion of participants with (i) ≥ 1-point reduction and (ii) ≥ 2 points reduction in NPS at Week 52.
• Participant reported NC	• Change from baseline over time in bi-weekly mean NCS evaluated by NPSD through Week 52.
• Loss of smell	• Change from baseline in loss of smell evaluated by UPSIT test at Week 52.
• Sinus opacification	• Change from baseline in modified LMK score evaluated by CT at Week 52. • Sinus severity score by Quantitative CT assessment at Week 52.
• Systemic corticosteroid use	• Exposure of SCS over 52 Weeks.
• NPSD	• Change from baseline by domain of NPSD through Week 52.
• Nasal peak inspiratory flow (NPIF)	• Change from baseline in NPIF through Week 52.
• Asthma control in participants with co-morbid asthma and AERD/NSAID-ERD	• Change from baseline in ACQ-6 at Week 52.
• To evaluate the PK and immunogenicity of tezepelumab	• PK: Serum Concentration. • Immunogenicity: Anti-drug antibody (ADA).
Safety Objectives:	**Endpoint/variables:**
To evaluate the safety and tolerability of tezepelumab	• Adverse events (AEs)/serious adverse events (SAEs)

	• Clinical chemistry/hematology/urinalysis • Vital signs • Electrocardiograms (ECG)
Exploratory	
To explore the off-treatment effect and the recurrence rate of nasal polyps after discontinuation of treatment with tezepelumab	• Change from baseline in NPS • Change from baseline in bi-weekly mean NCS • Participants requiring surgery and SCS for NP
To explore the effect of tezepelumab on exploratory biomarkers of inflammation and nasal polyposis disease and investigate biomarkers for predicting response to tezepelumab	Exploratory biomarker parameters: • Serum and plasma for protein biomarkers • Whole blood for transcriptomic profiling • Nasal epithelial lining fluid for protein biomarkers • Nasal polyp biopsies for inflammatory cells by histology and immunohistochemistry, and transcriptomic profiling.
To explore tezepelumab PK in nasal epithelial lining fluid	• Exploratory PK concentrations in nasal epithelial lining fluid.
Optional exploratory genomics sample	• A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study.
To evaluate the effect of tezepelumab on unplanned health care resource utilisation	• Hospitalisations, emergency room, unplanned out participant visits, and urgent care visits.
To evaluate the participant reported quality of life outcomes	• SF-36 v2 Health Survey • EQ-5D-5L • WPAI
Patient perception of overall symptom severity and change	• Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C)
To evaluate airway inflammation in participants with co-morbid asthma/AERD/NSAID-ERD	• Change from baseline in fractional exhaled nitric oxide (FeNO).
Resolution/near complete resolution of nasal polyps (defined as maximum NPS of 1 in each nostril)	• Proportion of participants who achieve a maximum NPS of 1 in each nostril at Week 52.

Resolution/near complete resolution of nasal polyps (defined as maximum NPS of 1 in each nostril) and NPSD TSS response.	• Proportion of participants who achieve a maximum NPS of 1 in each nostril and NPSD TSS response at Week 52.

4 STUDY DESIGN

4.1 Overall Design

For an overview of the study design see Section 1.2, Figure 1. For details on treatment given during the study, see Section 6.1.1.

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

This is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy and safety of repeat dosing of tezepelumab 210 mg SC versus placebo in participants with severe CRSwNP.

Approximately 400 participants will be randomised globally 1:1 to receive tezepelumab 210 mg or matching placebo.

Participants will be stratified by region, prior nasal polyp surgery and co-morbid asthma/ aspirin-exacerbated respiratory disease (AERD)/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). Randomisation will be monitored to ensure that 50%-70% of the study population will have co-morbid asthma/AERD/NSAID-ERD, and at least 50% will have had prior surgery for CRSwNP. When the target percentage of participants in a stratum in a region is reached, consideration will be given to closing the IWRS randomisation for that subgroup, which may be done either overall or within a specific region. Once a subgroup is closed, participants in the screening/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed.

After enrolment, eligible participants will enter a screening/run-in period and will have their current INCS therapy standardised to Mometasone furoate (MFNS) or equivalent INCS at Visit 1 and throughout the screening and study period. Two doses of MFNS (50µg/actuation) in each nostril twice daily (total 400µg daily) or equivalent INCS will be administered unless there is a medical rationale to use the lower dose (QD) regimen. Equivalent dose should refer to the highest approved country INCS dose for CRSwNP.

In countries that receive standardised MFNS centrally, each participant will receive enough background medication to cover the need until the next on-site visit. For equivalent INCS, this may be provided per local guidelines or pharmacy card provided by sponsor. Intranasal corticosteroids dispensation will be performed according to the SoA (Table 1).

Intranasal corticosteroid compliance will be recorded by the participant in the ePRO diary and

should be checked by investigators during the study period. If a participant cannot tolerate MFNS or equivalent INCS during screening period, the participant should be screen failed.

The Principal Investigator should ask participants about SCS (oral and/or, parenteral) use for NP at each visit and record in the eCRF. Participants who require SCS and/or hospitalisation for an asthma exacerbation (see Section 8.2.5.2) or nasal polyp exacerbation during the screening period, should be screen failed and may rescreen once their symptoms improve (see Section 5.4.1).

Participants who experience an asthma exacerbation or worsening of nasal polyposis symptoms during the screening/run-in period (before Visit 2), may extend their screening period to accommodate the time needed for a short course (5-7 days) of systemic corticosteroids (SCS) treatment and return to Visit 2 no sooner than 4 weeks after the last dose of oral corticosteroids. If asthma exacerbation or worsening of nasal polyposis symptoms that require SCS or hospitalisation occurred between Visit 2 and Visit 3 (randomisation), participants should be screened failed and may be rescreened once their conditions are stabilised.

Participants will be provided with an electronic patient reported outcome (ePRO) device to record symptoms throughout the study (see Section 8.1.2). Participants who continue to meet eligibility criteria will be randomised 1:1 at Visit 3 (Day 0) to receive either placebo or tezepelumab 210 mg SC at randomisation (Week 0) and every 4 weeks thereafter (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48). A total of 13 doses will be administered. An EOT Visit will be conducted at Week 52.

The first approximate 200 randomised participants will have a 24-week follow-up (FU) period without IP administration to assess durability of benefit. These participants will have the final safety assessment at Week 76. The remaining participants will be followed for 12 weeks after the end of treatment visit, with the final safety assessments at Week 64.

If for any reason a participant in the first set of randomised participants, as described above, is not willing to participate for a full 24-week FU period and would like to terminate participation in the study, the follow-up discontinuation (FUD) visit should be performed. The FUD visit should occur at V19 (Week 64).

At Week 0, the Health Care Professional (HCP) will administer the study drug. Optional home IP administration by HCP can take place only at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, and Week 48. The rest of the IP administration visits must occur at the study centre.

Participants will be evaluated for efficacy, safety, pharmacokinetics (PK), ADA, and sample collection of blood and nasal lining fluid for exploratory biomarkers will be performed

throughout the study. If at any point a participant meets IP discontinuation (IPD) criteria, an early IPD Visit will be performed (see Section 7.1).

At selected clinical sites, the participants may consent optionally to the nasal biopsy sub-study for up to approximately 60 participants. The target number will also be monitored closely throughout the study. A baseline nasal biopsy will be obtained prior to randomisation, at V2. The nasal biopsy at V2 must be performed prior to nasal endoscopy. Another biopsy of nasal polyp tissue will be obtained at EOT visit at V17 (Week 52) (see Section 8.6). The EOT nasal biopsy must be obtained after nasal endoscopy has been performed. Additionally, as part of the sub-study, nasal lining fluid will be collected at Visit 2 and a blood sample to assess Staph A enterotoxin-specific IgE status will be collected at Visit 3 and EOT/IPD.

CT scans will be performed for all participants. A baseline CT scan will be done between V2 and V3 (after ensuring the participant has met inclusion/exclusion criteria, including NPS score by central reader) and a post-baseline CT scan at EOT/IPD (V17/Week 52). CT scan is required before first NP surgery and/or initiation of first course of SCS treatment for NP (see Section 8.1.3).

An independent adjudication committee will be constituted to provide an external independent assessment of blinded data during the study to confirm the diagnosis of major adverse cardiac events (MACE) (to be defined in the charter) and investigator-reported malignancies that occur from randomisation until the end of the follow-up period; please refer to Section 8.3.9.

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

The guidance given should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

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

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

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Additional re-screening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The screening period may also be extended. Both re-screening and screening extension options should be discussed with the designated AstraZeneca study physician. Before randomisation, the Principal Investigator 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 Investigational Product (IP) administration: Performed by a qualified HCP. Additional information related to the visit can be obtained via telemedicine.

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

4.2 Scientific Rationale for Study Design

This is a global study designed to investigate the safety and efficacy of fixed dose tezepelumab (210 mg) administered SC starting at randomisation and then every 4 weeks (Q4W) for a total of 13 doses, on top of standardised INCS, in participants with severe bilateral NP who remain symptomatic despite standard of care therapy. To avoid bias the study will be randomised and double blinded. The population is composed of participants with ongoing chronic symptoms for at least 8 weeks prior to enrolment with moderate to severe participant reported nasal congestion, and a physician endoscopic diagnosis of bilateral NP (NPS of at least 5 out of a maximum of 8), despite documented treatment with SCS within the past 2 years and/or history of any NP surgical intervention. The disease severity at enrolment and history of failure with standard pharmacological treatment constitute an accepted indication for surgery or for a targeted biologic therapy such as tezepelumab, for participants who are not willing to or are contraindicated to have surgery.

CRSwNP is a heterogeneous disease (Hull and Chandra 2017). The eosinophilic (Type 2 high) endotype is most common in the United States, Europe, and Japan whilst non-eosinophilic endotype is more frequent in other Asian countries (Lou H et al 2018, Hull and Chandra 2017, Fokkens et al 2020, Shin SH et al 2014, Chitsuthipakorn W et al 2018). To ensure that endotypes are represented appropriately in all countries in this study capping will be used in China to ensure that approximately 80% of participants have an eosinophilic endotype

(defined by JESREC score of ≥ 11) (Tokunaga T et al 2015) to match the distribution predicted in the rest of the world.

The sample size (approximately 400 participants) is considered appropriate to demonstrate treatment effects with tezepelumab. The 52-week treatment duration is considered appropriate to capture maintenance effects in this chronic disease, assessment of endpoints of time to first SCS use and/or surgery (and the individual components), and proportion of participants with resolution/near complete resolution of nasal polyps as well as providing 1-year treatment safety data in the intended population. Approximately the first 200 randomised participants will have a 24-week follow-up period to evaluate durability of response and to provide off-treatment safety data.

Nasal polyp tissue will be obtained by biopsy in a subset of participants and in a limited number of sites globally. Histopathology of tissue inflammatory cells is commonly used globally as the most definitive method for defining participant endotype. The aim of the nasal biopsy is to characterise the inflammatory patterns of participants entering the sub-study as well as to explore the effect of tezepelumab treatment on nasal polyp inflammatory cells.

4.3 Justification for Dose

A 210 mg Q4W dosing regimen was selected for this Phase 3 study based on the similarity of the pathophysiology of CRSwNP and asthma and the efficacy, safety and exposure-response analysis from the Phase 2b Study CD-RI-MEDI9929-1146 (D5180C00001) in asthma. Efficacy data from Study CD-RI-MEDI9929-1146 demonstrated that the 210 mg tezepelumab Q4W dose led to improved clinical efficacy compared to 70 mg Q4W, whereas the 280 mg Q2W dose did not further increase efficacy compared to 210 mg Q4W, and the safety profiles were similar across the 3 doses. Exposure-response modelling further confirmed the 210 mg Q4W dose is at the plateau of the exposure-response curves for the effect of tezepelumab on asthma exacerbation rate and FeNO. Given these results, the dose of 210 mg SC Q4W was confirmed in the tezepelumab Phase 3 programme for patients with severe asthma.

Given the similarity of the underlying inflammatory pathophysiology of asthma and nasal polyps and significant overlap in patient populations (Fokkens et al 2020), it is expected that the same dose of 210 mg Q4W SC would effectively target the inflammatory pathways relevant to both diseases and show efficacy in CRSwNP. This is supported by the post-hoc analysis of data from study CD-RI-MEDI9929-1146 in asthma patients with co-morbid nasal polyps (N= 18 in the placebo group and N= 23 in the 210 mg Q4W tezepelumab group). In these patients, treatment with tezepelumab resulted in marked reductions in blood eosinophil, IL-5, and IL-13 levels, all of which play a role in the pathogenesis of CRSwNP. Furthermore, there was similar efficacy with respect to asthma outcomes in patients with and without a history of nasal polyps, and to date there has been no change in the benefit/risk profile based on the completed studies. Based on the above rationale, the same tezepelumab dose as used in

the asthma Phase 3 studies, 210 mg Q4W SC is selected for this Phase 3 study in patients with CRSwNP.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (Table 1).

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the study globally.

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

5 STUDY POPULATION

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

Each participant should meet all the inclusion and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (see Section 5.4).

In this protocol, "enrolled' participants are defined as those who sign informed consent. "Randomised" participants are defined as those who undergo randomisation and receive a randomisation number.

For procedures regarding withdrawal of incorrectly enrolled or randomised participants see Section 6.3.

5.1 Inclusion Criteria

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

Age

1 Participant must be 18 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Participants with physician-diagnosed CRSwNP for at least 12 months prior to Visit 1 that have:
   - Severity consistent with need for surgery as defined by total NPS ≥ 5 (at least 2 for each nostril) at screening, as determined by the central reader
   - Nasal Congestion Score (NCS) ≥ 2 at Visit 1

– Ongoing documented NP symptoms for > 8 weeks prior to screening such as rhinorrhoea and/or reduction or loss of smell

3 SNOT-22 total score ≥ 30 at screening (Visit 1).

4 Any standard of care for treatment of CRSwNP provided the participant is stable on that treatment for at least 30 days prior to Visit 1.

5 Documented treatment of nasal polyp exacerbation with SCS for at least 3 consecutive days or one IM depo-injectable dose (or contraindications/intolerance to) within the past 12 months prior to Visit 1 but not within the last 3 months prior to Visit 1 and/or any history of NP surgery (or contraindications/intolerance to).

Weight

6 Body weight of ≥ 40 kg at Visit 1.

Sex

7 Male or female.

8 Female participants: 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.

9 Female participants of childbearing potential must use one highly effective form of birth control. 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. Females 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 screening throughout the study and until at least 16 weeks after the final dose of IP. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. 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. All women of childbearing potential must have a negative serum pregnancy test results at Visit 1 and a negative urine pregnancy test at randomisation.

– Highly effective birth control methods include: true sexual abstinence, a vasectomised sexual partner, Implanon™, bilateral tubal occlusion, intrauterine device/levonorgestrel intrauterine system (IUD/IUS), Depo-Provera™ injections, oral contraceptive, and Evra Patch ™, Xulane™, or NuvaRing™. Women of childbearing potential must agree to use one highly effective method of birth control, as defined above, from screening throughout the study and until at least 16 weeks after the final dose of IP.

Informed Consent

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

11 Provision of signed and dated, written informed consent form (ICF) prior to any mandatory study specific procedures, sampling, and analyses and according to international guidelines and/or applicable EU guidelines.

12 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 (if applicable).

13 Provision of signed and dated written addendum to optional informed consent form for nasal biopsy sub-study prior to collection of nasal biopsy samples (if applicable).

Participant must meet the following criteria at the randomisation visit (Visit 3):

14 Confirmed central reading total NPS ≥ 5 (at least 2 for each nostril) at Visit 2.

15 Inclusion Criterion 15 replaced with Criterion 15a in a prior version of the Clinical Study Protocol

15a) At randomisation visit (Visit 3), a bi-weekly mean NCS≥ 2 (baseline bi-weekly score collected from study Day -13 to study Day 0).

16 SNOT-22 score ≥ 30 at randomisation (Visit 3).

17 At least 8 days of evaluable daily diary data in the 14-day period prior to randomisation (baseline bi-weekly mean score collected from study Day – 13 to study Day 0).

18 Minimum compliance with the daily eDiary during the screening and run-in periods (having a minimum of 70% fully compliant days from Visit 1 to the day of randomisation at Visit 3).

19 Minimum compliance with background INCS as captured in the eDiary during the screening and run-in periods (having a minimum of 70% fully compliant days from Visit 1 to the day of randomisation at Visit 3).

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

5.2 Exclusion Criteria

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

Medical Conditions

1 Any clinically important comorbidities other than asthma (eg, active lung infection, bronchiectasis, pulmonary fibrosis, cystic fibrosis, primary ciliary dyskinesia, allergic bronchopulmonary mycosis, hypereosinophilic syndromes, etc) that could confound interpretation of clinical efficacy results.

2 Exclusion criterion number 2 was removed and merged with Exclusion number 5.

3 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 or AstraZeneca and could:

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

   (b) Influence the findings of the studies or their interpretations;

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

4 Sinus surgery within 6 months of screening visit OR any sinus surgery in the past which changed the lateral wall of the nose making NPS evaluation impossible.

5 Participants with conditions or concomitant disease that makes them non-evaluable for the primary efficacy endpoint such as:

   – antrochoanal polyps;

   – nasal septal deviation that occludes at least one nostril;

   – acute sinusitis, nasal infection, asthma exacerbation or upper respiratory infection at screening or in the 2 weeks before screening; or Churg-Strauss syndrome (also known as known as Eosinophilic granulomatosis with polyangiitis (EGPA)), Young's syndrome or Kartagener's syndrome.

6 A history of known immunodeficiency disorder, including a positive human immunodeficiency virus (HIV) test at Visit 1, or the participant taking antiretroviral medications as determined by medical history and/or participants verbal report.

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

8 Known history of chronic drug or alcohol abuse within 12 months prior to Visit 1, based on Investigator's assessment.

9 Primary Ciliary Dyskinesia (PCD).

10 Uncontrolled epistaxis within 2 months of Visit 1.

11 Known or suspected history of immunosuppression, immune dysfunction or immune dysregulation which may include but is not limited to conditions such as: Guillain-Barré syndrome, invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), or unusually frequent, recurrent, or prolonged infections, per Investigator judgement.

12 History of cancer:

(a) Participants who have had basal cell carcinoma or localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible to participate in the study provided that the participant is in remission and 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.

13 A helminth parasitic infection diagnosed within 24 weeks prior to the date of informed consent that has not been treated with or has failed to respond to standard of care therapy.

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

15 Major surgery within 8 weeks prior to Visit 1 or planned nasal polyp surgery during the conduct of the study.

16 Infection requiring systemic antibiotics within 14 days prior to Visit 1.

17 Positive SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test) or COVID-19 entry screening questionnaire during the screening visit.

– Evaluation will be based on local standard of care as determined by current local guidelines.

Prior/Concomitant Therapy

18 Receipt of any marketed or investigational biologic (monoclonal or polyclonal antibody) within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer, and during the study period. This also applies to participants who previously participated in clinical studies and were treated with monoclonal antibodies (eg, mepolizumab, reslizumab, dupilumab, benralizumab, omalizumab). Note that this restriction does not apply to participants, who are confirmed to have only received treatment with placebo.

19 Initiation of new allergen immunotherapy is not allowed unless participant is already on stable therapy started 30 days prior to Visit 1 with no change during the treatment period.

