Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3252C00001
Version	4.0
Date	05 Aug 2020

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study Of Benralizumab in Patients with Severe Nasal Polyposis (OSTRO)

Sponsor: **AstraZeneca AB, 151 85 Södertälje, Sweden**

Regulatory Agency Identifying Number(s):

European Clinical Trials Database (EudraCT) number: 2017-003675-61

National Clinical Trial (NCT) number: 03401229

VERSION HISTORY

Version 4 (Amendment 3) (05-Aug-2020)

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

Overall Rationale for the Amendment:

The main rationale for this amendment is to provide updates to key secondary endpoints and statistical analyses to address FDA comments and add study mitigation language which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity.

The following changes were incorporated into version 4.0 dated 05 Aug 2020 of the Protocol:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis	Updated list of key secondary endpoints to include Difficulty with Sense of Smell (DSS) and Lund Mackay score (LMS) and remove University of Pennsylvania Smell Identification Test (UPSIT); Updated timepoint of primary analysis to Week 40. Updated estimands and description following FDA feedback. Updated language of inclusion in extended follow-up for clarity. Updated post-rescue imputation: after NP surgery the worst possible value is imputed through Week 56. Removed 'visit' as covariate in analysis model as no longer meaningful in ANCOVA. Reverted power and type I error rate to original values based on alpha of 0.01.	The primary analysis timepoint was moved to week 40, the latest nasal endoscopy assessment not substantially impacted by COVID-19 disruptions. Other modifications to key secondary endpoints and statistical analysis were made to address FDA comments [redacted]	Substantial
Section 3 Objectives and Endpoints	Timepoint of primary analysis changed to Week 40 for co-primary and key secondary endpoints. Week 56 is also multiplicity protected.	The primary analysis timepoint was moved to week 40, the latest nasal endoscopy assessment not substantially impacted by	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	UPSIT removed from key secondary endpoints, Difficulty with Sense of Smell (DSS) score from NPSD and Lund Mackay score (LMS) added to key secondary endpoints. Endpoint derivation modified to impute the worst possible value after the first occurrence of NP surgery.	COVID-19 disruptions. Other modifications to key secondary endpoints and statistical analysis were made to address FDA comments [redacted]	
Section 4.1 Overall design	Updated language of inclusion in extended follow-up for clarity.	The grammar was corrected.	Non-substantial
Section 4.1.1 (added section) Study Conduct Mitigation in the event of evolving SARS-CoV-2 (COVID-19) pandemic	Additional text regarding Study Conduct Mitigation During evolving SARS-CoV-2 (COVID-19) pandemic or other study disruption has been added to maintain the conduct of study-related activities during crisis, while securing data integrity and patient safety.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity.	Substantial
Section 4.2 Scientific Rationale for Study Design	Updated language of inclusion in extended follow-up for clarity.	To provide clarity about assignment to extended follow-up.	Non-substantial
Section 8. Study Assessments and Procedures	"Additional data to capture study disruptions caused by COVID-19 pandemic will be collected in the eCRF." wording has been added	To allow sponsor to collect additional data related to COVID-19 pandemic in newly designed eCRF pandemic modules.	Non-substantial
Section 8.1.1.1 Nasal Polyposis Symptom Diary	Added Total Symptom Score (TSS) as sum of first 8 items of NPSD.	Added analysis of NP-associated symptoms as a total score from NPSD, excluding symptom impact items.	Substantial
Section 8.1.1.1.1	Changed timepoint of primary endpoint to Week 40. Week 56 is included as a	Revised to be consistent with co-primary endpoint NPS timepoint	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Nasal Blockage Score	key secondary endpoint.	at Week 56 and to mitigate potential COVID-19 disruptions (e.g., missed doses).	
Section 8.1.1.1.2 Difficulty with Sense of Smell (DSS) score	Added section for DSS as a component of NPSD and a key secondary endpoint.	Added key secondary endpoint following FDA feedback [redacted]	Substantial
Section 8.1.1.2 SinoNasal Outcome Test 22 item	Changed timepoint of key secondary endpoint to Week 40. Week 56 is included as a key secondary endpoint.	To mitigate potential COVID-19 disruptions.	Substantial
8.1.2 Nasal Polyp Score	Changed timepoint of primary endpoint to Week 40. Week 56 is included as timepoint for a key secondary endpoint.	The primary analysis timepoint was moved to week 40, the latest nasal endoscopy assessment not substantially impacted by COVID-19 disruptions	Substantial
Section 8.5.1 Determination of drug concentration	Added information about analysis of baseline PK samples and on-treatment PK samples.	For clarification.	Non-Substantial
Section 9.1 Statistical Hypotheses	Changed timepoint of primary endpoints to Week 40. Week 56 outcomes are included as key secondary endpoints. Reverted power and type I error rate to original values based on alpha of 0.01. Removed list of tested endpoints and replaced with reference to section 9.4.4. Updated model specification from MMRM to ANCOVA with WP/WOCF and MI.	Revision made following FDA feedback [redacted]	Substantial
Section 9.2 Sample size determination	Updated model specification to ANCOVA with WP/WOCF and MI. Changed timepoint of primary endpoint to Week 40. Reverted power and type I error rate to	The primary analysis timepoint was moved to week 40, the latest nasal endoscopy assessment not substantially impacted by COVID-19 disruptions. Other modifications to key secondary	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	original values based on alpha of 0.01.	endpoints and statistical analysis were made to address FDA comments [redacted]	
Section 9.4.1 Efficacy analyses	Updated primary estimand to impute worst possible after NP surgery and WOCF after SCS for NP.	Revision made following FDA feedback [redacted]	Substantial
9.4.1.1 Calculation or derivation of variables for efficacy analyses	Updated list of key secondary endpoints: DSS and LMS added, UPSIT removed. Timepoint of primary endpoint changed to Week 40. Week 56 is also multiplicity protected for key secondary endpoints.	The primary analysis timepoint was moved to week 40, the latest nasal endoscopy assessment not substantially impacted by COVID-19 disruptions. Other modifications to key secondary endpoints and statistical analysis were made to address FDA comments [redacted].	Substantial
Section 9.4.1.2 Methods for efficacy analyses	Updated model specification to ANCOVA with WP/WOCF and MI. Updated primary estimand to impute worst possible after NP surgery and WOCF after SCS for NP.	Revision made following FDA feedback [redacted].	Substantial
Section 9.4.1.3 Subgroup analysis	Expanded subgroup analysis to include key secondary endpoints. Atopic status (determined by phadiatop test) added as a subgroup.	A phadiatop test is considered to be a reliable assessment of atopic status at study entry.	Not substantial
Section 9.4.3.3 Analyses of biomarkers	"A limited number of exploratory biomarkers may be reported in the CSR. Details regarding analyses can be found in the SAP. Any remaining exploratory biomarkers will be reported outside of the CSR." - wording has been added.	Exploratory biomarkers selected for their predicted ability to reveal PD effects of benralizumab may be included in the CSR. Remaining exploratory biomarkers will be reported outside of CSR as per previous version.	Not substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4.4 Methods for multiplicity control	List of endpoints and timepoints updated. Reverted type I error rate to original values based on alpha of 0.01.	Revision made following FDA feedback [redacted]	Substantial
Appendix A6	Updated to correct web link.	Previously link was not correct.	Not substantial
Appendix G	Additional text regarding Study Conduct Mitigation During evolving SARS-CoV-2 (COVID-19) pandemic or other study disruption has been added to maintain the conduct of study-related activities during crisis, while securing data integrity and patient safety.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity.	Substantial
Appendix F	List of abbreviation has been updated.	New abbreviations have been added.	Non-substantial