20 Regular use of decongestants (topical or systemic) at enrolment is not allowed unless used for endoscopic procedure.

21 Use of immunosuppressive medication (including but not limited to methotrexate, troleandomycin, cyclosporine, azathioprine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, systemic corticosteroids or any

experimental anti-inflammatory therapy) within 3 months prior to Visit 1 and during the study period.

- Systemic corticosteroid use is defined as treatment with a burst of systemic corticosteroids for at least 3 consecutive days or a single IM depo-injectable dose of corticosteroids (considered equivalent to a 3-day burst of systemic corticosteroids)

22 Use of corticosteroid-eluting intranasal stents within 6 months prior to Visit 1 and during the study period.

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

24 Receipt of any non-biologic investigational drug within 30 days or 5 half-lives whichever is longer prior to the date of informed consent.

25 Known history of allergy or reaction to any component of the IP formulation.

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

27 Recent Aspirin desensitisation within 6 months of enrolment.

28 Receipt of live attenuated vaccines 30 days prior to the date of randomisation.

- Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 5 days before/after any tezepelumab administration.

Diagnostic Assessments

29 Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/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.

30 Any clinically significant cardiac disease or any electrocardiogram (ECG) abnormality obtained during the screening/run-in period, which in the opinion of the investigator, may put the participant at risk or interfere with study assessments.

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

Other Exclusions

32 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

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

34 Previous randomisation in the present study.

35 For women only - currently pregnant (confirmed with positive pregnancy test), breastfeeding or lactating women.

- A serum pregnancy test will be done for women of childbearing potential at screening Visit 1 and a urine pregnancy test must be performed for women of childbearing potential at each treatment visit prior to IP administration. A positive urine test result must be confirmed with a serum pregnancy test. If serum test is positive, the participant should be excluded.

36 Chronic alcohol or drug abuse within 12 months prior to Visit 1 and throughout the conduct of the study.

- **For participants with co-morbid asthma:** Current smokers or participants with smoking history ≥ 10 pack-years at Visit 1 will not be allowed to randomise in the study. 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; this includes e-cigarettes.

37 Receipt of COVID-19 vaccine (regardless of vaccine delivery platform) 28 days prior to date of IP administration at V3 (randomisation visit).

5.3 Lifestyle Considerations

Participants must abstain from donating blood and plasma from the time of informed consent for 16 weeks after last dose of tezepelumab.

Fertile and sexually active female participants or their partners should use highly effective contraceptive methods throughout the study and 16 weeks after last dose of the IP.

5.3.1 Meals and Dietary Restrictions

Participants with co-morbid asthma should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the centre.

Participants should not eat or drink 1 hour prior to having FeNO assessment.

5.3.2 Alcohol, Tobacco and Other

Chronic alcohol or drug abuse within 12 months is restricted prior to Visit 1 and throughout the conduct of the study.

For participants with co-morbid asthma: 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 will abstain from strenuous exercise for at least 30 minutes before each blood collection for clinical laboratory tests.

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

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. 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 (RA). Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

These participants should have a reason for study withdrawal recorded in the electronic case report form (eCRF) as 'Screen Fail' (ie, Participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures, and not randomised participants.

5.4.1 Re-screening

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

Participants with respiratory infections requiring antibiotics or antiviral medication within 14 days prior to Visit 1 or during the screening/run-in period may be rescreened (exclusion criterion 16) 14 days after recovery, ie, completion of the therapy.

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

Participants who are positive for the SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test) or COVID-19 entry screening questionnaire and temperature screen during the screening visit and are screened failed may be re-evaluated after approximately 4 weeks for potential re-screening upon discussion with AstraZeneca global physician.

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

corticosteroids. If asthma or nasal polyp exacerbation requires SCS or hospitalisation occurred between Visit 2 and Visit 3 (randomisation), participants should be screened failed and may be rescreened once their conditions are stabilised.

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

Rescreened participants should re-sign informed consent. All procedures from the screening/run-in period should be repeated except the sinus CT, if this was already performed in the first screening/run-in period, unless express permission for a repeat screening CT has been given by the study physician. Re-screening should be documented so that its effect on study results, if any, can be assessed.

IMPORTANT! Participants may not be rescreened or have an extended screening period for failure to meet minimum symptom severity, NPS, or SinoNasal Outcome Test (SNOT-22) requirements.

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).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Such treatment in this study refers to tezepelumab 210 mg or matching placebo.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

All IPs will be manufactured in accordance with Good Manufacturing Practices (GMP).

Table 4 Investigational Products

ARM Name	Treatment 1	Treatment 2
Intervention Name	Tezepelumab	Placebo
Type	Biologic, combination product	Placebo, combination product
Dose 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

Table 4 Investigational Products

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 treatment will be provided in an APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into the local language where applicable.	Study treatment will be provided in an APFS with 1.91 mL fill volume. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into the local language where applicable.
Current/Former Name(s) or Alias(es)	Formerly MEDI9929 and AMG 157	N/A

APFS, Accessorised pre-filled syringe; Q4W, every 4 weeks; GMP, Good Manufacturing Practice; IMP, Investigational Medicinal Product; NIMP, Non-Investigational Medicinal Product; w/v, weight per volume.

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

The APFS consists of a pre-filled syringe sub-assembly (PFS-SA; 2.25 mL long 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 Including Combination Products with a Device Constituent

The sponsor's manufactured medical device/combination product, which includes a device constituent, is:

- Accessorised pre-filled syringe (Status, Investigational)

Instructions for medical device use are provided in IP Handling Instructions and Pharmacy Manual

All medical device deficiencies and device constituent deficiencies (including malfunction,

use error and inadequate labelling), hereafter referred to as medical device deficiencies, shall be documented and reported by the Investigator throughout the study (see Section 8.3.14.4 and appropriately managed by the manufacturer.

6.2 Preparation/Handling/Storage/Accountability of Interventions

6.2.1 Preparation and handling

IP will be supplied to the site in a kit containing APFS tezepelumab or matching 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 treatment received and any discrepancies are reported and resolved before use of the IP.

The IP is to be stored at the study centre in a secured facility with limited access and controlled temperature. The temperature should be monitored on a daily basis and documented in the temperature monitoring log while IP is stored at the study centre. The IP 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 centre staff should not use the affected IP and should immediately contact an AstraZeneca representative for further guidance:

- 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 IP

Damaged IP should be documented via IWRS (please refer to IWRS manual for further details).

6.2.2 Dose Preparation

Prior to each IP administration at clinic site and at home setting:

- Investigator/authorised delegate will assess injection site as per standards of medical care.

- For WOCBP, urine pregnancy test will be done; IP will be administered only when the result of the test is negative (see Section 8.2.4.3).

The APFS should be visually inspected prior to dose preparation. The IP will be provided to the study sites as a clear to slightly opalescent, colourless to light yellow liquid, practically free from particles contained in a pre-filled syringe to be stored between 2°C to 8°C (36°F to 46°F) until used.

If defects are noted with the IP, the Investigator and site monitor should be notified immediately. Preparation of the IP must be performed by a qualified person (eg, pharmacist, Investigator, or nurse) at the site.

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

To prepare the participant's dose, an IP kit will be selected for administration according to the kit identification number assigned by IWRS.

Dose preparation steps:

1 Allow the IP to equilibrate to room temperature 68°F to 77°F (20°C to 25°C) for at least 60 minutes prior to dose administration. Ensure that the APFS is in the original carton protected from light during the warming process.
2 To prepare the IP for administration, remove the syringe from the carton by holding the middle of the syringe body.
3 Unwrap, but do not detach, the wrap-around label attached to syringe body to view the syringe contents.
4 Look at the liquid through the viewing window. The liquid should be clear to slightly opalescent, colourless to light yellow liquid, practically free from particles. Do not inject the IP if the liquid is cloudy, discoloured, or contains large particles.
5 Re-wrap the label around the syringe body.

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

6.2.3 Dose Administration

The administration of all study drugs (including IPs) should be recorded in the appropriate

sections of the Case Report Form (CRF). The IP will be administered at the study centre. Optional at home IP administration by HCP can take place only at Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, and Week 48. The rest of the IP administration visits must occur at the study centre.

The IP will be administered by the Investigator/authorised delegate as specified in Table 1. If participant does not want to consent for optional home IP administration, participant can continue to receive the IP at the study centre.

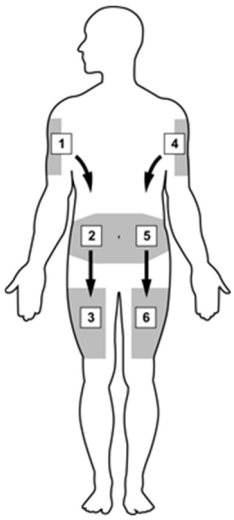
Each participant will receive tezepelumab 210 mg (one 1.91 mL injection) or matching placebo administered SC Q4W for 13 doses in the abdomen, thigh, or upper arm by APFS.

At Week 0, the Health Care Professional (HCP) will administer the study drug. The person administering the dose will wipe the skin surface of the upper arm, anterior thigh, or abdomen with alcohol and allow to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be fully inserted at a 45-degree angle approximately into the SC tissue. The injection site should not be rubbed after each injection. Starting from Week 16, tezepelumab can be administered by the HCP at home if the participant agrees to this option on the ICF. The HCP administering the dose will also fill out the source documentation to capture that the dose was successfully administered. Both the completed source documentation and the used device are to be returned to the site once the visit is completed for IP accountability.

It is suggested that the site of injection of the IP be rotated such that the participant receives IP at a different anatomical site each time. Suggested injection site rotation sequence is presented below (see Figure 2). In the case 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.

When the injection is performed by the health care professional (HCP), the injection can be made in the abdomen, thigh or upper arm. It is recommended that the same person should administer the IP throughout the study.

Figure 2 Suggested Scheme of Rotation of Injection Sites



Further details on IP administration are provided in the IP handling instructions. Investigational product administration must be carried out in line with the instructions provided.

At Visits 3 and 5 (Weeks 0 and 4), participants should be observed by the HCP for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits involving IP administration, participants will be observed by the HCP (or adult if injection was done at home) for a minimum of 1 hour after IP administration for the appearance of any such reaction.

If any of the following occur, the Investigator should reschedule the visit and the IP should not be administered until the rescheduled visit:

- The participant received allergen immunotherapy injection on the same day as scheduled IP 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 is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.
- The participant is confirmed to have an active COVID-19 infection based on positive SARS-CoV-2 test results.
- The participant is suspected to have an active COVID-19 infection based on assessment of COVID-19 symptoms.
- The participant is planning to receive COVID-19 vaccination during the screening or treatment period. Please refer to section 6.4.2.

The visit should be rescheduled within the allowed visit window and IP should be

administered at that visit. If this is not possible the IP administration should be skipped.

If the participant is suspected to have an active COVID-19 infection or fever (≥ 38°C; ≥ 100.4°F) suspected due to COVID-19 infection, the visit should be rescheduled (and IP 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 IP administrations.

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

6.2.4 Reporting Product Complaints

Any defects with the IP must be reported immediately to the AstraZeneca representative (s), as per the Pharmacy Manual. The Site Monitor must also be notified. All defects will be communicated to the Sponsor and investigated further with AstraZeneca

During the investigation of the product complaint, all IP must be stored at labelled conditions 2°C to 8°C (36°F to 46°F), separated from other IP 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 AstraZeneca representative(s) as per the Pharmacy Manual. The Study Monitor must also be notified. 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 IP. 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 IP 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 using the appropriate form as per the Pharmacy Manual and the Study Monitor should be notified. Please see 8.3.14.

If a device malfunction is identified at the study centre:

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

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

For definitions for recording, evaluating and follow-up of medical device AEs, SAEs, and deficiencies, please see Appendix I.

6.3 Measures to Minimise Bias: Randomisation and Blinding

The Investigator(s) will:

1 Obtain signed informed consent from the potential participant before any study specific procedures are performed.
2 Assign the potential participant a unique enrolment number (which begins with an ‘E’) via IWRS.
3 Determine participant eligibility.
4 Assign the eligible participant a unique randomisation code via IWRS.
5 Participants will be allocated to receive tezepelumab or placebo in a 1:1 ratio and according to the stratification factors listed in Section 4.1. Randomisation numbers will

be grouped in blocks. If a participant withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn participants will not be replaced.

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

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 medication. 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 withdrawn from the study.

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 treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the participant and 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 7.1.1.

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

Methods for assigning treatment groups

Randomisation codes will be assigned PPD 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 Calyx on behalf of AZ (AZRand). All participants will be stratified at randomisation by region, prior nasal polyp surgery and co-morbid asthma/AERD/NSAID-ERD).

Consideration will be given to closing the Interactive Web Response System (IWRS) randomisation for a subgroup to ensure that 50%-70% of the study population will have co-morbid asthma/AERD/NSAID-ERD, and at least 50% will have had prior surgery for CRSwNP, which may be done either overall or within a specific region. Once a subgroup is closed, participants in the screening/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed.

Ensuring blinding

This is a double-blind study in which tezepelumab and placebo are not visually distinct from each other. All packaging and labelling of IP will be done in such way as to ensure blinding for all sponsor and investigational site staff. Neither the 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, IP will be handled by a qualified person (eg, pharmacist or study nurse) at the site.

An AstraZeneca site monitor will perform IP 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 IP
- Those generating the randomisation list
- Personnel at the IWRS company
- Supply Chain Management department
- Patient Safety department at AstraZeneca
- Bioanalytical lab analyst performing the PK sample analysis

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.

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

Methods for unblinding

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

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

treatment given to the 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 an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented and until primary database lock occurs.

6.4 Concomitant Therapy

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

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

List of the restricted and prohibited medications can be found in Table 5 and Table 6, provided below:

Table 5 Restricted Medications

Medication/class of drug:	**Recommendation (including limits for duration permitted and special situations in which it is allowed):**
Inactive/killed vaccinations (eg, inactive influenza)	Not allowed within the 5 days before or within 5 days after any IP dosing study visit.
COVID-19 vaccinations (eg, whole virus, protein subunit, nucleic acid, viral vector)	If COVID-19 vaccination is in the best interest of the participant and the participant is vaccinated during the study, IP dosing can continue but the recommendation is that IP dosing should not occur within 14 days before and 28 days after a dose of vaccine. As these intervals might change, please discuss with the study physician for the most current recommended time interval, prior to any vaccine dose. Refer to section 6.4.2 for more details.
Any Immunosuppressive – topical	Topical administration of Immunosuppressive medication may be allowed at the discretion of the Investigator.
Allergen Immunotherapy	Allowed if on stable therapy started 30 days prior to V1; no change during the treatment period. Should not be administered on the same day as study intervention administration.
Decongestants (topical or systemic)	Only allowed for endoscopic procedure.

Table 5 Restricted Medications

Medication/class of drug:	Recommendation (including limits for duration permitted and special situations in which it is allowed):
Systemic Corticosteroids as maintenance treatment	Not allowed 3 months prior to V1. During study conduct, SCS are allowed as a rescue to relieve NP worsening of symptoms, to treat asthma exacerbations or to treat other indications at PI's discretion. However, it is recommended that participants abstain from using SCS for the first 3 months after randomisation, unless in case of an emergency or if it is deemed necessary by the PI.

Table 6 Prohibited Medications

Prohibited medication/class of drug:	
Corticosteroid-eluting intranasal stents	Not allowed 6 months prior to V1 or during the study.
Intranasal Medication including intranasal corticosteroids drops	Only study provided MFNS or equivalent INCS is allowed.
Any immunosuppressive treatment including but not limited to: methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide	Not allowed within 3 months prior to V1; during the study period and 3 months or 5 half-lives (whichever is longer) after last dose of the IP.
Aspirin desensitisation	Use of aspirin as a desensitisation regimen for the management of aspirin exacerbated respiratory disease (AERD) is not allowed; all other uses of aspirin are allowed for any other medical conditions.
Any marketed or investigational biologic (monoclonal or polyclonal antibody)	Not allowed within 4 months or 5 half-lives (whichever is longer) prior to V1; during screening/run-in and throughout the IP treatment, and 4 months or 5 half-lives (whichever is longer) after the last dose of IP.
Other investigational product	Not allowed within 30 days or 5 half-lives (whichever is longer) prior V1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Live attenuated vaccines	Not allowed within 30 days prior to randomisation; during the study period, and 16 weeks or 5 half-lives (whichever is longer) after the last dose of the IP.
Blood products or immunoglobulin therapy	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.
Herbal remedies for the treatment of CRSwNP	Not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP.

The Medical Monitor should be contacted if there are any questions regarding concomitant or

prior therapy.

Participants must abstain from taking prescription or non-prescription drugs for nasal polyps (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

6.4.1 Background Medication

The aim of this study is to evaluate the treatment effect of tezepelumab on polyp reduction. Therefore, the background INCS medications should be maintained at a stable dose from Visit 1 and throughout the screening and study period and no other medications intended to prevent polyp recurrence should be used. All participants will use INCS for a minimum of 4 weeks prior to V3 and continued throughout the study period.

Standardised MFNS (50 µg/actuation) nasal spray is contained in a bottle that contains 120 actuations for US and 140 actuations for all other countries. Two doses of MFNS (50µg/actuation) in each nostril twice daily (total 400µg daily) or equivalent INCS will be administered unless there is a medical rationale to use the lower dose (QD) regimen. Equivalent dose should refer to the highest approved country INCS dose for CRSwNP. The generic name of the INCS and the total daily dose should be recorded in the eCRF.

6.4.2 COVID-19 Vaccination

As there is an expected broad vaccination against COVID-19 virus in most countries, the CSP allows participants to be vaccinated following certain precautions.

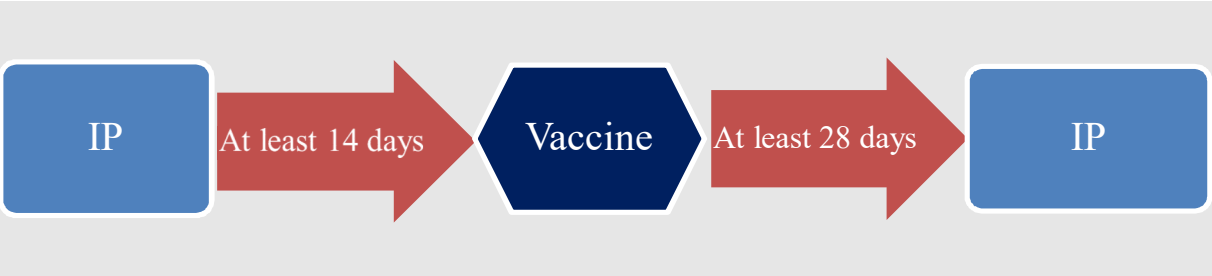
COVID-19 vaccines are either nucleic acid vaccines (which can include DNA plasmid and mRNA), recombinant vector vaccines (non-replicating viral vectors) or inactivated virus vaccines. DNA plasmid and mRNA vaccines are considered an inactivated vaccine. Recombinant vector candidates potentially may be in a new category. Based on available publications on mRNA and virus vector anti-SARS-CoV-2 vaccines, the immune response developed rapidly after both the prime vaccine and the booster dose. No live attenuated COVID-19 vaccines are currently available. For vaccines that are currently approved under emergency use authorisation (EUA), please refer to the relevant health authority websites for further guidance. As per this CSP, any live attenuated vaccine is prohibited during study conduct.