Version 3.0, 20 Sep 2019

The following changes were incorporated into version 3.0 dated 20 Sep 2019 of the Protocol:

Table 2 – Schedule of Assessment.

Headers referring to Follow-Up visits were updated – update of the wording from *First 200 pts* to *Approximately 200 pts* and from *Second 200 pts* to *Remaining pts.*

Footnote "b" under SoA was updated – update of the wording from *The first 200 patients who complete treatment will have a 24 weeks Follow-up period without dosing: V12a at Week 60; V13 at Week 68; V14 at Week 80.* to *Approximately 200 patients who first complete the 56-week treatment will have a 24-week follow-up period without dosing: V12a at Week 60; V13 at Week 68; V14 at Week 80*

Footnote "c" under SoA was updated - update of the wording from *The second 200 patients will have a 4-weeks Follow-up period without dosing: V12b at Week 60.* to *The remaining patients will have a 4-weeks Follow-up period without dosing: V12b at Week 60.*

The same update is implemented through the CSP content everywhere where this is mentioned.

Section 1.1 Objectives and Endpoints – Key Secondary Objective

Nasal polyps surgery and/or SCS use was added to the multiplicity testing strategy and Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) was added as a Key Secondary objective and removed from the Other Secondary Objective Section.

Section 1.1 Objectives and Endpoints – Other Secondary Objective

Removal of University of Pennsylvania Smell Identification Test (UPSIT) – upgraded to Key Secondary Objective.

Section 1.1 Study Period

Updated Estimated date of last patient completed- from Q1 2020 to Q3 2020.

Section 1.1 Number of Patients

Number of sites were updated.

Section 1.1 Statistical methods

Power value updated from 95% to 99% and alpha level value was updated from 0.01 to 0.05.

Section 1.2 Schema

Figure 1 – Study flow chart updated to reflect updates referring to Follow-Up visits. Update of the wording from *First 200 pts* to *Approximately 200 pts* and from *Second 200 pts* to *Remaining pts.*

Figure 2 – Study flow chart updated to reflect updates referring to Follow-Up visits. Update of the wording from *First 200 pts* to *Approximately to 200 pts.*

Section 3.2 Secondary objectives

Key Secondary Objective

Nasal polyps surgery and/or SCS use was added to the multiplicity testing strategy and Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) was added as a Key Secondary objective and removed from the Other Secondary Objective Section.

The same update is implemented through the CSP content everywhere where this is mentioned.

Other Secondary Objective

Removal of University of Pennsylvania Smell Identification Test (UPSIT) – upgraded to Key Secondary Objective.

Section 8.1.1 Clinical outcome assessments

Minor administrative change.

Section 8.1.1.4 Patient Global Impression of Severity and Change

PGIC – response options updated.

Section 8. 3.4 Adverse event data collection

Editorial change.

Section 8.3.5 Causality collection

Clarification added that NP surgery is not the study procedure.

Section 8.3.9 Disease-under study (DUS)

The definition of DUS and reporting criteria have been clarified.

Section 8.4.2 Pregnancy

Update of the sentence explaining when pregnancy and outcome of the pregnancy does not to have to be reported to AZ.

Section 8.4.2.1 Maternal exposure

Update of information about pregnancy reporting. It is clarified that paper-based pregnancy outcome report is used to report the outcome of the pregnancy.

Section 8.10 Health Economics

Clarification added on reporting hospitalizations as an SAE.

Section 9.1 Statistical hypotheses

Wording changed to reflect the update of key secondary objective – "Nasal polyp surgery and/or SCS use" and upgrading University of Pennsylvania Smell Identification Test (UPSIT) to the key secondary objective.

Alpha level value for testing of co-primary endpoints was updated from 0.01 to 0.05.

Section 9.2 Sample size determination

The change in significance level for hierarchical testing from two-sided alpha of 0.01 to two-sided alpha of 0.05 was added. Power value of at least 99% at alpha value of 0.05 was added.

Update of minimum observed mean difference that would be statistically significant at the two-sided alpha 0.05 level from -0.52 to -0.39 in total NPS and from –0.26 to –0.20 in NBS. Original critical values for two-sided alpha 0.01 level also included.

Section 9.4.1.1 Calculation or derivation of variables for efficacy analyses

Wording changed to reflect the update of key secondary objective – "Nasal polyp surgery and/or SCS use" and upgrading University of Pennsylvania Smell Identification Test (UPSIT) to the key secondary objective.

Section 9.4.1.1 Disease specific health-related quality of life: SNOT-22 (Key secondary endpoint)

The header name was updated from *Health-related-quality of life: SNOT-22* to *Disease specific health-related quality of life: SNOT-22 (Key secondary endpoint)*

Indicated that the health-related-quality of life is a key secondary endpoint.

Section 9.4.1.1 Time to first NP surgery

Added additional paragraphs on Time to first NP surgery and/or SCS use for NP and University of Pennsylvania Smell Identification Test (UPSIT).

Section 9.4.1.2 Methods for efficacy analyses

Analyses of secondary endpoints

Information added that the estimate of the treatment effect at Week 56 for SNOT-22 and UPSIT total score for the analyses of key secondary endpoints will be based on contrasts from the respective MMRM models.

Section 9.4.1.3 Subgroup analysis

UPSIT upgraded to key secondary endpoint.

Section 9.4.4 Methods for multiplicity control

Wording changed to reflect the update of key secondary objective – "Nasal polyp surgery and/or SCS use" and upgrading University of Pennsylvania Smell Identification Test (UPSIT) to the key secondary objective.

Alpha level value for testing of co-primary endpoints was updated from 0.01 to 0.05.

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations
Sentence added based on recent review comments from Swedish and Danish HAs.

Where applicable as per relevant laws and regulations, amendments will also be submitted to, reviewed and approved by regulatory authorities/national competent authorities.

A 9 Study and Site closure
To meet local Regulatory requirements, this section was updated with revised standard AstraZeneca protocol text.

Appendix B Adverse event definitions and additional safety information

B2 Definitions of serious adverse event – information added about AE/SAE for malignant tumors.

Version 2.0, 25 April 2018

The following changes were incorporated into version 2.0 dated 25 April of the Protocol:

Table 1. Schedule of Activities-Screening (run-in)

Table 1 was updated to emphasise that a minimum period of 4 weeks is required between V1 and V2 in order to ensure that all study patients receive 4 weeks of the same study-provided INCS dosing, and to highlight that the ICF needs to be signed prior to any study

procedure. Other minor changes and footnotes were made throughout Table 1 to add further clarity.

Table 2. Schedule of Activities-Randomization, treatment period and follow-up

Table 2 was updated to reflect the order of the procedures at the EOT visit and to highlight that IP administration is the last activity performed at the visit. Other minor changes were made throughout Table 2 to add further clarity.

Section 1.1 (Synopsis): Overall design and throughout the CSP content (Treatment and treatment duration; Scientific rationale for study design; Background medication sections)

Requirement for patients being on a stable dose of study provided INCS for 4 weeks prior to randomization was changed to 4 weeks prior to V2. The change was made to align patients profile in regards to INCS intake.

Section 1.1 (Synopsis): Treatment and Treatment duration

Information about patients with INCS intolerance was added.

Figure 2: Background medication scheme was added

Section 4.1 (Overall design)

Requirement to maintain a 4-week gap between V1 and V2 was added.

Section 5.1 (Inclusion criteria): Inclusion #5

Requirement of 4 weeks of INCS intake prior V1 was added.

Section 5.1 (Inclusion criteria): Inclusion #6 and #9

SNOT22 score was changed from >30 to ≥ 30.

Section 5.1 (Inclusion criteria): Inclusion #15

Male contraception requirements were updated.

Section 5.2 (Exclusion criteria): Exclusion#1

Number of months was updated from 6 months to 3 months to allow patients to be recruited sooner following their last nasal and/or sinus surgery.

Section 5.2 (Exclusion criteria): Exclusion#2

Allergic fungal sinusitis (AFS) was added.

Section 5.2 (Exclusion criteria): Exclusion#5

Time period was changed from 3 months to 4 weeks prior to V1 for asthma exacerbation requiring systemic corticosteroids treatment or hospitalization for treatment of asthma.

Section 5.2 (Exclusion criteria): Exclusion#10

Note about hormonal therapy was added.

Section 5.2 (Exclusion criteria): Exclusion#15

Screening/run-in period timeframe was removed from this exclusion criterion.

Section 5.2 (Exclusion criteria): Exclusion#16

Removal of usage of systemic corticosteroids for condition other than short course for nasal polyps.

Section 5.2 (Exclusion criteria): Exclusion#17

Change from 4 to 6 months in regards to the intake of biologic products. Additionally, allowance of previous receipt of mepolizumab, reslizumab and dupliumab was added.

Change was done to allow patients with documented previous participation in other mAB studies to be recruited.

Section 5.2 (Exclusion criteria): Exclusion#18

Mepolizumab, reslizumab and dupliumab were removed and described under Exclusion#17.

Section 5.2 (Exclusion criteria): Exclusion#22

Time period for systemic corticosteroids intake was changed from 2 months to 4 weeks prior V1. Note about sustained release steroids or depot injections was added.

Section 5.2 (Exclusion criteria): Exclusion#25

Typo was corrected from > 3 times to ≥ 3 times.

Section 5.4.1 (Re-screening)

Re-screening section wording was updated to allow extension of the screening period and to clarify in which cases re-screening is allowed. Additionally, it was highlighted that patient can be considered for re-screening once under the specific conditions.

Table 4 (Restricted medication) was updated

Table 5 (Prohibited medication) was updated

Section 6.5.1 (Background medication)

Requirement for patients being on a stable dose of study provided INCS for 4 weeks before randomization was changed to a requirement of 4 weeks on stable dose of study provided INCS prior to V2.

Information about MFNS intolerance was added. Additionally, information about SCS intake during screening period and possible extension was added.

Section 7.1.1 (Procedures of discontinuation of study treatment)

Change from week 60 to 56 was done in regards to the continuation of study participation in case patient prematurely discontinued IP treatment.

Section 8.1.1.6 (Asthma exacerbation - for asthma patient only)

Information that if patient experienced an asthma exacerbation and/or use of systemic corticosteroids during the screening, he/she should be screen failed was removed.

Section 8.1.3. Sinus Computed Tomography

Recommendation that for sites participating in both CT and nasal polyp biopsy procedure, Sinus CT-scan should be done after biopsy at V2, and prior biopsy at EOT/IPD.

Section 8.1.4 (Nasal polyp surgery)

List of assessment which are recommended to be done at unscheduled visit prior to surgery was updated (ePRO questionnaires and UPSIT).

Section 8.2.1 (Clinical safety laboratory assessments)

Recommendation about fasting before blood drawn was added.

Appendix A (Regulatory, ethical and study oversight considerations)

Section A9 Study and site closure was added.

Appendix F (Anaphylaxis: signs and symptoms, management): F4.1 Immediate intervention

Typo was updated – from IV to IM.

Other changes:

Grammar corrections and minor wording changes were done to add more clarity.

Table of contents was updated. Table of figures was updated to add Background medication scheme. Abbreviations table was updated.