Given the limited long-term safety data of COVID-19 vaccines and the potential to confound the interpretation of safety results in the study, the following COVID-19 vaccination guidance should be followed depending on the study phase of the participant. As the below intervals

might change, please consult with the study physician for the most current recommended time interval prior to any vaccine dose.

Study Period	Recommendations
Participant in screening/run-in period	• If COVID-19 vaccination is in the best interest of the participant and they are vaccinated or scheduled to be vaccinated before the screening or run-in visit, the randomisation visit should be scheduled to ensure that the first IP dose is administered at least 28 days after any vaccination dose.
Participant in treatment period	• If COVID-19 vaccination is in the best interest of the participant and they are vaccinated during the study, **IP dosing can continue but IP is not recommended to be administered within 14 days before or 28 days after a dose of vaccine.** • If the participant receives a COVID-19 vaccination less than 14 days from the last IP dose, the next IP administration is recommended to be rescheduled or skipped to ensure the next IP dose is at least 28 days after the vaccine administration. • The participant's COVID-19 vaccination schedule should follow country-specific health authority guidelines. Vaccination against COVID-19 should be planned in advance to ensure the IP dosing/COVID-19 vaccination intervals are maintained. • Study visits should still be conducted within the protocol-specified time window, even if a participant receives a COVID-19 vaccine dose. However, even if IP is not administered at a study visit because of COVID-19 vaccination restrictions, other site visit assessments should still be performed according to the CSP schedule. • 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 IP dosing (mentioned above) is maintained. • If it is anticipated that a participant will miss 2 consecutive IP administrations, the AstraZeneca study physician should be contacted to discuss further patient participation in the study. • The reason for skipping IP administration should be recorded with "COVID-19" prefix in medical records, protocol deviation and COVID-19 related eCRF modules.
Patient in Follow-up period	• If COVID-19 vaccination is in the best interest of the participant, COVID-19 vaccination could be administered. The participant should follow the schedule of assessments listed in CSP in the Schedule of Assessments (SoA, Section 1.3); no special adjustments are needed. • It is advised that the participant wait for 14 days after the last IP dose.

Figure 3 COVID-19 Vaccination Administration in Relation to IP Dosing



Reporting of COVID vaccination:

- COVID-19 vaccine details including vaccine's name/manufacturer, route of administration, and vaccination date should be entered without delay into the eCRF CM module. This includes any history of COVID-19 vaccination.
- If a participant experiences an AE/SAE associated with COVID-19 vaccination, the investigator should record this in source document and determine whether the IP should be continued, skipped, or permanently discontinued in accordance with the CSP.

6.5 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 if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

The study treatment provided for this study will be used only as directed in this Clinical Study Protocol (CSP). The investigational product will be administered at the study site or home (if applicable) on treatment visits and within visit windows as specified in the SoA.

In cases where a treatment visit needs to be rescheduled, the IP must be administered within the visit window or as soon as possible. The PI should make every effort to assure that no IP administrations are missed during the course of the study.

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

Principal Investigators should also assure that participants are compliant and on a stable dose of the background medication (INCS) during study period.

6.5.1 Rescue Medication

Rescue medications may be given at the discretion of the Investigator per local guidelines.

6.5.2 Other Concomitant Treatment

Medications other than the ones described above, which are considered necessary for the participant's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

6.6 Dose Modification

Dose modification of background medications is not allowed in the study. If the Investigator makes the clinical decision that a participant needs dose modification, the Investigator must contact the AstraZeneca Study Physician to discuss justification for modification and document outcome of discussion in the source documentation.

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.

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. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety as per follow-up. See the SoA (Table 1) for data to be collected at the time of discontinuation or study intervention and follow-up and for any further evaluations that need to be completed.

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

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluation that need to be completed. Participant may be discontinued from IP 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.
- IP unblinding (PI).

- Lost to follow-up.
- If participant had undergone NP surgery during the treatment period.
- Development of any study specific criteria for discontinuation:
  - Anaphylactic reaction to IP requiring administration of epinephrine;
  - Development of helminth parasitic infestations requiring hospitalisation;
  - 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 ALT or AST increase of ≥ 8 x ULN
  - Confirmed ALT or AST increase of ≥ 5 x ULN for more than 2 weeks
  - Confirmed ALT or AST increase of ≥ 3 x ULN and total bilirubin of ≥ 2 x ULN
  - ALT or AST of ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%)

Before a decision to discontinue a participant from IP is instituted, the AstraZeneca Study Physician should be consulted regardless of the reason for discontinuation. See the SoA (Table 1) for data to be collected at the time of IP discontinuation and follow-up and for any further evaluations that need to be completed.

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

7.1.1 Procedures for Discontinuation of Study Treatment

Participants are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Discontinuing study treatment is not the same as study withdrawal. Procedures to follow for study withdrawal are detailed below. If the participant decides to withdraw consent, then the reason for this must be recorded separately in the eCRF. A participant that decides to discontinue IP should always be asked about the reason(s) and the presence of any adverse events. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Participants permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. However, treatment with marketed or investigational biologics is not allowed until Week 76 (for the first 200 participants approximately) or Week 64 (last 200 participants randomised) even if the participant has discontinued IP. Interaction studies between tezepelumab and other biologics indicated for the treatment of asthma have not been

conducted. For additional information regarding pharmacokinetic and pharmacodynamic effects of tezepelumab reference should be made to the Investigator Brochure.

All participants who prematurely discontinue IP should return to the site and complete the procedures described for the premature IP Discontinuation visit (IPD) at 4 weeks (+/-5 days) post last IP administration, except in case of IP discontinuation due to NP surgery.

In case of IP discontinuation due to NP surgery, the IPD procedures (including CT scan if at least 12 weeks passed since the baseline CT scan) must be performed prior to the surgery. Sites are encouraged to schedule the IPD visit (in case of NP surgery) prior to, and as close as possible to the planned surgery date.

Participants who discontinue treatment should be encouraged to return for all regularly scheduled visits for safety and efficacy assessments. In case of IP discontinuation due to NP surgery, no further nasal endoscopies or CT scans are required after the IPD visit.

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

1 The participant should be encouraged to return for all regular clinic visits and perform all scheduled assessments (excluding IP administration and, in the case of IP discontinuation due to NP surgery, nasal endoscopy and CT) until the EOT visit at Week 52 (+/-5 days).
2 The participant will be offered follow-up on a monthly basis via telephone calls while continuing ePRO data collection on the handheld device at home until the participant completes the EOT visit at Week 52 (+/-5 days). The UPSIT assessments will not be completed as per SoA at home after IPD visit until the participant returns to site at the EOT visit.
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 eDiary), the Investigator will contact the participant at 52 weeks post-randomisation. No other study assessments will be performed prior to this contact.

The EOT visit will be completed immediately in the case of subsequent early withdrawal from option 1 or 2. Participants who do not wish to have any follow-up contacts will be discontinued from the study. All discontinued participants must return the eDiary at the EOT visit.

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

care utilisation, and asthma exacerbation information (asthma/AERD/NSAID-ERD participants). 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). 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).

A participant who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow-up participants as medically indicated. A withdrawal visit is essential to collect as much data as possible for the participant as per EOT visit described in SoA, Table 1.

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

If the participant only withdraws consent for the retention of blood samples for future exploratory use (eg, study of markers of CRSwNP, identifying potential new drug targets for CRSwNP, assay development purposes, or for other scientific health-related research), the participant will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the Investigator and recorded in the eCRF.

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

7.1.2 Withdrawal Due to Recruitment Completion in a Randomised Stratum

When randomisation in a specific stratum is completed, participants in the screening period who are assigned to the completed stratum will not be randomised and will be screen failed from the study. The reason of the screen failure should be documented in the source and eCRF as a development of study specific criterion for discontinuation. Same as with screen failures, no further study related follow-up of these participants is required.

7.1.3 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 withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF. As with screen failures, no further study related follow-up of these participants is required.

7.1.4 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; 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 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

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

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 investigational product. 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 (Table 1). Protocol waivers or exemptions are not allowed.
- The Investigator will ensure that data are recorded on the eCRF. Medidata Rave Web Based Data Capture system will be used for data collection and query handling.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- The amount of blood collected from each participant over the duration of the study will be approximately 450 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Instructions for the collection and handling of HBS 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 HBS see Section 8.5.
- The Investigator ensures the accuracy, and completeness, of the eCRFs including: the legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

8.1 Efficacy Assessments

8.1.1 Nasal Polyp Score (NPS)

The NPS is the sum of the right and left nostril scores (maximum 8), as evaluated by nasal endoscopy. Total NPS is graded based on polyp size described in Table 7. Nasal endoscopy may be preceded by local administration of anaesthetic drugs in combination with a decongestant, as per local medical practice.

Standard video sequences will be conducted by trained personnel and sent to a central reader. Centralised imaging data assessments and scoring by independent physician reviewer(s) who are blinded for the imaging data will be performed for all endoscopies. To confirm eligibility at V3, the V2 central reading results will be made available to the site.

The sites will verify image quality and remove participant-identifying information from the imaging data header prior to sending the imaging data to the central reader.

Further details on nasal endoscopy will be available in a separate Imaging Site Guide provided to the sites. The Imaging Core Lab will outline the equipment requirements and follow an Independent Review Charter (IRC). The IRC will define the logic and basis for the independent analysis methodology including the assessments to be recorded and corresponding assessment criteria to be used by the individual(s) conducting the analysis.

Table 7 Endoscopic NPS Within each Nostril

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate

Table 7 Endoscopic NPS Within each Nostril

Polyp score	Polyp size
3	Polyps reaching the lower border of the inferior turbinate or a middle meatal polyp with a score of 2 with any additional polyp medial to the middle turbinate
4	Large polyps causing complete or near complete obstruction of the inferior nasal cavity ie, touching the floor of the nose

8.1.2 Clinical Outcome Assessments

Participants will complete all patient reported outcomes assessments (PRO) using a handheld ePRO device. The ePRO device will be the only accepted source of patient reported data.

The Investigator or designee will ensure that participants are properly trained on the use of this device and the importance of completing assessments as scheduled. The ePRO device will be used to capture symptoms (Nasal Polyposis Symptom Screening Assessment) and health-related quality of life [(HRQoL) SNOT-22] screening data at Visit 1. If the participant does not meet the screening requirements, the device will be deactivated and retained at the site. If eligible to continue, the participant will receive additional training on the device regarding at home use.

The ePRO device will be programmed at Visit 1 with reminder alarms for the daily diary. Study site staff will be able to adjust alarms for specific participant needs as required. The participant will be required to complete a training module before taking the device home. If a participant fails to meet eligibility criteria after V1 (for example regarding total NPS), the participant will be scheduled to return to the site, return the ePRO device and will be screen failed at that time.

The Investigator or designee will be responsible for monitoring participant adherence with the daily diary and follow-up as necessary to minimise missing data. Participant compliance should be checked weekly (at minimum) to ensure that the participant is completing the assessments as scheduled.

Monitoring of participant adherence to the diary is critical during the baseline period (Study Day -13 to Day 0) to ensure that the participant meets applicable criteria for randomisation. Continued weekly monitoring of adherence throughout the study and follow-up with participants via phone and at the visits is required to ensure sufficient data are available for supporting the co-primary endpoint of this study.

All PRO assessments should be completed prior to any other interventional study procedure (eg, laboratory tests, nasal endoscopy) except for informed consent at Visit 1 and the CT scan. The at home PRO assessments scheduled for V3 will be completed at the site once the site staff enable the visit on the device. If a scheduled at home assessment has not been completed

at the time of the visit it will be completed at the site prior to other study procedures.

8.1.2.1 Nasal Polyposis Symptom Diary (NPSD) and Nasal Polyposis Symptom Screening Assessment (NPSSA)

The participant will complete an 11-item NP symptom diary (NPSD) each morning throughout the screening, treatment, and follow-up periods. The participant is asked to consider their experience with NP/nasal polyps over the past 24 hours when responding to each question. Participants are asked to report their experience with NP symptoms (nasal blockage, nasal congestion, runny nose, post-nasal drip (mucous drainage down the throat), headache, facial pain, facial pressure, and difficulty with sense of smell) and symptom impacts (difficulty with sleeping due to nasal symptoms and difficulty with daily activities due to nasal symptoms). Participants report the severity of each symptom and symptom impact at its worst using a 4-point verbal rating scale (0-None to 3-Severe). A total symptom score (TSS) is calculated by taking the sum of the 8 equally weighted symptom items. A single item to capture INCS compliance (yes or no) will be administered after the symptom and symptom impact items.

A 2-week recall version of the diary, the Nasal Polyposis Symptom Screening Assessment (NPSSA), will be used to evaluate minimum symptom criteria at Visit 1. This screening assessment has one additional item about consistency of symptoms over the past 12 weeks and omits the INCS compliance item.

The NPSD and NPSSA will be completed on the ePRO device per the SoA.

8.1.2.1.1 Nasal Congestion Score

Nasal congestion score (NCS) is captured by an item in the NPSD asking participants to rate the severity of their worst nasal congestion over the past 24 hours using the following response options: 0 – None; 1 – Mild; 2 – Moderate; 3 – Severe. Baseline will be the mean of daily responses from Day -13 to Day 0. Bi-weekly (14-day) mean NCS will be calculated if at least 8 days in each 14-day period has evaluable data; otherwise the bi-weekly mean is set to missing.

8.1.2.1.2 Loss of Smell

Loss of smell is captured by an item in the NPSD asking participants to rate the severity of their worst difficulty with sense of smell over the past 24 hours using the following response options: 0 – None; 1 – Mild; 2 – Moderate; 3 – Severe. Baseline will be the mean of daily responses from Day -13 to Day 0. Bi-weekly (14-day) mean loss of smell will be calculated if at least 8 days in each 14-day period has evaluable data; otherwise the bi-weekly mean is set to missing.

8.1.2.2 Sino-Nasal Outcome Test 22 item

The SNOT-22 is a condition-specific HRQoL assessment which captures participant reported

physical problems, functional limitations, and emotional consequences of SinoNasal conditions (Piccirillo et al 2002; Hopkins et al 2009). Patient reported symptom severity and symptom impact over the past 2 weeks are captured via a 6-point scale (0- No Problem to 5-Problem as bad as it can be). The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes). A Minimal Clinical Importance Difference (MCID) of 8.90 has been established for individual score change (Hopkins et al 2009).

The SNOT-22 will be completed on the ePRO per the SoA.

8.1.2.3 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 VAS, 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 using the eDiary in accordance with the SoA.

8.1.2.4 Short-Form 36-item Health Survey, Version 2

The Short-Form 36-item Health survey, Version 2 (standard recall) (SF-36v2) is a 36-item, self-report survey of functional health and well-being, with a 4-week recall period (QualityMetric 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks participants to rate how their current state of health compared to their state of health 1 year ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). Psychometrically-based physical and mental health component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and mental HRQoL.

Two types of thresholds have been developed for interpretation of SF-36v2 scores. The first type is suitable for comparing group mean scores and is generally referred to as the MCID. The second type is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (QualityMetric 2011). Threshold values are presented in Table 8

Table 8 Threshold Values for the SF-36v2 Scale and Summary Measures

	SF-36v2 score									
Threshold	**PCS**	**MCS**	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
Group difference	2	3	3	3	3	2	2	3	4	3
Individual change	3.4	4.6	4.3	3.4	6.2	7.2	6.2	6.9	4.5	6.2

BP Bodily Pain; GH General Health Perceptions; MCS mental health component summary; MH Mental Health; PCS physical component summary; PF Physical Functioning; RE Emotional Problems; RP Role Limitations due to Physical Health; SF Social Functioning; VT Vitality

The SF-36v2 will be completed on the ePRO per the SoA.

8.1.2.5 Asthma Control Questionnaire (for Asthma/AERD/NSAID-ERD Participants Only)

The Asthma Control Questionnaire (ACQ-6) is an assessment of asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting beta-agonist use).

Participants are asked to recall their level of asthma control during the previous week by responding to one bronchodilator use question and 5 symptom questions.

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. 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 not well-controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered to be clinically meaningful.

The questionnaire will be completed on ePRO as per SoA.

8.1.2.6 University of Pennsylvania Smell Identification Test

The University of Pennsylvania Smell Identification Test (UPSIT) is a quantitative test of olfactory function which uses microencapsulated odorants that are released by scratching standardised odour-impregnated test booklets (Doty et al 1984). Four booklets each with 10 odorants each are used for the test. Participants are asked to identify the odour using multiple choice format which lists different possibilities. The test is forced-choice, ie, the participant is required to mark one of the 4 alternatives even if no smell is perceived. Scores are based on number of correctly identified odours (score range 0 to 40).

Please note that the UPSIT smell test will be performed in all countries participating in the study except countries in which an UPSIT version in the native language is unavailable.

8.1.2.7 Patient Global Impression of Severity and Change

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the

participant's perception of overall NP symptom severity at the time of completion using a 6-point categorical response scale (0 - No Symptoms to 5 - Very Severe).

The Patient Global Impression of Change (PGI-C) instrument captures the participant's overall evaluation of response to treatment since first dose of IP. The participant is asked to report the degree to which their health status has changed using a 7-point scale (1 - Much Better to 7 - Much Worse).

Participants will complete the PGI-S and PGI-C at the site using the ePRO prior to other study procedures.

8.1.2.8 Work Productivity and Activity Impairment (WPAI) Questionnaire

The Work Productivity and Activity Impairment questionnaire (WPAI, General Health version 2.0) is a self-administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity (Reilly et al 1993).

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

8.1.3 Sinus Computed Tomography

Computed tomography (CT) will be performed in all participants. Referral for baseline CT scan should be provided at V2 (Week -2) and must be performed after nasal biopsy procedure (if applicable) at V2 only if the participant has met all eligibility criteria at V2 including NPS score confirmation by central readers. At V17 (EOT/IPD), the CT scan should be performed before the nasal biopsy procedure is completed for participants in the nasal biopsy sub-study.

For participants who undergo or are planned for surgery for NP during the treatment period, a CT scan should be performed prior to the first NP surgery per the IPD visit. For participants who require SCS for the treatment of NP, a CT scan should be performed prior to the first course of SCS, if possible, and at Week 52. For participants who receive multiple NP surgeries and/or SCS treatments for NP, the CT scan should be performed prior to the first occurrence of either NP Surgery or SCS treatment for NP. For participants who discontinue IP for other reasons, a CT scan should be performed at the IPD visit as well as at Week 52, if participant opts for follow-up option 1 or 2 per Section 7.1.1 of the CSP. CT should only be performed at IPD visit (regardless of the reason for IPD) if at least 12 weeks have passed since the baseline CT scan.

Sinus CT images will be used to derive Lund-Mackay scores (LMSs) and Zinreich (modified Lund-Mackay) scores based on the visual assessment by independent central readers (see Section 8.1.3.1), and for quantitative estimation of a sinus severity score (see Section 8.1.3.2)

which is representative of sinus disease burden.

The sites will remove participant-identifying information from the image data (DICOM) header prior to sending the imaging data to the central lab.

Further details on sinus CT will be available in a separate Imaging Site Guide provided to the sites. The Imaging Core Lab will outline the equipment requirements and follow an IRC. The IRC will define the logic and basis for the independent analysis methodology including the assessments to be recorded and corresponding assessment criteria to be used by the individual(s) conducting the analysis.