Version 1.0, 3 October 2017
Initial creation

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

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1. PROTOCOL SUMMARY

Table 1 Schedule of Activities – Screening (run-in)

Study period	**Enrollment/ Screening (run-in)**		**Refer to section**
Visit	**V1**	**V2[a)]**	
Week	**w-5**	**w-1**	
Visit window (days)	**±7**	**±7**	
General Procedures			
Informed Consent[b)]	X		Appendix A 3
Inclusion/Exclusion criteria review	X	X	5.1, 5.2
Demographics	X		N/A
Medical and surgical history (including respiratory and NP)	X		N/A
Safety Assessments			
Complete physical examination	X		8.2.2.1
Brief physical examination		X	8.2.2.2
Vital signs	X	X	8.2.3
Weight, height	X		8.2.5.1
ECG	X		8.2.4
Adverse events	X	X	8.3
Concomitant medications	X	X	6.5
Patient-reported outcome Assessments			
In-office PROs:			
Provide ePRO diary instructions	X		8.1.1
NP Symptom Screening Assessment (2 Week Recall)	X		8.1.1.1
Record visit in the eDiary. Confirm that all PRO assessments have been completed[c)]	X	X	8.1.1
Review compliance of at-home PRO assessments		X	8.1.1
At-home PROs completed by patients:			
NP Symptom Daily Diary (AM)	X	X	8.1.1.1
SNOT-22	X		8.1.1.2

HRU Assessment			
HRU	X		8.10
Nasal polyposis Assessments			
Nasal endoscopy	X	X[i)]	8.1.2
Sinus CT- scan[d)]		X[e)]	8.1.3
Assess nasal surgery or/and SCS use[f)]	X	X	8.1.4; 6.5.2
Laboratory Assessments			
Clinical chemistry	X		8.2.1
Hematology	X		8.2.1
Urine pregnancy test, dipstick		X	8.2.1.1
Serum pregnancy test[g)]	X		8.2.1.1
Serology (HepB, HepC, HIV1, HIV2)	X		8.2.1.2
FSH[h]	X		8.2.1.1
Exploratory biomarkers - nasal polyp biopsy[i)]		X	8.9
Other			
INCS distribution and accountability	X		6.5.1

[a] The time elapsed between V1 and V2 should be at least 4 weeks.
[b] ICF needs to be signed prior to any study activities/procedures.
[c] Patients to complete available assessments in-clinic prior to other interventional study procedures (e.g. lab tests, endoscopy, Sinus CT-scan).
[d] At selected clinical sites.
[e] Baseline Sinus CT- scan will be performed either at V2 or V3. CT-scan should be performed after biopsy.
[f] If the patient has surgery or uses SCS (e.g. oral, parenteral) during screening, the patient should be screen failed. Exception listed in section 5.4.1.
[g] This analysis will be only applicable for WOCBP patients.
[h] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months.
[i] At selected clinical sites, nasal polyp tissue will be obtained by biopsy. The screening biopsy should be done carefully without impact of NP score and prior to taking video for NP score assessment (and prior to CT-scan if applicable).

CT- Computed tomography; ECG- Electrocardiogram; FSH- Follicle stimulating hormone; HRU - Healthcare resource utilization; INCS- Intranasal corticosteroids; NP- Nasal polyposis; (e)PRO- (electronic) Patient-reported outcome; SCS- Systemic corticosteroids; SNOT-22- SinoNasal Outcome Test, 22 item

Table 2 Schedule of Activities – Randomization, treatment period and follow-up

Study period	Treatment								EOT /IPD	FU Approx. 200 pts[b]		FU/ FUD Approx. 200 pts[b]	FU Remaining pts[c]	UNS[d]	Refer to section
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12a**	**V13**	**V14**	**V12b**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**	**w60**	**w68**	**w80**	**w60**		
Visit window (days)[a]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
General Procedures															
Inclusion/Exclusion criteria review	X														5.1; 5.2
Safety Assessments															
Complete physical examination									X						8.2.2.1
Brief physical examination	X	X	X	X	X	X	X	X							8.2.2.2
Vital signs	X	X	X	X	X	X	X	X	X						8.2.3
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Patient-Reported Outcome Assessments															
In-office PROs:															
Record visit in the eDiary. Confirm that all PRO assessments have been completed[e]	X	X	X	X	X	X	X	X	X	X	X	X			8.1.1
Review compliance of at-home PRO assessments	X	X	X	X	X	X	X	X	X	X	X	X			8.1.1
UPSIT smell test[f]	X		X	X	X		X		X		X	X			8.1.1.7
At-home PROs completed by patients:															
NP Symptom Daily Diary (AM)	X	X	X	X	X	X	X	X	X	X	X	X			8.1.1.1
SNOT-22	X		X	X	X	X	X	X	X		X	X			8.1.1.2

Study period	Treatment								EOT /IPD	FU Approx. 200 pts[b]		FU/ FUD Approx. 200 pts[b]	FU Remaining pts[c]	UNS[d]	Refer to section
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12a**	**V13**	**V14**	**V12b**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**	**w60**	**w68**	**w80**	**w60**		
Visit window (days)[a]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
SF-36v2 (standard recall)	X		X	X	X				X		X	X			8.1.1.3
PGI-S	X	X	X	X	X	X	X	X	X						8.1.1.4
PGI-C		X	X	X	X	X	X	X	X						8.1.1.4
ACQ-6 (asthma patients only)	X		X	X	X	X	X	X	X						8.1.1.5
HRU Assessment															
HRU	X	X	X	X	X	X	X	X	X	X	X	X	X		8.10
Assess asthma exacerbations (asthma Pts only)	X	X	X	X	X	X	X	X	X	X	X	X	X		8.1.1.6
Nasal polyposis Assessments															
Nasal endoscopy			X	X	X		X		X[k]		X	X			8.1.2
Sinus CT- scan[g]									X[h]						8.1.3
Assess nasal surgery or/and SCS use	X	X	X	X	X	X	X	X	X	X	X	X	X		8.1.4; 6.5.2
Laboratory Assessments															
Clinical chemistry	X				X				X						8.2.1
Haematology	X			X	X		X		X		X	X	X		8.2.1
Urine pregnancy test, dipstick[i]	X	X	X	X	X	X	X	X	X						8.2.1.1
Phadiatop	X														8.2.1.3

Study period	Treatment								EOT /IPD	FU Approx. 200 pts[b]		FU/ FUD Approx. 200 pts[b]	FU Remaining pts[c]	UNS[d]	Refer to section
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12a**	**V13**	**V14**	**V12b**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**	**w60**	**w68**	**w80**	**w60**		
Visit window (days)[a]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Total IgE	X														8.2.1.3
PK[j]	X			X	X		X		X		X	X			8.5
ADA/nAb[j]	X			X	X		X		X		X	X			8.6
[redacted]	[redacted]				[redacted]				[redacted]						[redacted]
[redacted]	[redacted]				[redacted]				[redacted]						[redacted]
[redacted]	[redacted]				[redacted]				[redacted]						[redacted]
[redacted]									[redacted]						[redacted]
[redacted]	[redacted]														[redacted]
Randomization, Investigational Product Administration and INCS management															
Randomization[m]	X														4.1
Investigational Product Administration[n]	X	X	X	X	X	X	X	X							6.1; 6.2
INCS distribution and accountability	X		X	X	X	X	X	X	X	X	X				6.5.1

[a] All visits to be scheduled from the date of randomization, not from the date of previous visit, except for early discontinuation from IP.
[b] Approximately first 200 patients who complete the 56-week treatment will have a 24-week follow-up period without dosing: V12a at Week 60; V13 at Week 68; V14 at Week 80.
[c] The remaining patients will have a 4-weeks Follow-up period without dosing: V12b at Week 60.
[d] Unscheduled visits may be initiated as needed, and additional assessments may be performed at these visits as indicated.
[e] Patients to complete available assessments in-clinic prior to other study procedures.
[f] UPSIT smell test will be performed in all countries except Denmark. No Danish version of the test is available.
[g] For selected sites only.

[h] Assessed at EOT. For IPD patients only do assessment if the time period between randomization and IPD visit is ≥24 weeks. To avoid blood contamination, nasal secretion collected at EOT needs to be done after nasal endoscopy and before nasal biopsy.
[i] At dosing visits, must be collected pre-dose.
[j] Neutralizing antibody (nAb) testing will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.
[k] At selected clinical sites, nasal polyp tissue will be obtained by biopsy. For EOT visit, biopsy should be done after NP score assessment, nasal secretion sampling and sinus CT-scan (if applicable).
[l] Samples can be collected at any time from Week 0 (V3) after genetic consent form is obtained.
[m] All V3 procedures and assessments must be performed prior to randomization/IP dosing.
[n] IP administration should be the last activity of the visit. All visit procedures should be done prior to dosing.

ACQ-6- Asthma Control Questionnaire-6; ADA- Anti-drug antibodies; ClinRO- Clinician-reported outcome; CT- Computed tomography; EOT- End of treatment; FU- Follow-up; FUD- Follow-up discontinuation; HRU- Healthcare resource utilization; IgE- Immunoglobulin E; INCS- Intranasal corticosteroids; IPD- Investigational product discontinuation; nAb- Neutralizing antibody; NP- Nasal polyposis; PGI-C- Patient Global Impression of Change; PGI-S- Patient Global Impression of Severity; PK- Pharmacokinetics; PRO- Patient -reported outcome; 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

1.1 Synopsis

[redacted]

Protocol Title

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Benralizumab in Patients with Severe Nasal Polyposis (OSTRO).

Rationale

Nasal polyposis (NP) is a chronic inflammatory disease of the nasal mucosa characterized by the presence of polyps in the upper nasal cavity, originating from within the ostiomeatal complex. The presence of polyps can cause long-term symptoms such as prominent nasal obstruction, post-nasal drip, loss of smell, and discharge. These symptoms can impact greatly upon a patient's quality of life [redacted]

[redacted] he effect of benralizumab 30 mg on nasal polyps will be assessed on top of standard of care therapy with INCS over a 56 week treatment period.

Objectives and Endpoints

Primary objectives	Estimand Description / Endpoints
• To evaluate the effect of benralizumab on nasal polyp burden and patient-reported nasal blockage (NB)	• Population[a] : Full analysis set: • Co-primary endpoints: Change from baseline in endoscopic total nasal polyp score (NPS) Change from baseline in mean nasal blockage score (NBS) • Intercurrent event strategy: Treatment discontinuation - treatment policy NP Surgery – composite (worst possible) SCS for NP – composite (WOCF) • Summary Measure: differences in least squares mean change from baseline in NPS and NBS between benralizumab and placebo. Week 40 is the primary timepoint.[b]

Secondary objectives:	Endpoint/variable:
To evaluate the effect of benralizumab on:	
• Disease specific health-related quality of life (HRQoL)	• Change from baseline in SinoNasal Outcome Test (SNOT-22) score[bc]
• Nasal polyp surgery and/or SCS use	• Time to first NP surgery and/or SCS use for NP[c] • Time to first NP surgery[c]
• Sense of smell	• Change from baseline in mean difficulty with sense of smell (DSS) score[bc] • Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) score

Secondary objectives:	Endpoint/variable:
• Sinus opacification by CT scan (subset of patients)	• Change from baseline in Lund Mackay score[c] and sinus severity score by Quantitative CT analysis
• Proportion of NP surgery	• Proportion of patients with surgery for NP
• Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for NP • Time to first SCS course for NP, number of courses of SCS for NP, total SCS dose used and total duration of SCS use for NP
• Symptoms associated with nasal polyps	• Change from baseline in nasal symptom score(s) as captured in the daily diary
• Patient-reported general health status	• Change from baseline in Short Form 36-item Health survey, Version 2 (SF-36v2) Physical Component Score (PCS), Mental Component Score (MCS) and domains

a Treatment condition for primary estimand: Treatment with benralizumab versus placebo, regardless of compliance, where rescue with NP surgery and/or SCS for NP represents failure.
b Week 56 will also be a multiplicity protected timepoint for co-primary and key secondary repeated measures endpoints.
c Key secondary efficacy endpoints. A similar estimand as outlined for the co-primary endpoints will be used for analyses of repeated measures secondary endpoints.

Safety objective:	Endpoint/variable:
• To assess the safety of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination
• To assess the pharmacokinetics and immunogenicity of benralizumab	• Serum PK • Benralizumab anti-drug antibodies (ADA)

• To evaluate the effect of benralizumab on unplanned health care resource utilization	• Hospitalizations, emergency room and urgent care visits

Overall design

This is a randomized, double-blind, placebo-controlled, parallel-group, international, multicenter, Phase 3 study to evaluate the efficacy and safety of repeat dosing of benralizumab 30 mg administered subcutaneously (SC) versus placebo in patients with severe NP.