Sites are encouraged to consult the Study Physician and their CRA in case of any unclarity regarding timing of sinus CT during the study.

8.1.3.1 Lund-Mackay Score

The Lund-Mackay score scoring system is used to provide a semi-quantitative assessment of nasal sinuses on sinus CT scans (Lund and Mackay 1993). Based on the sinus CT images, the 5 sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) on each side are scored by central radiologist as described in Table 9:

Table 9 Lund-Mackay Score

Score	CT scan assessment
0	No abnormality
1	Partial opacification
2	Total opacification

The ostiomeatal complex (Table 10) is scored for right and left sides:

Table 10 Ostiomeatal Complex Score

Score	CT scan assessment
0	Not occluded
2	Occluded

The maximum total score is 24.

8.1.3.2 Quantitative Measurement of Sinus Disease Burden on Sinus Computed Tomography

Quantitative assessment of sinus CT image data will be used to derive an objective measure of sinus disease burden called sinus severity score (Pallanch et al 2013).

This is defined as:

Sinus severity score = sinus mucosal volume/
(sinus mucosal volume + sinus air volume) *100%.

The following parameters used to calculate the sinus severity score:

- sinus air volume (mL);
- sinus mucosal volume (mL).

Image analysis will be performed centrally.

8.1.3.3 Zinreich (Modified Lund-Mackay) Score

In addition to the Lund-Mackay scoring described above, the same CT images will also be scored using the modified Lund-Mackay (Zinreich) scoring system (Okushi et al 2013, Likness et al 2014).

All 5 sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) on each side will be scored based on the percentage of opacification from mucosal thickening according to Table 11.

Table 11 Modified Lund-Mackay (Zinreich) Score

Score	Percent opacification
0	0%
1	1%-25%
2	26%-50%
3	51%-75%
4	76%-99%
5	100%

The maximum total Zinreich score is 50 (54 when including the ostiomeatal complex score described above).

Scoring will be performed centrally by the imaging core lab.

8.1.4 Post-randomisation Nasal Polyp Surgery and/or SCS Use

Participants who have a scheduled NP surgery at the time of the study enrolment and randomisation should not be randomised (refer to exclusion criterion 15). After randomisation, surgery should not be planned for the first 3 months unless emergent or deemed necessary by the PI. These cases should be discussed with the AstraZeneca study physician.

Post-randomisation nasal polyposis surgery will, by definition, define a study endpoint. Both the date the decision is made that surgery is warranted (as agreed jointly by both the

participant and the investigator), as well as the date of actual surgery (if available), will be recorded in the eCRF. NP surgery is defined as any procedure involving instruments resulting in an incision and removal of tissue (eg, polypectomy, endoscopic sinus surgery). Post-randomisation surgery procedures performed for NP during the study, including reason for surgery and information whether the surgery was performed as an outpatient or inpatient (ie, including an overnight stay in the hospital) procedure, should be recorded in the Nasal Polyp Surgery eCRF. A nasal endoscopy assessment of NPS (to provide evidence of NP recurrence), a CT scan and PROs should be performed prior to the first (post-randomisation) actual NP surgery. If no such assessment is available, a visit should be scheduled to obtain those assessments. At the time of surgery, participants will be permanently discontinued from IP and assessed as soon as possible per the EOT visit described in the SoA. If surgery is planned during the follow-up period, participants will be assessed by the Investigator and may decide to continue follow-up to the time of surgery or final visit of the study, whichever date comes first.

Rescue treatment of NP or other reasons is defined as requiring treatment with systemic corticosteroids (SCS) for at least 3 consecutive days (a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids). A course of SCS is considered continuous if treatment episodes are separated by less than 7 days. Participants receiving SCS during the study should continue on IP unless the Investigator decides to withdraw the participant from IP due to safety reasons.

- If SCS is used for treatment of NP for ≥ 3 consecutive days, a CT scan and a nasal endoscopy assessment of NPS should be performed prior to first course of treatment with SCS (unless the subject has already had a CT scan prior to a NP surgery post randomisation). If no such assessment is available, an unscheduled visit should be scheduled to obtain those assessments.
- If SCS use for treatment of any other reason than NP is close to V10 (Week 24) or V17 (Week 52), the visit should be rescheduled at least 2 weeks after the last dose of SCS.
- If SCS will be used for any other reason than NP, the investigator is recommended to consult with the AstraZeneca study physician.

8.1.5 Spirometry (Asthma/AERD/NSAID-ERD Participants Only)

8.1.5.1 General Requirements

Lung function (FEV1, FEF 25-75% and FVC) will be measured by spirometry at the study site using equipment provided by a central vendor. The MasterScope is a system which will be used on-site to perform and record results for procedures including, but not limited to, spirometry, NPIF and FeNO.

Spirometry will be performed by the Investigator or authorised delegate according to

American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines or local guidelines (Graham et al 2019)

The MasterScope kit will include a spirometer handle which will be used to record spirometry values at the site. The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study centre personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important!

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

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

Time of day for scheduled centre visit spirometry

Spirometry testing should be done according to the SoA. Spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the randomisation visit (Visit 3).

All spirometry assessments should be performed within ± 1.5 hours of the time it was performed during Visit 3. For example, if the Visit 3 spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry techniques

Detailed procedures for performing spirometry will be described in a separate instruction

manual. Details regarding assessment of the quality of spirometry and the best test report process will also be detailed in the manual.

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the Predicted Normal Values (PNV) and are pre-programmed into the spirometer (Quanjer et al 2012) FEV_1, expressed as percent of the PNV, will be calculated as follows:

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

Record Keeping

A signed and dated copy of the pre-BD printout must be kept at study centre for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, and visit number. If a printout cannot be printed, the mean value of the measurements will be recorded in the participant's charts.

8.1.6 FeNO (Asthma/AERD/NSAID-ERD Participants Only)

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

Participants will be asked whether they have had a respiratory infection in the 2 weeks prior to the measurement. The FeNO measurements will not be performed within 2 weeks of a respiratory infection. The FeNO test will be performed prior to spirometry. Participants should not eat or drink 1 hour prior to having the FeNO test. 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 till after the required time has passed since the meal or drink or the visit must be rescheduled within the allowed visit window.

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

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

8.1.7 Nasal Peak Inspiratory Flow

Nasal peak inspiratory flow (NPIF) evaluation represents a physiological measure of the air flow through both nasal cavities during forced inspiration expressed in liters per minute. Nasal

inspiration correlates most with the participative feeling of obstruction and is the best validated technique for monitoring nasal flow in clinical trials.

A minimum of 3, up to a maximum of 8NPIF efforts will be performed by the participant; all values will be recorded by the participant on the MasterScope and the highest value will be used for evaluation.

The NPIF will be performed at enrolment/screening V1 (Week -5), V3 (Week 0), V7 (Week 12), V10 (Week 24), V13 (Week 36), V17 (Week 52), V19 (Week 64), V21 (Week 76).

The nasal flow is expressed in liters per minute, and consecutive measurements are performed.

Taking the best of 3 outcomes with less than 10% variation is considered to be the best means of expression of the result (Scadding et al 2011).

8.2 Safety Assessments

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

8.2.1 Physical Examinations

Investigator's 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.

- 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, muscular-skeletal (including spine and extremities) and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). For the brief physical assessment only, information on whether the assessment was performed or not is to be recorded.

Physical examination will be performed at timepoints as specified in the SoA.

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA.

Vital signs are to be taken prior to IP administration, and if possible, before blood draw.

Body temperature, pulse rate, respiratory rate, and blood pressure (BP) will be assessed:

- Body temperature will be measured in Celsius before IP administration in accordance with local standards;

- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available;
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones);
- Pulse rate will be obtained before blood pressure if the manual technique is used.
- Respiration rate will be obtained after participant has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

8.2.3 Electrocardiograms

An electrocardiogram (ECG) will be performed at timepoints as specified in the SoA.

ECG will be taken in supine position, after the participant has been resting for at least 5 minutes. The assessment should be performed before interventions with the participant (eg, nasal endoscopy, blood draw).

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, and quality checked and kept in case of further need for re-evaluation.

It is highly recommended that the same machine is used for assessment throughout the participant’s participation in the study. ECG evaluation will be recorded in the eCRF. ECG evaluation will be recorded in the eCRF.

8.2.4 Clinical Safety Laboratory Assessments

See Table 12 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA. Fasting before blood draw is recommended but not mandatory.

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the visits indicated in the SoA. The date and results 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 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/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S-Alkaline phosphatase (ALP)
B-Leucocyte count	S-Alanine transaminase (ALT)
B-Leucocyte differential count (absolute count)	S-Aspartate transaminase (AST)
B-Platelet count	S-Bilirubin, total
B-Haematocrit	S-Blood urea nitrogen
B-Mean Corpuscular Volume	S-Calcium, total
B-Red blood cell (RBC) count[a]	S-Chloride
	S-Creatinine
Urinalysis (dipstick)	S-Creatinine kinase (CK)
U- Blood	S-CRP
U-Protein	S-Gamma-glutamyl transpeptidase (GGT)
U-Glucose	S-Glucose
U-Microscopy and culture as required[b]	S-Lipid Profile[c]
	S-Phosphorus
	S-Potassium
	S-Sodium
	S-Total Cholesterol
	S-Uric acid

[a] The sponsor personnel involved in the analysis and conduct of the study and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte (both absolute and percentage) values from the central laboratory reports except screening visits (V1 and V2) and any repeat testing that is performed during the screening period and prior to Investigational Product (IP) administration at V3.

[b] Urine sample will be analysed by urine dipstick at site and sent to the central laboratory only for analysis when a positive dipstick result for any parameter is observed.

[c] 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 Friedewal (calculation).

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

8.2.4.1 COVID-19 Entry Screening Questionnaire

A COVID-19 screening questionnaire must be completed via telephone approximately within 72 hours prior to every study visit, regardless of the visit being on-site, at participant's home, or at an alternative location. 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 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 RAVE. 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.

8.2.4.2 SARS-CoV-2 Testing

Laboratory safety variables for SARS-CoV-2 testing are described in Table 13.

At screening visit (V1), sites should perform testing for SARS-CoV-2 in line with local guidelines. Either a nasopharyngeal swab (PCR) test or a rapid antigen test are acceptable. PCR tests should be analysed at the central laboratory. Rapid antigen tests should be analysed locally and the results entered on the eCRF.

SARS-CoV-2 nasopharyngeal swab test and SARS-CoV-2 serology (collected at Visit 3) will be analysed at central laboratory. Instructions for sample collection, processing, storage, and shipment will be included in a separate laboratory manual provided to the sites. SARS-CoV-2 serology data will be used to assess individual AEs but will not be used for subgroup analyses (eg, serology positive/negative).

In case of re-screening due to previous screen failure because of a positive SARS-CoV-2 nasopharyngeal swab (PCR) test, a rapid antigen test should be performed locally at site instead of performing a repeat central laboratory nasopharyngeal swab (PCR) test (as long as this is acceptable with respect to local guidelines).

Table 13 SARS-CoV-2 Laboratory Safety Variables

Laboratory Test	Visit
SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test)	Visit 1
SARS-CoV-2 serology test	Visit 3

Sites should also follow local SARS-CoV-2 testing guidelines outside of CSP study assessments, if applicable.

8.2.4.3 Pregnancy Test

The following tests are applicable to female participants only and will be conducted in accordance with the schedules provided in the SoA.

- Serum ß-human chorionic gonadotropin (ß-HCG) – To be performed for all females at Visit 1 except for those who are NOT of childbearing potential as defined in inclusion criterion 8. This test is to be sent to and analysed at the central laboratory;
- FSH: To be performed at Visit 1 only, for female participants to confirm postmenopausal status in women < 50 years who have been amenorrheic for > 12 months;
- Urine HCG: To be performed at the study site or at home for all females at each treatment visit **before IP** administration using a dipstick except for those females who are NOT of childbearing potential as defined in inclusion criterion 8. A positive urine test result must be confirmed with serum ß-HCG.

8.2.4.4 Serology

Hepatitis B surface antigen, hepatitis C antibody: To be performed only at screening; test to be performed at central laboratory.

HIV-1 and HIV-2 antibodies: To be performed only at screening; test to be performed at central laboratory.

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

8.2.5 Other Safety Assessments

8.2.5.1 Weight and Height

Weight and height will be measured in accordance with schedules provided in the SoA.

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.

8.2.5.2 Asthma Exacerbations (for Asthma/AERD/NSAID-ERD Participants Only)

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

- A temporary bolus/burst of systemic corticosteroids (or a temporary increase in stable OCS background dose) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day burst of systemic corticosteroids.
- An emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care 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.

In addition, participants are required to report any of the following in the eDiary:

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or;
- An additional nebulised β2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or;

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

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

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

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

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

See section 8.3.5 for additional information on recording asthma exacerbations as an AE/SAE during the study.

8.2.5.3 Nasal Polyp Exacerbations

During the study, nasal polyp exacerbation will be defined as a worsening of nasal polyp symptoms that leads to use of systemic corticosteroids or systemic antibiotics for at least 3 consecutive days or requires hospitalisation.

The start of nasal polyp exacerbation is defined as the start date of systemic corticosteroids/systemic antibiotics or hospitalisation whichever is earlier and the end date of nasal polyp exacerbation is defined as the last date of systemic corticosteroids/systemic antibiotics or hospitalisation whichever is later.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

All SAEs will be recorded and reported to AstraZeneca or designee within 24 hours, as

indicated in Appendix B. The Investigator will submit any updated SAE data to AstraZeneca within 24 hours of it being available.

If the investigator becomes aware of a serious adverse event with a suspected causal relationship to the investigational medicinal product 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 serious adverse event 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 events variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum Intensity of the AE
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- 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 (specify the SAE criteria per definition in Appendix B)

- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product 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 investigational product?'

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 of the CSP.

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, vital signs and ECG will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values/vital signs/ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (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).

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

When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. Asthma symptoms or signs, such as wheeze, cough, chest tightness, 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 IP 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 V1) as judged by the Investigator.

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

8.3.6 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 IP. An AESI may be serious or non-serious. For this study, AESIs include:

- Serious hypersensitivity reaction
- Serious infections[1]
- Helminth infections
- Guillain Barre Syndrome
- Malignancy
- Serious cardiac events

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 ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

[1] eCRF 'Infection' pages to be completed for infections which are defined as SAE, or requiring treatment with systemic antiviral medications, intravenous antibiotics, or medications for helminth parasitic infection or requiring a permanent discontinuation of study drug.

8.3.8 Reporting of Serious Adverse Events

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

If any SAE occurs during 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 works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Participant 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 is 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 EDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via a secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

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 Clinical Study Protocol.

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

8.3.9 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 major adverse cardiac events (MACE; defined in the IAC charter), serious cardiac events, and deaths, as well as diagnosis of malignancies that occur from randomisation until the end of the follow-up period. Details on

the adjudication process, including score of adjudication and the committee membership, will be included in the Adjudication Committee Charter/Manual of Operations.

8.3.10 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of worsening signs and/or symptoms of CRSwNP should be considered as disease progression and not an unless they meet protocol defined criteria for NP exacerbation (Section 8.2.5.3). Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.3.11 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of CRSwNP. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet protocol defined thresholds for NP exacerbation (Section 8.2.5.3), SAE criteria or lead to discontinuation of the IMP.

8.3.12 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except 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, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) are considered SAEs.

8.3.12.1 Maternal Exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the 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 Participant Safety data entry site within **1 or 5 calendar days** for SAEs (see Section 8.3.10) 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.

8.3.12.2 Paternal Exposure

Pregnancy of the participant's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 16 weeks (5 half-lives) after the last administration of IP should, 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.

8.3.13 Management of IP-Related Reactions

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

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis to an IP that the participant has not been previously exposed to (such as tezepelumab) is deemed highly likely when Sampson criterion 1 is fulfilled. Sampson criteria 2 and 3 are also listed for completeness:

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 had a pre-assessment (ie, vital signs and lung function) prior to IP administration. At Visits 3 and 5, participants should be observed for a minimum of 2 hours after IP administration for the appearance of any acute drug reactions. For the remaining visits

involving IP administration, participants will be observed for a minimum of 1 hour after IP administration for any such reaction.

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

8.3.14 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 study drug combination product.

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 in the device constituent of a combination product is an inadequacy of the 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 I of the protocol.

The AstraZeneca Clinical Study Medical Device/Device Constituent Report Form and/or Product Complaint Intake Form will be used to collect the deficiency.

8.3.14.1 Time Period for Detecting Medical Device Deficiencies

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

The method of documenting medical device deficiency is provided in Appendix I and the Pharmacy Manual.

8.3.14.2 Follow-up of Medical Device Deficiencies

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

8.3.14.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Only deficiencies associated with the 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 e-mail, 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 8.3.8.

The sponsor will be the contact for the receipt of medical device deficiency reports.

8.3.14.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for 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 I of the CSP.

8.4 Overdose

For this study, any dose of study intervention greater than 280 mg administered within a 2-week period will be considered an overdose.

There is currently no specific antidote in the event of overdose of IP. No specific antidote to tezepelumab is available, so adverse reactions should be treated symptomatically as per local standards.

- 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 Participant Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.1. For other overdoses, reporting must occur within 30 days.

8.4.1 Reporting of Overdose

Refer to Section 8.4 for definition and treatment of overdose.

An overdose with associated AEs is recorded as the AE diagnoses/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 IMP or AstraZeneca non-investigational medicinal product (NIMP) 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 8.4) and **within 30 days** for all other overdoses.

8.4.2 Medication Error, Drug Abuse, and Drug Misuse

8.4.2.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during 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 they become 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 calendar days** (other serious initial and follow-up) if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.8) and **within 30 days** for all other events.

8.4.2.2 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.

8.4.2.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca 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.

8.4.2.4 Drug Misuse

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

8.5 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 date of the last subject's last visit (LSLV) in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic (PK) samples will 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 may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).
- Remaining anti-drug antibody (ADA) sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the LSLV. Additional analyses may be conducted on the anonymised, pooled ADA samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

Serum samples will be collected for measurement of serum concentrations of tezepelumab as specified in the SoA. Serum will be collected pre-dose.

For the PK analysis, it is important that the date and time of each SC injection is recorded for each participant.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded by sites.

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 a 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.

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

A summary of PK concentration results will be reported in the CSR.

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.

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

The immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 15 years following the date of last subject last visit (LSLV) to properly address potential questions from RAs.

8.5.2.1 Anti-drug Antibodies

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

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 (see Section 8.6).

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to participate in the mandatory research components of the study.

- Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA.
- This analysis is required so biological samples can be tested for exploratory analyses to evaluate the effect of tezepelumab on biomarkers of inflammation, recurrence, NP disease, pharmacology of tezepelumab and for potential predictors of clinical responses.
- Whole blood, serum and plasma samples, as well as nasal epithelial lining fluid will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA. Whole blood will be collected for transcriptomic (RNA) profiling. Serum, plasma, and nasal epithelial lining fluid samples will be collected for exploratory biomarker analysis. Results from these exploratory assessments will be blinded to sponsor and sites after the randomisation visit (Visit 3).
- The levels of total immunoglobulin E (IgE) and an assessment for the presence of allergen-specific IgE (IgE FEIA) will be collected at the pre-specified scheduled visits

prior to IP administration (pre-dose) according to the SoA and evaluated by a central laboratory. Results from total serum IgE results will be blinded to sponsor and sites after the randomisation visit (V3).