Approximately 400 patients will be randomized globally to receive benralizumab 30 mg sc or matching placebo.

Patients will be stratified by region (United States [US] vs non-US) and by baseline comorbid asthma status (yes vs no). It is intended that approximately half of the randomized patients recruited into this study will have comorbid asthma.

After enrolment, eligible patients will receive a centrally sourced standardized dose of INCS and will enter a 5-week screening/run in period. Patients who meet eligibility criteria will be randomized 1:1 at Week 0 (Day 0) to receive either placebo or benralizumab 30 mg SC every 4 weeks for the first 3 doses (Weeks 0, 4 and 8) and every 8 weeks thereafter (Weeks 16, 24, 32, 40 and 48). A total of 8 doses will be administered to patients who complete the treatment period per protocol. An end of treatment (EOT) visit will be conducted at Week 56.

The first approximately 200 patients who complete the 56-week treatment will have a 24-week follow-up (FU) period without dosing to assess durability of benefit. These patients will have the FU for the final safety assessment at week 80. The remaining patients will have a last FU visit 12 weeks after last dose for final safety assessments at week 60.

Study Period

Estimated date of first patient enrolled: **Q1 2018**

Estimated date of last patient completed: **Q3 2020**

Number of Patients

This study will be conducted in approximately 8 countries at approximately 100 sites. The target is to randomize 400 patients.

Treatments and treatment duration

Benralizumab 30 mg will be administered SC every 4 weeks for the first 3 doses (Weeks 0, 4, and 8) and every 8 weeks thereafter (Weeks 16, 24, 32, 40, and 48) with an EOT at Week 56. Matching placebo will be administered SC at the same time points. In total patients will receive 8 doses of investigational product (IP).

All patients will have their current INCS therapy standardized to Mometasone Furoate Nasal Spray (MFNS) at V1 and for a minimum of 4 weeks prior to V2 and continued throughout the screening and study period. If a subject cannot tolerate MFNS during screening, the subject would be screen failed.

Statistical methods

Randomization will be stratified by region (US vs non-US) and by baseline comorbid asthma status (yes vs no). At least 50% of the randomized patients will have comorbid asthma.

The primary analysis will compare the effect of benralizumab versus placebo on the change from baseline in total NPS at Week 40 and the change from baseline in the mean daily nasal blockage score (NBS) at Week 40 using a hybrid of worst possible/worst observation carried forward (WP/WOCF) and multiple imputation (MI), followed by an analysis of covariance (ANCOVA) with treatment arm, baseline score, region (US vs non-US), and baseline comorbid asthma status (yes vs no) as covariates.

All safety parameters will be analyzed descriptively.

1.2 Schema

The study design schema is summarized in Figure 1.

The background medication scheme is summarized in Figure 2.

Figure 1 Study flow chart

Screening (run-in)		Treatment				Follow-up	
V1	V2	V3	V3, V4, V5	V6, V7, V8, V9, V10	V11	V12a/ V12b	V13, V14
w-5	w-1	w0	w0, w4, w8	w16, w24, w32, w40, w48	w56	w60	w68, w80

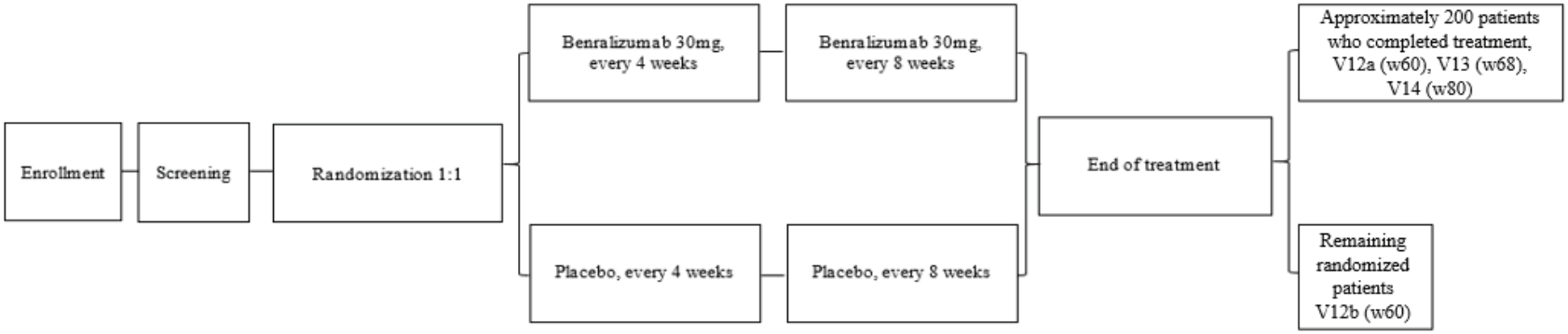

Figure 2 Background Medication scheme

IxRS allocation:		
Enrolment/Screening (run-in)	Treatment	Follow up – approximately 200 pts
V1	V3, V5, V6, V7, V8, V9, V10, V11	V12a, V13
w-5	w0, w8, w16, w24, w32, w40, w48	w60, w68
Dosing:		
All eligible patients will receive MFNS through the screening period. Two doses (50mc g/actuation) in each nostril twice daily (total daily dose of 400mcg) will be administered unless there is a medical rationale to use the lower dose (QD).	All randomized patients will receive MFNS through the treatment period. Two doses (50mc g/actuation) in each nostril twice daily (total daily dose of 400mcg) will be administered unless there is a medical rationale to use the lower dose (QD).	Approximately 200 patients, who completed treatment, continue MFNS Through the follow up period. Two doses (50mc g/actuation) in each nostril twice daily (total daily dose of 400mcg) will be administered unless there is a medical rationale to use the lower dose (QD).

2. INTRODUCTION

2.1 Study rationale

The role of eosinophils and basophils is considered important to the pathology of nasal polyps in a majority of patients with severe bilateral NP.