- Nasal epithelial lining fluid samples will be obtained at the scheduled visits according to the SoA. Nasal epithelial lining fluid biomarkers will be measured to evaluate the pharmacology of tezepelumab and to evaluate changes in biomarkers related to CRSwNP, inflammation and the TSLP pathway. Baseline and early post-dose levels of nasal epithelial lining fluid biomarkers may also be used to explore for potential predictive biomarkers of response or exposure to tezepelumab. The specific biomarkers that may be analysed include but are not limited to cytokines, chemokines and inflammatory mediators associated with CRSwNP and the TSLP pathway. Drug concentrations may also be measured in the nasal epithelial lining fluid samples, if feasible. If appropriate, urea concentrations may be measured to correct for the dilution factor of the nasal lining fluid samples. Results from these exploratory assessments will be blinded to sponsor and sites after randomisation visit (Visit 3).
- In addition, a nasal biopsy sub-study will be conducted at selected sites, for up to approximately 60 participants in total. Nasal biopsies will be collected at V2 (Week -2) and EOT (Week 52) to evaluate the effect of tezepelumab on inflammatory cell infiltrate and gene expression by transcriptomic profiling. At V2, nasal biopsy should be performed after nasal epithelial lining fluid collection and before NPS assessment or CT scan. If nasal biopsy sample cannot be collected at Visit 2, then participant should be withdrawn from nasal biopsy sub-study and can continue on the main study. In this event, NLF collection at Visit 2 and Staph A enterotoxin specific IgE status sample collection at Visit 3 should be not performed. At EOT, nasal biopsy should be performed after NPS assessment, nasal epithelial lining fluid collection, and CT scan. Collection of nasal biopsy sample may be postponed for up to 7 days after EOT visit, only if appropriate kit supplies are not available at the time of EOT visit. Refer to Order of Assessments under Table 1 for more details. Results from these exploratory assessments will be blinded to sponsor and sites after randomisation visit (Visit 3).
- Staph A enterotoxin IgE will only be performed in the nasal biopsy sub-study participants. Staph A bacterial culture from nasal swabs will be collected for all participants and evaluated by a central laboratory. These tests will be performed at the scheduled visits according to the SoA. Results from these exploratory assessments will be blinded to sponsor and sites after randomisation visit (Visit 3).

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

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

For storage, re-use and destruction of biomarker samples see Section 8.6.2.

8.6.2 Storage, Re-use and Destruction of Exploratory Biomarker Samples

AstraZeneca or a designee will retain biomarker samples (including nasal biopsy tissue) for investigation of research NP disease, the pharmacology of tezepelumab and potential predictors of response no longer than 15 years after LSLV or other period as per local requirements.

The results of this biomarker research may be pooled with biomarker data from other studies with the study treatment to generate hypotheses to be tested in future research. Any residual samples may be used for future biomarker research (eg, scientific health-related research). If a participant does not allow samples to be used for future biomarker research, they may continue with their samples being used for the main study.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and consent will be provided via separate ICF.

The blood sample for DNA isolation will be collected from participants who have consented to participate in the genomics initiative. Participation is optional.

Participants who do not wish to participate in the genetic research may still participate in the study. Exploratory genetic samples will be collected in participating countries, except China.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

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

8.7.1 Storage and Destruction of Genetic Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored no longer than 15 years following LSLV or other period as per local requirements, after which they will be destroyed. DNA is a finite resource that may be used up during analyses.

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

For storage and destruction of genetic samples see Appendix D.

8.8 Health Resource Utilisation

Health resource utilisation (HRU) 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 enrolment (V1), HRU information will be collected with a 'one year' recall period. At subsequent visits, HRU information will be collected with a recall period of 'since the last scheduled visit'. Overall, NP-specific and asthma specific HRU data will be collected.

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

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient), including type of surgery performed
- Duration of hospitalisation (total days or length of stay, including duration by wards [eg, intensive care unit])
- Visits
- Type of NP surgery
- Asthma-related and other reason procedures
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient participant medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

Use of systemic corticosteroids (oral, parenteral) for at least 3 days, an emergency room/urgent care visit with use of SCS 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

The co-primary endpoints are the change from baseline in total NPS at Week 52 and the change from baseline in bi-weekly (a 14-day period) mean NCS at Week 52.

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

Endpoint	Null Hypotheses	Alternative Hypotheses	Direction of superiority of tezepelumab is indicated by
Co-primary endpoints			
NPS at Week 52	H01a: Difference in mean change from baseline in NPS at 52 weeks (tezepelumab minus placebo) = 0	H11a: Difference in mean change from baseline in NPS at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
NCS at Week 52	H01b: Difference in mean change from baseline in NCS at 52 weeks (tezepelumab minus placebo) = 0	H11b: Difference in mean change from baseline in NCS at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
Key secondary endpoints			
Loss of smell at Week 52	H02a: Difference in mean change from baseline in loss of smell at 52 weeks (tezepelumab minus placebo) = 0	H12a: Difference in mean change from baseline in loss of smell at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
SNOT-22 at Week 52	H02b: Difference in mean change from baseline in SNOT-22 at 52 weeks (tezepelumab minus placebo) = 0	H12b: Difference in mean change from baseline in SNOT-22 at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
LMK at Week 52	H02c: Difference in mean change from baseline in LMK at 52 weeks (tezepelumab minus placebo) = 0	H12c: Difference in mean change from baseline in LMK score at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
Time to SCS and/or surgery decision up to Week 52	H02d: HR of time to first SCS and/or surgery decision (tezepelumab/placebo) = 1	H12d: HR of time to first SCS and/or surgery decision (tezepelumab/placebo) ≠ 1	A HR less than 1.
Time to surgery decision up to Week 52	H03: HR of time to first surgery decision (tezepelumab/ placebo) = 1	H13: HR of time to first surgery decision (tezepelumab/placebo) ≠ 1	A HR less than 1.

Endpoint	Null Hypotheses	Alternative Hypotheses	Direction of superiority of tezepelumab is indicated by
Time to SCS up to Week 52	H04: HR of time to first SCS (tezepelumab/placebo) = 1	H14: HR of time to first SCS (tezepelumab/placebo) ≠ 1	A HR less than 1.
NPSD TSS	H05: Difference in mean change from baseline in NPSD TSS at 52 weeks (tezepelumab minus placebo) = 0	H15: Difference in mean change from baseline in NPSD TSS at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means less than 0.
FEV_1 at Week 52 Subset of participants with co-morbid asthma /AERD/ NSAID-ERD	H06: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) = 0	H16: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) ≠ 0	A difference in means greater than 0.

BD bronchodilator; $FEV_{1\ forced}$ exhalation volume in 1 second; LMK Lund-MacKay score; NPS nasal polyp score; NCS nasal congestion score; SCS systemic corticosteroids; SNOT-22 SinoNasal outcome test.

Testing strategy for confirmatory endpoints

The overall type I error rate will be strongly controlled at the 0.05 level across primary and key secondary endpoints. The NPS and NCS are co-primary endpoints and, as such, both primary endpoints will be tested at the 5% level to determine the success of the study. If both are significant at 5%, then testing will proceed to the key secondary endpoints.

The following hierarchical testing strategy will be applied:

Level 1

The null hypotheses H01a and H01b (for endpoints NPS and NCS at Week 52) will be tested at a 2-sided 5% significance level

Level 2

If both H01a and H01b are rejected at the 2-sided 5% significance level, then the null hypotheses H02a, H02b, H02c, and H02d will be tested using the truncated Holm procedure (truncation parameter gamma = 0.8) at an overall 2-sided 5% significance level for endpoints:

- Change from baseline in loss of smell at Week 52
- Change from baseline in SNOT-22 at Week 52

- Change from baseline in LMK at Week 52
- Time to SCS and/or surgery decision for NP up to Week 52

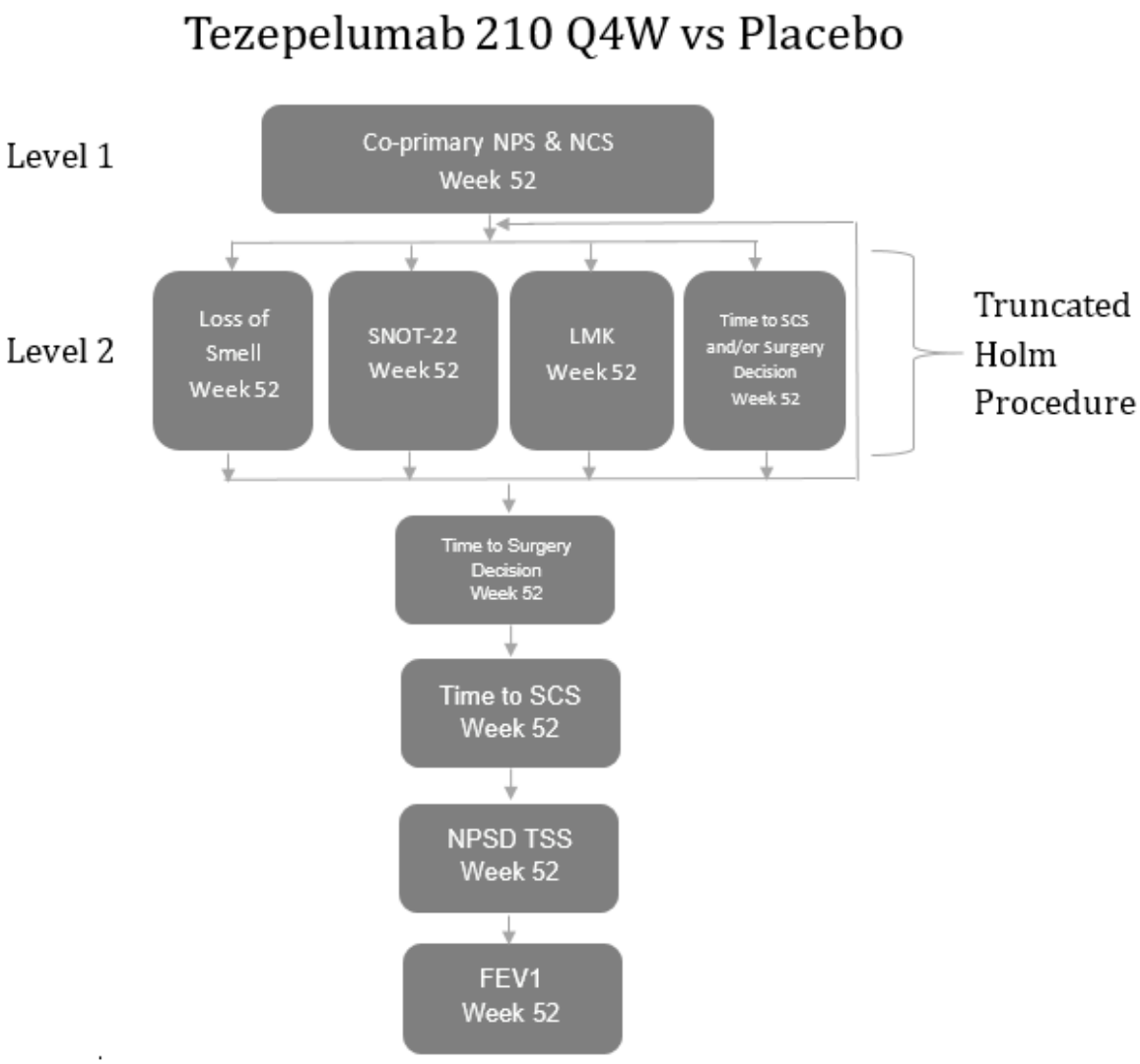
Under this approach, the 4 p-values are first ordered from smallest to the largest. If the smallest p-values (2-sided) within level 2 is < 0.0125, the treatment effect for the endpoint associated with this p-value is considered significant. The test then evaluates the next smallest p-value at (0.05 + 0.8/3)*5% significance level (2-sided) and if significant, the third smallest at (0.05 + 0.8/2)*5% significance level (2-sided), and if significant, the fourth at (0.05 + 0.8)*5% significance level (2-sided). If none of the level 2 hypotheses are rejected, the procedure will stop.

Level 3 - 6

If one, two, three, or four of H02a, H02b, H02c, and H02d are rejected the null hypotheses H03, H04, H05, and H06 will be tested in a sequential order at 0.25%, 0.5%, 0.75%, or 5% significance level (2-sided), respectively.

The testing procedure is summarised graphically in Figure 4. For the US FDA, the described testing procedure will be applied to the US FDA primary estimand described in Section 9.4.1.2.

Figure 4 Testing Procedure



FEV1, forced expiratory volume in 1 second; LMK, Lund-Mackay score; NCS, nasal congestion score; NPSD, nasal polyp symptom diary; NPS, nasal polyp score; Q4W, every four weeks; SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test, 22 item; TSS, total nasal symptom score.

9.2 Sample Size Determination

Approximately 400 participants will be randomised to tezepelumab 210 mg Q4W or matching placebo in a 1:1 ratio.

The study is sized to provide compelling statistical evidence for the co-primary endpoints (NPS and NCS) and key secondary endpoints of change from baseline in loss of smell, LMK, and SNOT-22 (considering a significance level of 0.01 in the sample size calculations), as well as sufficient power to assess the composite endpoint of time to SCS and/or surgery (2-sided level of 1%). In addition, this sample size allows assessment of the effect of tezepelumab vs placebo on NPS and NCS in key subgroups and provides a reasonably-sized safety database.

Assuming a population standard deviation (SD) of 2.25 in total NPS change from baseline and 1.22 in NCS change from baseline, this sample size of 200 participants per arm will provide at least 95% total power to observe a statistically significant difference at a 2-sided 1% level on both co-primary endpoints if the true effect of tezepelumab is -1.8 in total NPS change from baseline and -0.87 in NCS change from baseline. The assumption of true effects is based on reported estimates in the dupilumab Phase III nasal polyp studies. It is expected that treatment with tezepelumab will demonstrate similar or better treatment effects over a 52-week period. The assumed SD was estimated based on the CIs of the corresponding endpoints in the dupilumab Phase III nasal polyp studies (Bachert et al 2019).

Two hundred participants per arm also provides at least 95% power to detect a statistically significant difference at a 2-sided 1% level in secondary endpoints of change from baseline in loss of smell LMK, and SNOT-22 (assuming mean [SD] of -1 [1.3], -5 [5.45], and -17.4 [26.8], respectively). The size of the study also provides at least 95% power to detect a statistically significant difference at the 2-sided 1% level in the key secondary endpoint time to SCS and/or decision of surgery for NP, assuming a true reduction in risk of 67% (hazard ratio [HR] of 0.33) with a placebo rate at Week 52 of 35% (placebo data estimated from dupilumab SINUS-52). In addition, this provides at least 80% power to detect a difference (at a nominal 5% significance level) in the key secondary endpoint of time to decision of surgery, assuming a true HR of 0.33 and a placebo rate at Week 52 of 11% (placebo data estimated from pooled dupilumab studies SINUS-24 and SINUS-52). Assuming 50-70% of participants will have co-morbid asthma, the sample size will also provide > 80% power for the co-primary endpoints at a 2-sided 5% significance level in the co-morbid asthma subgroups.

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 informed consent form (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 IMP, irrespective of their protocol adherence and continued participation in the study.
Safety Set	All participants who received at least one dose of IMP.
Pharmacokinetic analysis set (PK)	All participants in the FAS who received active (tezepelumab) treatment and had at least one detectable tezepelumab serum concentration from a sample collected post-treatment that is assumed not to be affected by factors such as protocol deviations (PDs).

Efficacy analyses will be based on the FAS (defined above) according to their randomised treatment.

Safety analyses and anti-drug antibodies (ADA) analyses 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 SAP. Any important deviations from the randomised treatment assignment, and any participants that have received investigational product 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

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before primary database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses. Any deviations from this plan will be reported in the clinical study report. Additional analyses assessing the impact of COVID-19 will be included in the SAP, as needed.

9.4.1 General Considerations

There will be 2 database locks (DBLs) in this study. The primary DBL will be conducted after the last participant completes Week 52, and the final DBL will be conducted once the last participant has completed the last safety follow-up visit (Week 76 for the first 200 participants

completing the treatment period and Week 64 for the remaining participants). All analyses of the primary and key secondary endpoints will be performed based on the primary DBL data.

All personnel involved with the analysis and conduct of the study will remain blinded until primary database lock and important protocol deviations during the double-blind treatment period identified.

After primary DBL, treatment allocation for participants during this study will become known to the Sponsor staff and/or designated CRO. The blind will be maintained for the Investigator, investigational site staff, and for the participant. Frequency and percentages of participant disposition and reasons for discontinuation of IP will be presented. 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 participant reporting usage.

Important protocol deviations during the double-blind treatment period will be defined prior to unblinding and will be summarised by treatment group. The definitions of each category of important protocol deviation will be specified in the study Non-Compliance Handling Plan, and will include (but may not be limited to): participants who were randomised to study treatment without fulfilling key entry criteria; participants who received prohibited or restricted concomitant medications, participants who received the incorrect study treatment or study dose at any time during the 52-week double-blind treatment period.

9.4.1.1 Primary Estimand

The primary estimand is described as follows:

- **Treatment:** Randomised treatment of tezepelumab 210 mg Q4W or placebo
- **Population of interest:** Adult participants with severe CRSwNP (total NPS ≥ 5) and an inadequate response to standard of care therapy, based on their randomised treatment and receiving at least one dose of IP
- **Endpoints of interest:** Change from baseline in co-primary endpoints: NPS and bi-weekly mean NCS at Week 52.
- **Population level summary for the endpoint:** Difference in means between tezepelumab and placebo treatment groups
- **Handling of intercurrent events (ICEs):**
  - **Nasal polyp surgery:** The participants who had nasal polyp surgery during the study conduct would be considered poor outcome. The composite variable strategy will be applied where the worst possible score (ie, 8 for NPS and 3 for NCS) will be used for the post-surgery scores.
  - **SCS for NP:** The participants who received SCS (at least 3 consecutive days of OCS or equivalent 1 intramuscular injection) for NP would be considered poor outcome but less severe than surgery. The composite variable strategy will be applied where the worst observation prior to the SCS will be carried forward (WOCF) for the post-SCS scores.
  - **Treatment discontinuation:** The treatment policy strategy will be applied. Data collected for participants who do not have rescue therapy are used regardless of whether treatment discontinuation occurs.
  - **Adherence to background MFNS or an equivalent INCS and IP:** The treatment policy strategy will be applied. Data collected for participants who do not have rescue NP surgery or SCS are used regardless of the adherence of background MFNS or an equivalent INCS and IP.
  - **Biologic use for NP:** The participants who received another biologic for NP would be considered poor outcome but less severe than surgery. The composite variable strategy will be applied where the worst observation prior to the biologic for NP will be carried forward (WOCF) for the post-biologic scores.
  - **Steroids or biologic use for co-morbid conditions:** The treatment policy strategy will be applied for the participants who received steroids or another biologic for co-morbid conditions.
  - **COVID-19 related:** intercurrent events caused by COVID-19 including protocol deviations caused by COVID-19, COVID vaccination, and COVID-19 infection. The treatment policy strategy will be applied.

9.4.1.2 US FDA Primary Estimand

Following the US FDA Chronic Rhinosinusitis with Nasal Polyps: Developing Drugs for Treatment Guidance for Industry (FDA 2023), different strategies will be used for the ICEs of SCS rescue for NP and biologic use for NP.