2.2 Background

[redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab 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 and SCS) and surgical interventions. [redacted]

[redacted]

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

Computed tomography is incorporated into this study design with reference to the European Union (EU) guidance (Directorate-General – Environment, nuclear safety and civil protection 1998). The potential benefits of the study are expected to be Category IIB as described in the guidance document aimed directly at the diagnosis, cure, or prevention of disease. The use of CT involves ionizing radiation that increases the risk of radiogenic tumours in patients. Patients will be informed of the risks associated with CT before entering the study. Because CT scans in this study may not offer direct individual benefit to the patient, a dose constraint has been applied based on the as low as reasonably achievable principle [redacted]

3. OBJECTIVES AND ENDPOINTS

3.1 Primary objectives

Primary objectives	Estimand Description / Endpoints
• To evaluate the effect of benralizumab on nasal polyp burden and patient-reported nasal blockage (NB)	• Population[a]: Full analysis set: • Co-primary endpoints: Change from baseline in endoscopic total nasal polyp score (NPS) • Change from baseline mean nasal blockage score (NBS) • Intercurrent event strategy: Treatment discontinuation – treatment policy NP surgery – composite (Worst Possible) SCS for NP – composite (WOCF) • Summary Measure: differences in least squares mean change from baseline in NPS and NBS between benralizumab and placebo. Week 40 is the primary timepoint[b]

3.2 Secondary objectives

Secondary objectives:	Endpoint/variable:
To evaluate the effect of benralizumab on:	
• Disease specific health-related quality of life (HRQoL)	• Change from baseline in SinoNasal Outcome Test (SNOT-22) score[bc]
• Nasal polyp surgery and/or SCS use	• Time to first NP surgery and/or SCS use for NP [c] • Time to first NP surgery[c]

Secondary objectives:	**Endpoint/variable:**
• Sense of smell	• Change from baseline in mean difficulty with sense of smell (DSS) score[bc] • Change from baseline in University of Pennsylvania Smell Identification Test (UPSIT) score
• Sinus opacification by CT scan (subset of patients)	• Change from baseline in Lund Mackay score[c] and sinus severity score by Quantitative CT analysis
• Proportion of NP surgery	• Proportion of patients with surgery for NP
• Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for NP • Time to first SCS course for NP, number of courses of SCS for NP, total SCS dose used and total duration of SCS use for NP
• Symptoms associated with nasal polyps	• Change from baseline in nasal symptom score(s) as captured in the daily diary
• Patient-reported general health status	• Change from baseline in Short Form 36-item Health survey, Version 2 (SF-36v2) Physical Component Score (PCS), Mental Component Score (MCS) and domains

a Treatment condition for primary estimand: Treatment with benralizumab versus placebo, regardless of compliance, where rescue with NP surgery and/or SCS for NP represents failure
b Week 56 will also be a multiplicity protected timepoint for co-primary and key secondary repeated measures endpoints.
c Key secondary efficacy endpoints. A similar estimand as outlined for the co-primary endpoints will be used for analyses of repeated measures secondary endpoints.

3.3 Safety objectives

Safety objective:	Endpoint/variable:
• To assess the safety of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination
• To assess the pharmacokinetics and immunogenicity of benralizumab	• Serum pharmacokinetics (PK) • Benralizumab anti-drug antibodies (ADA)

3.4 Exploratory objectives

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• To evaluate the effect of benralizumab on unplanned health care resource utilization	• Hospitalizations, emergency room and urgent care visits

4. STUDY DESIGN

4.1 Overall design

This is a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to evaluate the efficacy and safety of repeat dosing of benralizumab 30 mg administered SC versus placebo in patients with severe NP.

Approximately 400 patients will be randomized, globally, to receive benralizumab 30mg SC or matching placebo.

Patients will be stratified by region (US vs non-US) and by baseline comorbid asthma status (yes vs no). At least 50% of the randomized patients will have comorbid asthma.

After enrolment, eligible patients will enter a screening/run in period on a stable dose of study provided MFNS. It is required to maintain a 4-week gap between V1 and V2 during the screening/run-in period. Patients will be provided with an electronic patient-reported outcome (ePRO) device to record symptoms throughout the study (see Section 8.1.1 Clinical outcome assessments). Patients who continue to meet eligibility criteria will be randomized 1:1 at Visit 3 (Day 0) to receive either placebo or benralizumab 30 mg SC every 4 weeks for the first 3 doses (Weeks 0, 4 and 8) and every 8 weeks thereafter (Weeks 16, 24, 32, 40 and 48). A total of 8 doses will be administered. An EOT visit will be conducted at Week 56.

Patients will return to the study site at dosing visits and at EOT during the treatment period for evaluation of efficacy, safety, pharmacokinetics (PK), ADA, sample collection of blood and nasal secretion for exploratory biomarkers. Throughout the entire study period, participants will continue to receive daily MFNS. If at any point a patient meets IP discontinuation (IPD) criteria, an early IPD visits will be performed (see Section 7.1 Discontinuation of study treatment).

At selected clinical sites, nasal polyp tissue will be obtained by biopsy according to the schedule of activities (SoA). A baseline biopsy will be obtained prior to randomization, at visit 2 (V2). Another biopsy of nasal polyp tissue will be obtained at Week 56 (EOT) (see Section 8.9 Biomarkers).

At selected clinical sites, CT scans will be performed. A baseline CT scan will be done at V2 or V3 and the next one at the EOT/IPD visit (Week 56) (see Section 8.1.3 Sinus Computed Tomography).

The first approximately 200 patients who complete the 56-week treatment will have a 24-week follow-up (FU) period without dosing to assess durability of benefit. These patients will have the FU for the final safety assessments at week 80. The remaining patients will have a last FU visit 12 weeks after last dose for final safety assessments at week 60.

If for any reason a patient in the first set of randomized patients 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 as soon as it is convenient to the patient and site, but not prior to Week 60 (visit 12).

For an overview of the study design, see Figure 1, Section 1.2 Schema. For details on treatments given during the study, see Section 6.1 Treatments administered.

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

4.1.1 Study Conduct Mitigation in the event of evolving SARS-CoV-2 (COVID-19) pandemic or other study disruption

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during COVID-19 global pandemic (e.g. during quarantines resulting in site closures, regional travel restrictions, and considerations regarding the safety of site

personnel and study patients, to avoid events of infection with SARS-CoV-2) or other study disruptions, which may prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient'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 the COVID-19 pandemic or other study disruptions, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

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

- Obtain verbal consent for the mitigation procedures (e.g. remote visits and study supplies delivery to patient's home) and capture it accordingly in the source documentation.
- Remote contact with patients may be performed by Site qualified Health Care Professional (HCP) using telecommunications technology including phone calls, virtual or video visits and mobile health devices (telemedicine visit).
- Missing assessments may be performed outside a visit window.
- Study procedures (e.g. nasal endoscopy, nasal biopsy and nasal secretion) which may represent a safety risk to patients or site staff if performed during the peak period of the COVID-19 pandemic or other study disruption may be postponed based on Sponsor´s recommendation, Investigator's clinical judgement and local, international or professional guidance and recommendations.
- Remote completion of on-site ePRO assessments
- Home delivery of study supplies, where applicable

For further details on study conduct during COVID-19 global pandemic or other study disruptions, please refer to Appendix G.