- **SCS for NP:** The treatment policy strategy will be applied and data after SCS rescue will be included in the analysis.
- **Biologic use for NP:** The composite variable strategy will be applied where the worst possible score (ie, 8 for NPS and 3 for NCS) will be used for the post-biologic scores.

9.4.1.3 Supplementary Estimand

Composite variable strategy will be used for SCS for NP, biologic use for NP, and treatment discontinuation: the worst possible score will be used after the ICEs.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

For the primary estimand, data collected after surgery will be replaced with the worst possible score. Data collected after SCS will be replaced with the worst observation prior to the SCS (WOCF). Data collected after treatment discontinuation without surgery or SCS will be included in the analysis. For participants whose post-baseline data are all missing, the baseline value will be used in the analysis. For participants who discontinue the study without surgery or SCS, multiple imputation will be used to impute missing data assuming missing at random (MAR).

Each of the imputed datasets will be analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate, and treatment group, baseline co-morbid asthma/AERD/NSAID-ERD status, prior surgery status, and regions as factors. Rubin's rule will be applied to combine analysis results (point estimates and standard errors) from the imputed datasets. Descriptive statistics including number of participants, mean, standard error, and least squares (LS) means will be provided for each time point. In addition, difference in LS means and the corresponding 95% confidence intervals (CIs) will be provided along with the p-values.

For the FDA and supplementary estimands, strategies for the ICEs are described in Sections 9.4.1.2 and 9.4.1.3 and will be applied accordingly. Additional sensitivity analyses will be performed to examine the MAR assumptions about missing data. Details of the supplementary and sensitivity analyses will be included in the SAP.

Subgroup analyses

For the purpose of exploring consistency of treatment effect across subgroups, a similar model will be fitted as for the primary analysis with additional factors for the relevant subgroup variable and its interaction with treatment. Key subgroups include:

- Age
- Gender
- Race
- Prior surgery status
- Allergic rhinitis
- Co-morbid asthma status
- AERD/NSAID-ERD
- Baseline eosinophil count
- Body mass index
- Region

9.4.2.2 Secondary Endpoint(s)

The analyses of the key secondary endpoints are described as follows:

The change from baseline in LMK, SNOT-22, loss of smell, and NPSD TSS at Week 52 will be analysed using the method as described in the primary analyses approach for the co-primary endpoints.

Time to first decision of surgery or SCS for NP during the 52-week treatment period will be analysed using a Cox proportional hazards model, adjusting for treatment, baseline co-morbid asthma/AERD/NSAID-ERD status, prior surgery status, and regions. The event of interest is the first SCS use or decision for nasal polyp surgery, whichever is earlier if both occur. Hazard ratios and corresponding 95% CIs and p-values will be presented. The proportion of participants having a surgery decision or SCS up to Week 52 will be estimated using the Kaplan-Meier method. The same method will be used to analyse the time to first surgery decision and time to first SCS separately.

Analysis of the change from baseline in FEV1 at Week 52 will use a treatment policy for all intercurrent events defined in Section 9.4.1.1. The population of interest will be the subset of participants with baseline co-morbid asthma/AERD/NSAID-ERD. The model includes baseline value of FEV1 as a covariate and treatment, prior surgery status, and regions as factors.

Details on statistical analyses for other secondary endpoints, including the tezepelumab serum

concentration and ADA for the evaluation of PK and immunogenicity, will be provided in the SAP.

9.4.3 Safety

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

The number and percentage of participants with on treatment and post-treatment adverse events will be tabulated separately by preferred term and system organ class. An event that occurred one or more times during a period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all participants in the safety population. On treatment adverse events 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. Adverse events, SAEs, AEs leading to death, and AEs leading to discontinuation of IP 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.

AEs of Special Interest (AESIs), as defined in Section 8.3.6 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). The incidence of clinically notable laboratory abnormalities will be summarised.

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. Abnormal ECGs as per Investigator's overall interpretation will be summarised.

9.4.4 Other Analyses

Biomarker and selected exploratory endpoint analysis details will be described in the exploratory analysis plan, which will be finalised before primary database lock. The results may be reported outside the CSR. Analyses for other exploratory endpoints will be detailed 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 ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, Investigator Brochure, 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 revised 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 Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca 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.
- AstraZeneca 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the [Investigator's Brochure or state other documents] 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 (e-mail 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 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant 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.
- If a participant's partner becomes pregnant from the date of the first administration of IP until 16 weeks after the last administration of IP, the partner is asked to sign the Adult Study Informed Consent Form for Pregnant Partners of Study Participant and provide information about the pregnancy accordingly.

Participants who are rescreened 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 AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca 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.
- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[2] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

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

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

[2]The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Participant Safety. Issues identified will be

addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov 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 on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or 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.
- Monitoring details describing strategy, including definition of study critical data items and processes (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.
- AstraZeneca 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. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) 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 a minimum of 25 years after study archiving or as required by local regulation, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

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 reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the monitoring plan.

A 9 Study and Site Start and Closure

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

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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

B 1 Definition of adverse events

An 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 treatment has been administered.

B 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality 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-SAE**. 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 emergency room 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 emergency room 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 assessing 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, and 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** intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

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

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

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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 IMP or AstraZeneca 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 involves 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)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the 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 to facilitate assault in another person
- The drug is deliberately administered by the wrong route

- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- 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 or destroyed according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

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

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 organization(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 documented, and study site notified.

C 3 International Airline Transportation Association (IATA) 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 UN3373 and IATA 650

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA analysis from consenting participants.

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tezepelumab continues but no longer than 15 years after LSLV or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic 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-leucocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main Clinical Study Protocol.

Collection of samples for genetic research

- The blood sample for this genetic research will be obtained from the participants at the Randomisation Visit. 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 the Randomisation Visit, 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 date of last subject last visit or may differ depending on local retention, 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 genetic research component, are outlined in Appendix A.

Informed consent

- The genetic component of this study is optional, and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic 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 Principal Investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal 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, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research

purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

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

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

E 1 Introduction

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

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 Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

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

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

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 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the participant's condition
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which the tests available in the Hy's Law lab kit should be used.
  - Complete the 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 total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the study physician if there is any uncertainty.

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

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

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

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

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for 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 Potential Hy's Law 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 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that

there is no alternative explanation until such time as an informed decision can be made:

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

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 IgM and IgG anti-HBc HBsAg HBV DNA [a] IgG anti-HCV HCV RNA [a] 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) [b]
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 [b] Transferrin saturation

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive
[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 7 References

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

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

Appendix F Anaphylaxis: signs and symptoms, management

F 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 F 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix F 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognise and treat anaphylaxis according to local guidelines. If an anaphylactic reaction occurs, a blood sample will be drawn from the participant as soon as possible after the event, at 60 minutes ± 30 minutes after the event, and at discharge for analysis of serum tryptase.

F 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

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

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

   AND AT LEAST ONE OF THE FOLLOWING

   (a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, 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

Immune Complex Disease

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

F 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal 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

F 4 Management of Acute Anaphylaxis

Immediate intervention

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

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

Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place participant in recumbent position and elevate lower extremities.
(b) Establish and maintain airway.
(c) Administer oxygen.
(d) Establish venous access.
(e) Normal saline IV for fluid replacement.

Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.
(b) Consider H1 and H2 antihistamines.
(c) Consider nebulised β2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.
(d) Consider systemic corticosteroids.
(e) Consider vasopressor (eg, dopamine).
(f) Consider glucagon for participant taking β-blocker.
(g) Consider atropine for symptomatic bradycardia.
(h) Consider transportation to an emergency department or an intensive care facility.
(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

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

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.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-drug antibodies
ADE	Adverse Device Effect
AE	Adverse Event
AERD	Aspirin exacerbated respiratory disease
AAER	Annualised asthma exacerbation rate
AESI	Adverse Event of Significant Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APFS	Accessorised pre-filled syringe
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BD	Bronchodilator
BP	Blood Pressure
BP	Bodily Pain (in SF-36v2 scale only)
BUN	Blood urea nitrogen
CDC	The Centers for Disease Control and Prevention
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CRF	Case Report Form
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTIS	Clinical Trials Information System
DBL	Database Lock
DCO	Data Cut Off
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EMA	European Medical Agency
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
ER	Emergency Room
ERS	European Respiratory Society
EU	European Union
EUA	Emergency Use Authorisation
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FEF	Forced Expiratory Flow
FeNO	Fractional Exhaled Nitric Oxide
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating Hormone
FSI	First Participant In
FU	Follow-up
FUD	Follow-Up Discontinuation Visit
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBS	Human Biological Sample
HCG	Human Chorionic Gonadotropin
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life

Abbreviation or special term	Explanation
HRU	Healthcare Resource Utilisation
IATA	International Airline Transportation Association
IB	Investigator's Brochure
IAC	Independent Adjudication Committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
ILC2	Group 2 Innate lymphoid cells
IMP	Investigational Medicinal Product
INCS	Intranasal corticosteroids
IP	Investigational product
IPD	Investigation Product Discontinuation
IRC	Independent Review Charter
ISF	Investigator Study File
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Integrated Web Response System
JESREC	Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis Classification
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LMK	Lund-Mackay score
LS	Least Squares
LSLV	Last Participant Last Visit
LTRA	Leukotriene Receptor Antagonists
mAb	Monoclonal Antibody
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MCID	Minimal Clinical Importance Difference
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	Mometasone Furoate Nasal Spray
MoA	Mechanism of Action
nAb	Neutralising Antibody
NC	Nasal Congestion

Abbreviation or special term	Explanation
NCS	Nasal Congestion Score
NIMP	Non-Investigational Medicinal Product
NP	Nasal polyposis
NPIF	Nasal peak inspiratory flow
NPS	Nasal polyp score
NPSD	Nasal Polyp Symptom Diary
NPSSA	Nasal Polyposis Symptom Screening Assessment
NSAID-ERD	Nonsteroidal anti-inflammatory drug exacerbated respiratory disease
OCS	Oral Corticosteroids
PCD	Primary Ciliary Dyskinesia
PCR	Polymerase Chain Reaction
PD	Protocol Deviation
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PNV	Predicted Normal Values
PRO	Patient reported outcome
PSSR	Project Specific Safety Requirements
Q4W	Every four weeks
QD	Once a day
RA	Regulatory Authority
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SABA	Short-Acting Beta-Agonist
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SF-36v2	Short-Form 36-Item Health Survey Version 2
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOP	Standard Operating Procedure

Abbreviation or special term	Explanation
SC	Subcutaneously
SCS	Systemic corticosteroids
SNOT-22	Sino-Nasal Outcome Test, 22 item
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA	Therapeutic Area
TBL	Total Bilirubin
TSLP	Thymic stromal lymphopoietin
TSS	Total Nasal Symptom Score
ULN	Upper Limit of Normal
UPSIT	University of Pennsylvania Smell Identification Test
USADE	Unanticipated Serious Adverse Device Effect
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential
WOCF	Worst Observation Prior to the SCS Carried Forward
WPAI	Work Productivity and Activity Impairment
w/v	Weight per volume

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

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

H 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 H 2 to H 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.

H 2 Re-screening of Participants to Reconfirm Study Eligibility

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

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

H 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site will visit the participants home/or other remote location as per local 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.

H 4 Telemedicine Visit to Replace On-site Visit (where applicable)

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

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

H 5 At home or Remote Location IP Administration Instructions

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

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

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

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

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

H 6 Data Capture During Telemedicine or Home/Remote Visits

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

Appendix I 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 8.3.14.
- 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.
- For simplicity, medical device will be used to cover device constituent parts of combination products and standalone medical device whether investigational or approved.

I 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of 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 medical devices.
- An adverse device effect (ADE) is defined as an AE related to the use of an 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 medical device.

I 2 Definition of Medical Device SAE, SADE and USADE

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

a. Led to death

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

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalisation. Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

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

A Medical Device SADE 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)

I 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 issues with information supplied by the manufacturer.

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

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

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

- Mild (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)

Other measures to evaluate AEs and SAEs may be used (eg, National Cancer Institute CTCAE)

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.
- 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 postmortem 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.

I 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 8.3.8.

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

- Any medical device deficiency that is associated with an SAE must be reported to AstraZeneca **within 24 hours** after the investigator determines that the event meets the definition of a medical device deficiency.
- In addition to the reporting process described in Section 8.3.8, the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form will be used to capture details of the device and related deficiency.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

Appendix J Summary of Changes

Amendment v5.0 17-Oct-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 and in the EU Clinical Trial Regulation Article 2, 2 (13) because it significantly impacts the safety or physical/mental integrity of participants and the scientific value of the study.

Overall Rational for the Modification:

This Clinical Study Protocol has been amended to update the nasal polyp surgery endpoint, and to align the risk assessments with the updated Investigator Brochure edition 5.1, and to add assessment of pre-specified events by an Independent Event Adjudication Committee to the study design.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Protocol title page and Section 1.1 Synopsis	Added EudraCT/EU CT Number, clinicaltrials.gov Number and Study Physician details	To align with regulatory requirements related to Clinical Trial Transparency (CTT) language.	Non-substantial
1.1 Key Secondary Objectives	Time to surgery and/or SCS for NP up to Week 52 updated to Time to surgery decision and/or SCS for NP up to Week 52 Time to NP surgery up to Week 52 updated to Time to NP surgery decision up to Week 52	Change to use the date of decision for NP surgery as this indicates when NP surgery is judged necessary and is not impacted by logistical issues and the backlog of surgeries, due to COVID-19 pandemic, which can be inconsistent across the sites/countries.	Substantial
1.1 Overall Design	Added “randomised” and removed “that complete the 52 week treatment” as well as updated “the remaining participants” to the follow-up groups	To clarify that the first 200 participants randomised should have a 24-week follow-up period, and the remaining participants will have a 12-week follow-up.	Non-substantial
1.1 Overall Design	Added independent adjudication committee details	To adopt a uniform approach to independently review the diagnosis and causality assessments by the investigator.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 Schedule of Activities: Visit Window 7.1.1 Procedures for Discontinuation of Study	Updated the Treatment window from ± 3 days to ± 5 days and the Follow-Up window from ± 5 days to ± 7 days	To align with other clinical study protocols within the programme and to minimise the occurrence of out of window visits.	Non-substantial
1.3 Schedule of Activities: Removed asthma exacerbations	Removed the assessment of asthma exacerbations	Removed this as an assessment, since this information is being collected as AEs.	Non-substantial
1.3 Schedule of Activities: Table 1 subpoint C	Removed "who complete the 52 week treatment"	To clarify that the first approximately 200 participants randomised should have a 24-week follow-up period, even if they did not complete the 52-week treatment.	Non-substantial
1.3 Schedule of Activities: Table 1 subpoint D	Updated to "the remaining, approximately 200 participants"	To clarify that the remaining participants will have a 12-week follow-up period.	Non-substantial
1.3 Schedule of Activities: Table 1 subpoint T	Added "For IPD (for any reason), only do a CT scan if at least 12 weeks since the V2 CT scan"	To avoid repeat radiation exposure. It is unlikely to observe a change in disease < 12 weeks.	Non-substantial
2.3.1 Risk Assessment: Table 2	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, serious hypersensitivity reactions and COVID-19 updated.	To align with the updated Investigator's Brochure edition 5.1. The rationale for each risk is included in Table 2.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
2.3.3 Overall Benefit: Risk Conclusion	Updated table to include a new category of "Important potential risks" including serious infections, malignancies, and serious cardiac events. The "Potential risks of clinical significance" was updated to "Potential risks" and text on risk of serious infections and serious hypersensitivity reasons updated.	Updated to include the new important potential risks as per the updated Investigator's Brochure edition 5.1.	Substantial
3.0 Objectives and Endpoints: Table 3	Time to surgery and/or SCS for NP up to Week 52 updated to Time to surgery decision and/or SCS for NP up to Week 52 Time to NP surgery up to Week 52 updated to Time to NP surgery decision up to Week 52	Change to use the date of decision for NP surgery as this indicates when NP surgery is judged necessary and is not impacted by logistical issues which can be inconsistent across the sites/countries.	Substantial
4.1 Overall Design	Removed "that complete the 52 week treatment" as well as updated "the remaining participants" to the follow-up groups Updated to include Independent Event Adjudication to the study Updated "worsening of nasal polyp symptoms" to "nasal polyp exacerbation"	To clarify that the first approximately 200 participants randomised should have a 24-week follow-up period, and the remaining participants will have a 12-week follow-up. To adopt a uniform approach to independently review the diagnosis and causality assessments by the investigator. Updated to nasal polyp exacerbations since it is now defined in the protocol.	Non-substantial
4.2 Scientific Rationale for Study Design	Removed "who complete the 52 week treatment".	To clarify that the first 200 participants randomised should have a 24-week follow-up period.	Non-substantial
5.1 Inclusion Criteria #15	Updated from "in Version 4.0" to "in a prior version"	Updated to clarify EC#15 in subsequent protocol versions.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
5.2 Exclusion Criteria #17	Updated COVID-19 testing requirements to "Evaluation will be based on local standard of care as determined by current local guidelines"	Updated to reflect real world practice and to be less burdensome for sites.	Non-substantial
5.3.3 Activity	Removed "Participants may participant in light recreational activities during the study (eg, watching television, reading)"	Determined this language was misleading and not necessary.	Non-substantial
6.1.1 Investigational Products: Table 4	Added "combination product" to Type	To reflect the most recent updates made to the Investigator's Brochure edition 5.1.	Non-substantial
6.1.2 Medical Devices	Updated section title to Medical Devices Including Combination Products with a Device Constituent Updated to "combination product which includes a device constituent"	To be aligned with International Organization for Standardization 14155 (edition 3) and European Medical Device Regulation.	Non-substantial
6.2.2 Dose Preparation	Replaced "adequately" with "in the original carton"	To clarify the requirements for dose preparation.	Non-substantial
6.4 Concomitant Therapy: Table 5	Added that allergen immunotherapy "Should not be administered on the same day as study intervention administration"	To align with the updated Investigator's Brochure edition 5.1.	Non-substantial
7.1.1 Procedures for Discontinuation of Study Treatment	Added "scan if at least 12 weeks passed since the baseline CT scan"	To avoid repeat radiation exposure, and unlikely to observe a change in disease < 12 weeks.	Non-substantial
7.2.1 Withdrawal Due to Recruitment Completion in a Randomised Stratum	Added "screening period who are assigned to the" completed stratum.	To clarify that participants in screening that are assigned to a completed stratum will be screen failed from the study, as they are still in screening.	Non-substantial
8.0 Study Assessments and Procedures	Added language that collection and handling of HBS will be outlined in the laboratory manual	To clarify that specific details for handling and collecting HBS will be in the laboratory manual.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.1.3 Sinus Computed Tomography	Updated to only do CT scan if at least 12 weeks passed since the baseline CT	To avoid repeat radiation exposure, and unlikely to observe a change in disease < 12 weeks.	Non-substantial
8.1.4 Post-randomisation Nasal Polyp Surgery and/or SCS Use	Added “decision” date to NPS surgery. Added “as agreed jointly both by the participant and the investigator”	To clarify that the date for decision to surgery is jointly by the Investigator and participant.	Non-substantial
8.2.4 Clinical Safety Laboratory Assessments: Table 12 and subpoints A and C	Added “S-Lipid Profile” Updated language in footnote “a” Added footnote “c” to detail the tests included in the Lipid Profile.	To assess participant lipid profile for a better understanding of participant's risk for cardiovascular disorder.	Substantial
8.2.4.2 SARS-CoV-2 Testing	Added guidance to perform SARS-CoV-2 testing as per local guidelines	Updated to reflect real world practice and to be less burdensome for sites.	Non-substantial
8.2.4.3 Pregnancy Test	Added “or at home”	To clarify that the Urine HCG test should be collected on-site or at home if the IP administration visit takes place at home.	Non-substantial
8.2.5.3 Nasal Polyp Exacerbations	Section added to provide nasal polyp exacerbation definition	To clarify nasal poly exacerbation definition.	Non-substantial
8.3.6 Adverse Events of Special Interest	Re-organised and added “serious cardiac events” and “including opportunistic infections” Added footnote “a” for the eCRF Severe Infection pages to be completed	To align with the updated Investigator’s Brochure edition 5.1.	Substantial
8.3.9 Independent Adjudication Committee	Added Independent Adjudication Committee section	To adopt a uniform approach to independently review the diagnosis and causality assessments by the investigator.	Substantial
8.3.10 Disease Progression	Added Disease Progression section	Updated to clarify definition of disease under study progress as per updated SOP.	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.3.11 Disease Under Study	Added Disease Under Study section	Updated to clarify reporting of disease under study progress as per updated SOP.	Non-Substantial
8.3.14 Medical Device Deficiencies	Updated language on how to properly report medical device deficiencies, and that they will be not be reported in the CSR, but as required per local regulations.	To align with the updated processes as outlined in the SOP for medical device deficiencies, AEs, and SAEs.	Non-substantial
8.4.1 Reporting of Overdose Appendix B	Added definition and timelines for reporting overdose. Also ensure information aligned with Appendix B.	To align with EU regulatory trials regulations.	Non-substantial
8.4.2 Medication Error, Drug Abuse, and Drug Misuse 8.4.2.1 Timelines 8.4.2.2 Medication Error 8.4.2.3 Drug Abuse 8.4.2.4 Drug Misuse Appendix B4	Added definition and timelines for reporting drug misuse and abuse. Also ensure information aligned with Appendix B with updated title.	To align with EU regulatory trials regulations.	Non-substantial
9.1 Statistical Hypothesis	Added “decision” to NP Surgery endpoint.	To align with the key secondary endpoints.	Non-Substantial
9.2 Sample Size Determination	Added “decision” to NP Surgery endpoint.	To align with the key secondary endpoints.	Non-substantial
9.4.2.2 Secondary Endpoints	Added “decision” to NP Surgery endpoint.	To align with the key secondary endpoints.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix A1	Added language relating to the investigator requirements for oversight and conduct of the study Added language for regulatory reporting requirements for serious breaches	To align with EU regulatory trials regulations.	Non-substantial
Appendix A4	Added additional language for data protection	To align with EU regulatory trials regulations.	Non-substantial
Appendix B2	Added additional language relating to AE reporting of malignancies	Updated to clarify safety reporting as per updated SOPs	Non-substantial
Appendix I Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device/Device Constituent Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up I2 Definition of Medical Device SAE, SADE and USADE I3 Definition of Medical Device Deficiency I5 Reporting of Medical Device SAEs and SADEs	Added “Device Constituent” to appendix title Added definitions and details outlining the reporting for SAEs and SADEs as well as assessment of intensity	To be aligned with International Organization for Standardization 14155 and European Medical Device Regulation.	Non-substantial
I3 Definition of Medical Device Deficiency	Added “issues with” to the Medical Devices Deficiency Definition	To correct an error of omission in the previous CSP version.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix G Abbreviations	Updated the table of abbreviations	To ensure relevant abbreviations have been included as seen throughout the protocol.	
Appendix J Summary of Changes	Relocated the previous Summary of Changes to a new appendix.	To ensure the most relevant information is at the beginning of the protocol.	Non-substantial
Typographical and grammatical corrections have been made to this Clinical Study Protocol.			

Amendment v4.0 28-Jan-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 because it impacts the safety or physical/mental integrity of participants and the scientific value of the study.

Overall Rationale for the Amendment:

This Clinical Study Protocol has been amended to update the Co-primary, key secondary and other secondary endpoints and also to update inclusion Criterion 15 for bi-weekly mean NCS instead of NCS on the day of randomisation visit. APFS device malfunction, Medical device deficiencies, Appendix I Medical Device AEs were added to align with International Organization for Standardization 14155 and European Medical Device Regulation.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 – Synopsis (Objectives and Endpoints)	Co-primary endpoint updated: "Change from baseline in NCS evaluated as part of…NPSD at Week 52" changed to "Change from baseline in bi-weekly mean Nasal Congestion Score (NCS) evaluated as part of …NPSD at Week 52."	To ensure correct evaluation of NCS between baseline and Week 52.	Substantial
Section 1.1 – Synopsis (Objectives and Endpoints)	Key secondary endpoint updated: "Change from baseline in loss of smell evaluated as part of…NPSD at Week 52" to "Change from baseline in bi-weekly mean loss of smell evaluated as part of…NPSD at Week 52."	To ensure correct evaluation of participant loss of smell between baseline and Week 52.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 – Synopsis (Objectives and Endpoints)	Key secondary endpoint updated: "Change from baseline in NPSD TSS at Week 52" to "Change from baseline in bi-weekly mean NPSD TSS at Week 52."	To ensure correct evaluation of NPSD TSS between baseline and Week 52.	Substantial
Section 1.1 – Synopsis (Objectives and Endpoints)	Other secondary endpoint updated: "Change from baseline over time in NCS evaluated as part of NPSD through Week 52" to "Change from baseline over time in bi-weekly mean NCS evaluated as part of NPSD through Week 52."	To ensure correct evaluation of NCS from baseline through Week 52.	Substantial
Section 1.3 – Table 1: Schedule of Activities	Footnote h updated to state that "subjects, sites and Sponsor will be unblinded to FeNO values prior to randomisation and blinded to FeNO post randomisation"	To clarify FeNO blinding procedures for subjects, sites and sponsor.	Non-substantial
Section 2.1 – Study Rationale	Added reference "Phase 3 NAVIGATOR study" in asthma patients showed that tezepelumab benefited participants with low and high baseline eosinophil counts and a low and high baseline T2 profile.	To include analysis findings from Phase 3 study.	Non-substantial
Section 2.1 – Study Rationale	Added Journal Article reference "Emson C et al. 2021"	To include findings which support the rationale of a broad effect of tezepelumab in asthma and potential efficacy in Chronic rhinosinusitis with nasal polyps (CRSwNP).	Non-substantial
Section 2.3.1 – Table 2	Removed the word "important" from Potential Risks of tezepelumab	To align with Investigator's Brochure Edition 5.0 (dated 21Oct2021).	Non-substantial
Section 2.3.3 – Overall Benefit: Risk Conclusion	Added "Phase 3" study where the use of tezepelumab has been demonstrated to show an important benefit in asthma study.	To reference Phase 3 study which demonstrated important benefit in asthma study with the use of tezepelumab.	Non-substantial
Section 2.3.3 – Overall Benefit: Risk Conclusion	Added "Phase 3" and removed "Phase 2" for no serious allergic reactions or anaphylactic reactions considered related to the tezepelumab were reported in the programme	To reference Phase 3 programme where no serious allergic reactions or anaphylactic reactions were reported.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 2.3.3 – Overall Benefit: Risk Conclusion	"Tezepelumab has been well tolerated with no safety signals identified in the completed studies to date" updated to "Tezepelumab has been well tolerated with an acceptable safety profile and no safety signals in subjects with severe, uncontrolled asthma identified in the completed studies to date."	To align with Investigator's Brochure Edition 5.0 (dated 21Oct2021).	Substantial
Section 3 (Objectives and Endpoints)	Co-primary endpoint updated: "Change from baseline in NCS evaluated as part of…NPSD at Week 52" changed to "Change from baseline in bi-weekly mean Nasal Congestion Score (NCS) evaluated as part of …NPSD at Week 52."	To ensure correct evaluation of NCS between baseline and Week 52.	Substantial
Section 3 (Objectives and Endpoints)	Key secondary endpoint updated: "Change from baseline in loss of smell evaluated as part of…NPSD at Week 52" to "Change from baseline in bi-weekly mean loss of smell evaluated as part of…NPSD at Week 52."	To ensure correct evaluation of participant loss of smell between baseline and Week 52.	Substantial
Section 3 (Objectives and Endpoints)	Key secondary endpoint updated: "Change from baseline in NPSD TSS at Week 52" to "Change from baseline in bi-weekly mean NPSD TSS at Week 52"	To ensure correct evaluation of NPSD TSS between baseline and Week 52.	Substantial
Section 3 (Objectives and Endpoints)	Other secondary endpoint updated: "Change from baseline over time in NCS evaluated as part of NPSD through Week 52" to "Change from baseline over time in bi-weekly mean NCS evaluated as part of NPSD through Week 52."	To ensure correct evaluation of NCS from baseline through Week 52.	Substantial
Section 3 (Objectives and Endpoints)	Exploratory endpoint updated: "Change from baseline in NCS" changed to "Change from baseline in bi-weekly mean NCS"	To ensure effective evaluation of off-treatment effect and recurrence rate of nasal polyps after discontinuation of treatment with tezepelumab.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.3 – Justification for Dose	"Given these results, the dose of 210 mg SC Q4W was selected for evaluation in the tezepelumab Phase 3 programme for patients with severe asthma" updated to "Given these results, the dose of 210 mg SC Q4W was confirmed in the tezepelumab Phase 3 programme for patients with severe asthma"	To clarify dose of 210 mg SC Q4W was confirmed from Phase 3 programme for patients with severe asthma.	Non-substantial
Section 5.1 – Inclusion Criteria	Inclusion Criterion 15 "NCS≥ 2 at Visit 3" removed. Inclusion 15a added to replace previous Inclusion Criterion 15. Inclusion 15a added: "At randomisation visit (Visit 3), a bi-weekly mean NCS≥ 2 (baseline bi-weekly mean score collected from study Day -13 to study Day 0)."	A new Inclusion Criterion 15a added to align with corresponding co-primary endpoint.	Substantial
Section 5.1 – Inclusion Criteria	Inclusion Criterion 18 updated from "Minimum compliance with the daily eDiary during the run-in period (having a minimum of 70% fully compliant days during run-in period from Visit 1 to the day of randomisation at Visit 3)" to "Minimum compliance with the daily eDiary during the screening and run-in periods (having a minimum of 70% fully compliant days from Visit 1 to the day of randomisation at Visit 3)."	To clarify that the compliance with daily diary is evaluated for the entire period from Visit 1 up to the day of Visit 3 that includes both the screening period (between Visit 1 and 2) and the run-in period (between Visit 2 and 3).	Non-substantial
Section 5.1 – Inclusion Criteria	Inclusion Criterion 19 updated from "Minimum compliance with background INCS as captured in the eDiary during the run-in period (having a minimum of 70% fully compliant days during run-in period from Visit 1 to the day of randomisation at Visit 3)" to "Minimum compliance with background INCS as captured in the eDiary during the screening and run-in periods (having a minimum	To clarify that the compliance with background INCS is evaluated for the entire period from Visit 1 up to the day of Visit 3 that includes both the screening period (between Visit 1 and 2) and the run-in period (between Visit 2 and 3).	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	of 70% fully compliant days from Visit 1 to the day of randomisation at Visit 3)."		
Section 5.2 – Exclusion Criteria	Exclusion Criterion 12 has been updated. Participants who have had basal cell carcinoma or localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are now also eligible to participate, provided that "the patient is in remission", in addition to the previous statement that the participant completed curative therapy at least 12 months prior to Visit 1	To align this Clinical Study Protocol with programme-level safety documentation regarding participants with a history of cancer.	Substantial
Section 5.4.1 – Re-screening	Added clarification for Re-screening that all procedures from the screening/run-in period should be repeated "except the sinus CT, if this was already performed in the first screening/run-in period, unless express permission for a repeat screening CT has been given by the study physician"	To clarify sinus CT does not need to be repeated if already performed during the initial screening/run-in period and study physician should be consulted if a repeat is required.	Non-substantial
Section 6.1.2 Medical Devices	Added section 6.1.2 regarding sponsor manufactured medical device use in this study and all medical device deficiencies should be documented and reported by investigator throughout the study	To align with International Organization for Standardization 14155 and European Medical Device Regulation.	Substantial
Section 6.2.4 Reporting Product Complaints	Added clarification regarding any defects with IP must be reported immediately to the AstraZeneca representative as per the pharmacy manual and defects will be investigated further with AstraZeneca.	To align with Pharmacy manual.	Non- substantial
Section 6.2.5 Reporting Product Defects	Added clarification regarding product defects should be reported to the AstraZeneca representative as per the pharmacy manual	To align with Pharmacy manual.	Non- substantial
Section 6.2.6 Single Use	Added clarification that Device malfunctions should be reported using appropriate form as per the	To align with Pharmacy manual.	Non- substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
APFS device malfunction	pharmacy manual and removed Device Malfunction return form. "Address and attention for malfunctioning device is available in the Device Malfunction Return Instructions" removed		
Section 6.4 – Concomitant Therapy	Table 5: Systemic Corticosteroids as maintenance treatment: "Not allowed 3 months prior to V1. During study conduct, SCS is allowed as a rescue to relieve symptoms of NP worsening or asthma exacerbations at PI's discretion. However, participants are not recommended to use SCS for the first 3 months after randomisation, unless emergent or deemed necessary by the PI." updated to "Not allowed 3 months prior to V1. During study conduct, SCS are allowed as a rescue to relieve NP worsening symptoms, to treat asthma exacerbations or treat other indications at PI's discretion. However, it is recommended that participants abstain from using SCS for the first 3 months after randomisation, unless in case of an emergency or if it is deem necessary by the PI"	To clarify SCS is allowed as a rescue to treat other indications at PI's discretion.	Non-substantial
Section 7.1.1 – Procedure for Discontinuation of Study Treatment	Added "In case of IP discontinuation due to NP surgery, no further nasal endoscopies or CT scans are required after the IPD visit"	To clarify no further nasal endoscopies or CT scans are required if IP discontinuation is due to NP surgery.	Non-substantial
Section 8.2.4 Table 12 – Footnote a	Footnote a was changed from "The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte counts from the central laboratory reports except screening visits (V1 and V2), any repeat testing that is performed during the screening period and	To clarify that both absolute and percentage values are blinded post randomisation.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	prior to Investigational Product (IP) administration at V3" to "The sponsor and site will be blinded to the immunoglobulin, eosinophil, basophil and monocyte (both absolute and percentage values) from the central laboratory reports except screening visits (V1 and V2), any repeat testing that is performed during the screening period and prior to Investigational Product (IP) administration at V3"		
Section 8.3.14 Medical Device Deficiencies	Added Section 8.3.14 definitions of medical device deficiency and requirements to fulfil regulatory reporting obligations worldwide and investigator's responsibility for detection and documentation of events meeting the definition of device deficiency occur during the study.	To align with International Organization for Standardization 14155 and European Medical Device Regulation.	Substantial
Section 8.6 – Human Biological Sample Biomarkers	Added "Whole blood will be collected for transcriptomic (RNA) profiling. Serum, plasma, and nasal epithelial lining fluid samples will be collected for exploratory biomarker analysis."	To clarify sample analysis.	Non-substantial
Section 8.6 – Human Biological Sample Biomarkers	Added that results from the following exploratory assessments will need to be blinded to sponsor and sites: Whole blood for transcriptomic RNA profiling, serum, plasma, and nasal epithelial lining fluid Total IgE samples Staph A enterotoxin samples in Nasal biopsy sub-study	To clarify blinding of key exploratory laboratory results to sponsor and sites after randomisation Visit 3.	Non-substantial
Section 9.4.1 – General Considerations	Endpoints of interests: "Change from baseline in co-primary endpoints: NPS and mean daily NCS at Week 52" updated to "Change from baseline in co-primary endpoints: NPS and bi-weekly mean NCS at Week 52. "	To align with corresponding co-primary endpoint.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix F Anaphylaxis: signs and symptoms, management	Corrected formatting of "Anaphylaxis: signs and symptoms, management"; from sub-heading to lettered Appendix F. Subsequent appendices lettering changed by one letter.	To correct a previous error in the formatting of this protocol and allow for proper referencing of this appendix.	Non-substantial
Appendix I	Added Appendix I Medical Device AEs, ADEs, SAEs, SADEs, US ADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating and Follow-up	To align with International Organization for Standardization 14155 and European Medical Device Regulation.	Substantial
Typographical and grammatical corrections have been made to this Clinical Study Protocol.			

Amendment v3.0 26-May-2021

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

Overall Rationale for the Amendment:

This Clinical Study Protocol has been amended to clarify procedures regarding CT scan use

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Table 1 - Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up	From footnote "a" - removed the sentence "except for early discontinuation from IP"	Procedures for discontinuation are noted clearly in Section 7.1.1.	Non-substantial
Table 1 - Schedule of Activities - Screening, Randomisation, Treatment Period, and Follow-Up	From footnote "t" - clarified scenarios for CT scans during the study in case of the subject's first post-randomisation nasal polyps (NP) surgery and first course of systemic corticosteroid (SCS) treatment for NP.	Clarifies scenarios where CT scan is required due to NP surgery or SCS treatment during study conduct.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.1 - Overall Design	Clarified that CT scan "...is required before first NP surgery and/or initiation of first course of SCS treatment for NP."	Clarifies scenarios where CT scan is required due to NP surgery or SCS treatment during study conduct.	Non-substantial
Section 7.1.1 - Procedures for Discontinuation of Study Treatment	Clarified that subjects who prematurely discontinue from IP due to NP surgery must follow modified timing for IPD procedures. Instead of returning to the site to complete IPD visit procedures at 4 weeks +/- 3 days after the participant's last IP administration, IPD procedures must simply be performed prior to, and as close as possible to, the planned surgery date.	In cases of premature IPD due to post-randomisation NP surgery, it is possible that the subject may have scheduled surgery for a date outside the 4 weeks +/- 3 days window prescribed for IPD visits performed due to other reasons. The language was changed to allow for the collection of the patient's CT scan results before surgery.	Non-substantial
Section 8.1.2.1 - Nasal Polyposis Symptom Diary (NPSD) and Nasal Polyposis Symptom Screening Assessment (NPSSA)	The assessment that captures NP symptom data at Visit 1 is properly known as the "Nasal Polyposis Symptom Screening Assessment". This section's title and text were corrected to ensure consistency with the information added to Table 1 (Schedule of Activities) in the previous amendment.	Ensures consistency between CSP body text and the description of assessments as per the Schedule of Activities.	Non-substantial
Section 8.1.3 - Sinus Computed Tomography	Clarified use cases for CT scans during the study in case of post-randomisation NP surger(ies), course(s) of SCS treatment for NP or any combination of either intervention. The site has also been encouraged to consult the study physician to ensure a clear understanding of the timing of CT scans during the study.	Clarifies the guidance given in the previous amendment and ensures consistency with the rest of the CSP and regulatory considerations. CT scan is required prior to the subjects' first post-randomisation NP surgery, or their first SCS treatment for NP. In case of a combination of NP surger(ies) or SCS treatment(s), the CT scan should be performed prior to the first occurrence of either NP surgery or SCS treatment for NP.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.1.4 - Post-randomisation Nasal Polyp Surgery and/or SCS use	Clarified use cases for CT scans during the study in case of post-randomisation NP surger(ies), course(s) of SCS treatment for NP or any combination of either intervention.	Clarifies the guidance given in the previous amendment and ensures consistency with the rest of the CSP and regulatory considerations.	Non-substantial
Section 8.1.5 - Spirometry (asthma/AERD/ NSAID-ERD participants only)	Provided readers with a summary of the MasterScope; the system which will be used to perform procedures including but not limited to spirometry, nasal peak inspiratory flow (NPIF) and fractional exhaled nitric oxide (FeNO).	Minor content change: helps to introduce readers to the tool being used to perform spirometry, NPIF and FeNO.	Non-substantial
Table 12 - Laboratory Safety Variables	List of safety tests updated.: Haematology/Hemostasis (whole blood): Added B-Leucocyte differential count (absolute count); Added B-Haematocrit Urinalysis (dipstick): Removed U-Hb/Erythrocytes/Blood, changed to U-Blood; Removed U-Protein/Albumin, changed to U-Protein; Clinical Chemistry: Removed serum/plasma albumin.	Ensures consistency with safety tests performed at the programme level.	Non-substantial
Section 8.5.2 - Immunogenicity Assessments	Changed period for immunogenicity samples retention from "3 years following publication of CSR" to "15 years following date of last subject last visit (LSLV)".	This change is consistent with internal processes regarding sample retention after a study.	Non-substantial
Various typographical and grammatical corrections have been made to this Clinical Study Protocol.			

Amendment v2.0 06-Apr-2021

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

Overall Rationale for the Amendment:

This Clinical Study Protocol has been amended to align the study assessments with the scientific and operational objectives of the study. Language was also added to clarify guidance for enrolling and treating patients during significant regional disruptions and/or public health crises such as the COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page	Added International Coordinating Investigator details	To ensure the International Coordinating Investigator's details are available	Non-substantial
Section 1.1 – Objectives and Endpoints and Section 3 – Objectives and Endpoints (Table 3)	Removal of NPS and Participant reported NC at Week 24 as a key secondary endpoint/variable	To simplify and reduce the number of endpoints included in the multiplicity control procedure	Non-Substantial
Section 1.1 – Objectives and Endpoints and Section 3 – Objectives and Endpoints (Table 3)	Added "sinus severity score by quantitative CT assessment at Week 52" as a secondary endpoint	To be aligned with Section 8.1.3.2 of the CSP	Non-substantial
Section 1.1 – Objectives and Endpoints	Added that "The co-primary and key secondary endpoints will also be tested at the 1% level."	To include additional statistical methods for the co-primary and key secondary endpoints	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Included SARS-CoV-2 nasopharyngeal swab test to be tested locally COVID-19 rapid test allowed per local regulations	Additional SARS-CoV-2 testing added for flexibility at the site level	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Removed Visit 13 (Week 36) for Nasal epithelial lining fluid for PK and Exploratory biomarkers	Additional sample for Nasal epithelial lining fluid at Visit 13 is removed to reduce patient burden of NLF sampling where information afforded by this time point is not critical	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Limited sampling at Visit 2 (Week -2) for Nasal epithelial lining fluid for PK and Exploratory biomarkers, only to sub-study participants	Limited to sub-study participants to reduce patient burden of NLF sampling where information afforded	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		by this time point is not critical	
Section 1.3 - Schedule of Activities (Table 1)	Removed the word "including" from "At Visit 1, the suggested order of assessments should be followed as: ePRO, Vital Signs, ECG, Blood Draws including SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test) "	Clarification that SARS-CoV-2 nasopharyngeal swab test (or COVID-19 rapid test) is not part of the blood draw.	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Removed ECG and Nasal Endoscopy from the following text under Table 1: At Visit 3, the suggested order of assessments should be followed: ePRO, UPSIT, Vital Signs, FeNO (asthma/AERD/NSAID-ERD participants), Spirometry (asthma/AERD/NSAID-ERD participants), NPIF, Blood Draws including SARS-CoV-2 serology test, Staph A nasal culture, Nasal epithelial lining fluid collection, IP administration.	To clarify that ECG and Nasal Endoscopy are not performed at Visit 3.	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Added the following text under Table 1, “Based on investigator’s judgement and site resources, EOT assessments (V17) will be performed over more than one day, within a 5-day window” under Table 1	Additional visit window is added to accommodate flexibility at the site level to complete all the assessments as part of EOT	Non-substantial
Section 1.3 - Schedule of Activities (Table 1) and Section 8.1.2.1 - 8.1.2.1 Nasal Polyposis Symptom Diary (NPSD)	Added NPSSA (Nasal Polyposis Symptom Screening Assessment) to SoA for Visit 1 and description about assessment	The NPSSA is only used to evaluate minimum symptom criteria over the past 12 weeks prior to Visit 1.	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Removed INCS Distribution and Accountability from V18, V20 and V21. Relabelled INCS Distribution and Accountability to INCS Distribution	INCS distribution and accountability cannot be performed during remote visits (V18 and V20) and V21 is the final visit of the study so it is not needed.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Added footnote v to the Schedule of Activities table to explain where to find information on accountability procedures	Accountability procedures are described in detail in the study Pharmacy Manual, which is also made available to sites.	
Section 1.3 - Schedule of Activities (Table 1)	In footnote h, updated the wording that the sponsor will be unblinded to the FENO values prior to randomisation and blinded to the FENO values post randomisation.	To clarify that FENO is unblinded during screening visits but is blinded after randomisation.	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	For footnote i, added that "CT should be performed between V2 and V3 after the participant meets the inclusion/exclusion criteria and receive a confirmation from central readers that the inclusion criteria of NPS score is met."	Clarification was added when CT scan should be performed during the screening period	Non-substantial
Section 1.3 - Schedule of Activities (Table 1) and Section 8.6.1 - Collection of mandatory samples for biomarker analysis	For footnote o, added that "If nasal biopsy cannot be collected at V2, then participant should be withdrawn from nasal biopsy sub-study, and can continue on the main study. In this event, NLF collection at Visit 2 and Staph A enterotoxin-specific IgE sample collection at Visit 3 should not be performed as well. Please note that CT scans are done after nasal biopsy at baseline, while at EOT/IPD, the CT scan will be done before nasal biopsy. Moreover, Collection of NLF at V3, V7, V10, V17/EOT/IPD, and V19 is required for all study participants.	Clarification was added about the collection of nasal biopsy assessments if Visit 2 sample is not collected.	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Added footnote t to specify CT scan assessment requirements if the participant has planned surgery for NP or uses SCS during the study	Details regarding CT scan have been added to clarify scenario if the participant undergoes post-randomisation surgery or uses SCS	Non-substantial
Section 1.3 - Schedule of Activities (Table 1)	Added footnote u to indicate nasal endoscopy requirements if the participant has planned surgery for NP or uses SCS during the study	Details regarding nasal endoscopy have been added to clarify scenario if the participant undergoes post-	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		randomisation surgery or uses SCS	
Section 2.3.3 - Overall Benefit: Risk Conclusion	Added “completed” to clarify no safety signals identified in the completed studies to date. Used “the completed studies” to replace “the tezepelumab programme”	To clarify no safety signal detected in the completed studies	Non-substantial
Section 4.1 – Overall Design	Added that participants who require SCS and/or hospitalisation for an asthma exacerbation or worsening of nasal polyp symptoms during the screening period, should be screen failed and may rescreen once their symptoms improve.	To address discrepancy in the CSP and consistency with Section 5.4.1 to extend the screening period until worsening event is resolved.	Non-substantial
Section 4.1 - Overall Design	Added that a second, post-baseline CT scan will be done at EOT/IPD (Week 52).	To clarify that CT scan is also now performed at post-baseline at EOT/IPD	Non-substantial
Section 5.1 – Inclusion Criteria	For inclusion criterion #5, added that documented treatment with SCS should be for at least 3 consecutive days or one IM depo-injectable dose within the past 12 months prior to Visit 1. but not within the last 3 months prior to Visit 1	To clarify length of period for SCS treatment prior to Visit 1 and include IM depo-injectable dose	Non-substantial
Section 5.2 – Exclusion Criteria	Removed exclusion criterion #2	All information from exclusion #2 is consolidated into exclusion criterion #5 as a result of overlapping information.	Non-substantial
Section 5.2 – Exclusion Criteria	For exclusion criteria #17, Clarified SARS-CoV-2 nasopharyngeal swab test description to include local swab testing (or COVID-19 rapid test) per local regulations.	Additional SARS-CoV-2 testing added for flexibility at the site level	Non-substantial
Section 5.2 – Exclusion Criteria	Added additional exclusion criterion #37 regarding COVID-19 vaccination	To specify exclusion criterion for enrolling new participants in the study that are vaccinated with a COVID-19 vaccine.	Non-substantial
Section 5.2 – Exclusion Criteria	Added a bullet point that systemic corticosteroid use is defined as treatment with a burst of systemic	To clarify exclusion criteria #21 with further definition	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	corticosteroids for at least 3 days or a single IM depo-injectable dose of corticosteroids (considered equivalent to a 3-day burst of systemic corticosteroids) to exclusion #21	on systemic corticosteroid use	
Section 5.2 – Exclusion Criteria and Section 5.3.2 – Alcohol, Tobacco and Other	Added a new exclusion criteria #36 regarding chronic alcohol or drug abuse and smoking Also, clarified that for participants with co-morbid asthma: current smokers or participants with smoking history ≥ 10 pack-years at Visit 1 are not allowed.	To clarify lifestyle restrictions addressed in section 5.3 of the CSP that is now added as part of the exclusion criteria	Non-substantial
Section 6.2.2 - Dose Preparation	Visual characteristics of the IP were provided	To specify more details related to appearance and clarity of the IP	Non-substantial
Section 6.2.2 - Dose Preparation	Dose preparation steps were added	To specify details in the CSP that references the separate handling instructions.	Non-substantial
Section 6.2.3 – Dose Administration	Dose administration steps were added	To specify details in the CSP that references the separate handling instructions.	Non-substantial
Section 6.2.3 – Dose Administration	Added an additional point , “The participant is planning to receive COVID-19 vaccination during the screening or treatment period. Please refer to section 6.4.2.”	To specific dose administration criteria for the Investigator if participant decides to take a COVID-19 vaccine	Non-substantial
Section 6.3 - Measures to Minimise Bias: Randomisation and Blinding	Vendor name, Parexel was changed to Calyx	To specify vendor name change supporting IWRS services	Non-substantial
Section 6.4 – Restricted Medications (Table 5)	Clarified that SCS as maintenance treatment is not allowed 3 months prior to V1, and that SCS may be used as a rescue medication during study conduct.	To clarify acceptable use of systemic corticosteroid during the study.	Non-substantial
Section 6.4 - Concomitant Therapy (Table 5) and	COVID-19 vaccination restrictions were added	To specify criteria for COVID-19 vaccination during the study conduct	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.4.2 – COVID-19 Vaccination			
Section 6.4 - Concomitant Therapy (Table 6)	Added "Herbal remedies for the treatment of CRSwNP not allowed 30 days prior to Visit 1, during screening/run-in and throughout the IP treatment and preferably 4 weeks after the last dose of IP."	To add additional restrictions to concomitant medications	Non-substantial
Section 7.1 – Discontinuation of Study Intervention	Added additional bullet point "If participant had undergone NP surgery during the treatment period"	To clarify details for IP discontinuation if participant undergoes/plans for NP surgery during the treatment period	Non-substantial
Section 7.1.1 - Procedures for Discontinuation of Study Treatment	Clarified that if option 2 was selected, the participant completing ePRO data collection on the handheld device at home and UPSIT assessment will not be completed after IPD visit until participant returns back for EOT.	As participant will not be attending site visits, the ePRO data are completed on the handheld device and UPSIT can only be completed at the site as a paper questionnaire so this is an exception	Non-substantial
Section 8.1.1 – Nasal Polyp Score (NPS) – Table 7	Clarified for polyp score Grade 3 that "Polyps reaching the lower border of the inferior turbinate or a middle meatal polyp with a score of 2 with any additional polyp medial to the middle turbinate" For Grade 4, clarified that "Large polyps causing complete or near complete obstruction of the inferior nasal cavity ie, touching the floor of the nose"	Additional clarification for nasal polyp score 3 and 4	Non-substantial
Section 8.1.3 – Sinus Computed Tomography	Added that "For participants who undergo or who have planned NP surgery during the treatment period, a CT scan should be performed prior to the NP surgery per the IPD visit. For participants who require SCS (at least 3 consecutive days of OCS or equivalent 1 intramuscular injection) for the treatment of NP, a CT scan should be performed prior to starting	Details regarding CT scan have been added to clarify scenario if participant undergoes post-randomisation surgery, uses SCS or discontinues IP	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	treatment with SCS if possible, and at Week 52 per the SoA. For participants who discontinue IP for other reasons, a CT scan should be performed at the IPD visit as well as at Week 52, if participant opts for follow-up option 1 or 2 per section 7.1.1 of the CSP."		
Section 8.1.4 - Post-randomisation Nasal Polyp Surgery and/or SCS use	Clarified procedures to be performed prior to SCS treatment of NP.	To support the statistical analysis of SCS use in the study.	Non-substantial
Section 8.1.4 - Post-randomisation Nasal Polyp Surgery and/or SCS use	Shortened time window for rescheduling visits in case of non NP-related SCS use close to V10 (Week 24) or V17 (Week 52), to 2 weeks after last dose of SCS	To ensure proper timing of visits, whilst aligning with information previously provided to regulatory authorities	Non-substantial
Section 8.1.5 – Spirometry (asthma/AERD/ NSAID-ERD participants only)	Added that spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the randomisation visit (Visit 3).	To clarify spirometry test timing at Visit 3 (randomisation visit)	Non-substantial
Section 8.1.5.1 – General requirements	Removed Reversibility as part of Lung Function testing	To clarify that reversibility will not be measured by spirometry at the study site	Non-substantial
Section 8.2.4 – Clinical Safety Laboratory Assessments (Table 12)	For footnote b under Table 12, clarified that the safety urine sample will be analysed by urine dipstick at site.	To provide clarification that the safety urine sample is not performed as a local test but is completed on-site with a urine dipstick provided by Covance	Non-substantial
Section 8.2.4.1 – COVID-19 Entry Screening Questionnaire	Clarified that the COVID-19 screening questionnaire must be completed via telephone approximately within 72 hours prior to every study visit. This section previously specified 24 hours.	To provide additional flexibility for investigator site to conduct COVID-19 screening questionnaire prior to visit	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.2.4.2 – SARS-CoV-2 Testing	Clarified SARS-CoV-2 nasopharyngeal swab test description to include local swab testing (or COVID-19 rapid test) per local regulations.	Additional SARS-CoV-2 testing added for flexibility at the site level	Non-substantial
Section 8.2.4.4 - Serology	Removed the following text, "In case of positive result of hepatitis B surface antigen or hepatitis C virus antibody, additional testing (eg, hepatitis C RNA PCR test) may be performed to confirm eligibility."	Additional confirmatory test in case of positive result of hepatitis B surface antigen or hepatitis C virus antibody is not needed	Non-substantial
Section 8.5 – Human Biological Samples, Section 8.6.1.2 - Storage, re-use and destruction of exploratory biomarker samples, Section 8.7.1 - Storage and destruction of genetic samples. Appendix D1 - Use/analysis of DNA and Appendix D2 - Genetic research plan and procedures	Updated retention period of human biological samples, exploratory biomarker samples and genetic samples for a maximum of 15 years from the date of the last subject's last visit (LSLV)	To align retention period with human biological samples SOP	Non-substantial
Section 8.6.1 Collection of mandatory samples for biomarker analysis	Text changed: • Whole blood for transcriptomic profiling (RNA profiling), serum and plasma samples, nasal epithelial lining fluid and urine for proteins and inflammatory markers will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA.	To clarify that urine will not be collected to analyse proteins and inflammatory markers in the study	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	• Whole blood for transcriptomic profiling (RNA profiling), serum and plasma samples, nasal epithelial lining fluid will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA.		
Section 8.6.1 Collection of mandatory samples for biomarker analysis	Text changed: • The levels of total immunoglobulin E (IgE) and a quantitative assessment for the presence of allergen-specific IgE (IgE FEIA) will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA and evaluated by a central laboratory. All total serum IgE results will be redacted from the laboratory reports after randomisation visit (V3). • The levels of total immunoglobulin E (IgE) and an assessment for the presence of allergen-specific IgE (IgE FEIA) will be collected at the pre-specified scheduled visits prior to IP administration (pre-dose) according to the SoA and evaluated by a central laboratory. All total serum IgE results will be redacted from the laboratory reports after randomisation visit (V3).	To clarify that the IgE FEIA test is not a quantitative assessment.	Non-substantial
Section 9.1 – Statistical Hypotheses, Section 9.2 – Sample Size Determination, Section 9.4.1 – General Considerations and Section 9.4.2.3 – Secondary Endpoint(s)	Removal of NPS and Participant reported NC at Week 24 as a key secondary endpoint/variable in the text and Figure 3.	To simplify and reduce the number of endpoints included in the multiplicity control procedure	Non-Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.1 – Statistical Hypotheses	Moved "time to surgery up to Week 52" to level 3 in the testing strategy text and Figure 3.	To reflect the higher clinical importance of the "time to surgery up to Week 52" as compared to the lower level endpoints.	Non-Substantial
Section 9.1 – Statistical Hypotheses	Added more details about Holm procedure for the level 2 endpoints in the testing strategy.	To clarify that the Holm procedure controls the familywise type I error in a strong sense because the full alpha will only be passed to the next level endpoint when all level 2 endpoints are significant.	Non-substantial
Section 9.4.2.1 Primary Endpoints, Subgroup Analyses	Removed Baseline NCS, NPS, number of prior surgeries and time since last surgery from the list of key subgroups which will be analysed to explore consistency of treatment effect.	Baseline NCS, NPS, number of prior surgeries, and time since last surgery will be included in the summary of baseline characteristics	Non-substantial
Section 9.4.2.1 Primary Endpoints, Subgroup Analyses	Added age, gender and race to the list of key subgroups which will be analysed to explore consistency of treatment effect.	To clarify that subgroup analyses will be performed for the key demographic characteristics.	Non-substantial
Appendix B - Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added that 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.	Additional information was added to reflect latest CSP template language.	Non-substantial
Appendix D - Optional Genomics Initiative Sample	Clarified that "Samples will be stored for a maximum of 15 years from date of last subject last visit or may differ depending on local retention, after which they will be destroyed."	To align with the current AstraZeneca HBS retention policy of 15 years from LSLV for the genomics initiative sample.	Non-substantial
Appendix E - Actions Required in Cases of Increases in Liver Biochemistry	Removed "Determine whether PHL criteria were met at any study visit prior to starting study treatment" Removed the sections – E6 and E7:	This is only applicable for studies with target population of malignant disease with liver involvement, severe infection or liver disease.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
and Evaluation of Hy's Law	•Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment •Actions Required for Repeat Episodes of Potential Hy's Law	Additional information was added to reflect latest CSP template language.	
Various typographical and grammatical corrections have been made on the Clinical Study Protocol.			

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Document ID:	Doc ID-004240992	
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