[redacted]

[redacted]

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

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

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

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

For procedures regarding withdrawal of incorrectly enrolled or randomized patients see Section 7.4 Procedures for handling incorrectly enrolled or randomized patients.

5.1 Inclusion criteria

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

Informed consent

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions, listed in the informed consent form (ICF) and in this protocol.

2. 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.

3. Provision of signed and dated written genetic informed consent in patients that agree to participate in the genetic sampling, prior to collection of sample for genetic analysis.

The ICF process is described in Appendix A 3.

Age

4. Female or male patients aged 18 to 75 years inclusive, at the time of signing the ICF.

Type of patient and disease characteristics

5. Patients with bilateral sinonasal polyposis that, despite treatment with a stable dose of INCS for at least 4 weeks prior to V1, in addition to a history of treatment with SCS (oral, parenteral) or prior surgery for NP, have severity consistent with a need for surgery as described by:

   - A minimum total NPS of 5 out of a maximum score of 8 (with a unilateral score of at least 2 for each nostril) at V1, and continuously maintained at V2 to meet the randomization criterion, as determined by the study Imaging Core Lab;
   - Ongoing symptoms for at least 12 weeks prior to V1;
   - Patient-reported moderate to severe nasal blockage (score 2 or 3) over the 2-weeks prior to V1 (2-week recall assessment of symptoms, scores 0-none to 3-severe).

6. SNOT-22 total score ≥ 30 at enrolment (V1).

Patient must meet the following criteria at the randomization visit (V3):

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

8. At randomization, a bi-weekly mean NBS ≥ 1.5.

9. SNOT-22 total score ≥ 30 at randomization (V3).

10. At least 70% compliance with INCS during the run-in period based on daily diary.

Weight

11. Patients with a minimum weight of 40kg.

Reproduction

12. Negative serum pregnancy test result at V1 and a negative urine pregnancy test at randomization for female patients of childbearing potential.

13. Women of childbearing potential (WOCBP) must use an effective form of birth control (confirmed by the Investigator) eg, total sexual abstinence, a vasectomized sexual partner, Implanon. Female sterilization by tubal occlusion, any effective IUD

intrauterine device/IUS levonorgestrel Intrauterine system, Depo-Provera™ injections, oral contraceptive, Evra Patch™, or Nuvaring™. Women of childbearing potential must agree to use highly effective method of birth control, as defined above, from enrolment, throughout the study duration and for 16 weeks after the last dose of IP.

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

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

15. Male subjects who are sexually active must be surgically sterile at least one year prior to Visit 1 or must use an adequate method of contraception (condom or condom with spermicide depending on local regulations) from the first dose of IP until 16 weeks after their last dose. Men with a partner or partners who is (are) not of childbearing potential are exempt of these requirements

5.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled.

Medical conditions

1. Patients who have undergone any nasal and/or sinus surgery within 3 months prior to V1.

2. Patients with conditions or concomitant disease that makes them non evaluable for the co-primary efficacy endpoint such as:

    - Unilateral antrochoanal polyps;
    - Nasal septal deviation that occludes at least one nostril;
    - Acute sinusitis, nasal infection, or upper respiratory infection at screening or in the 2 weeks before screening;

- Current rhinitis medicamentosa;
- Allergic fungal rhinosinusitis(AFRS) or Allergic fungal sinusitis (AFS);
- Nasal cavity tumors.

3. Clinically important comorbidities that could confound interpretation of clinical efficacy results including, but not limited to: active upper or lower respiratory tract infection, cystic fibrosis, primary ciliary dyskinesia, eosinophilic diseases other than asthma (eg, allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangitis [Churg-Strauss syndrome], hypereosinophilic syndromes), granulomatosis with polyangitis (Wegener's granulomatosis), Young's syndrome, etc.

4. 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:
   - Affect the safety of the patient throughout the study;
   - Influence the findings of the studies or their interpretations;
   - Impede the patient's ability to complete the entire duration of study.

5. Patients experiencing an asthma exacerbation requiring systemic (oral and/or parenteral) corticosteroids treatment or hospitalization (>24hrs) for treatment of asthma within 4 weeks prior to V1.

6. History of anaphylaxis to any biologic therapy or vaccine.

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

8. History of Guillain-Barré syndrome.

9. A helminth parasitic infection diagnosed within 24 weeks prior to V1 and has not been treated with, or has failed to respond to standard of care therapy.

10. Current malignancy, or history of malignancy, except for:
    - Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that patient is in remission and curative therapy was completed at least 12 months prior to V1.

- Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to V1.

  NOTE: Hormonal therapy is allowed. As long as the cancer is in remission for 5 years, the patient is eligible.

11. Any clinical 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 patient at risk, because of his/her participation in the study, or may influence the results of the study, or the patients' ability to complete entire duration of the study.

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

13. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology (confirmed by additional testing, e.g. hepatitis C RNA test, if indicated), or a positive medical history for hepatitis B or C (Note: Patients with history of hepatitis B vaccination without history of hepatitis B are allowed to enrol).

14. History of known immunodeficiency disorder, including a positive human immunodeficiency virus (HIV) test.

15. Infection requiring systemic antibiotics (Ab) within 14 days prior to V1.

Prior/concomitant therapy

16. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, or any experimental anti-inflammatory therapy) within 3 months prior to V1 and during the study period.

17. Receipt of any marketed or investigational biologic products (monoclonal or polyclonal antibody) within 6 months or 5 half-lives, whichever is longer, prior to V1 and during the study period. This also applies to patients who previously participated in clinical studies and were treated with monoclonal antibodies (e.g. mepolizumab, reslizumab, dupilumab, omalizumab). Note that this restriction do not apply to patients, who are confirmed to have only received treatment with placebo.

18. Previous receipt of benralizumab.

19. Receipt of immunoglobulin or blood products within 30 days prior to V1.

20. Receipt of live attenuated vaccines 30 days prior to the date of randomization.

21. Receipt of any investigational drug within 30 days or 5 half-lives whichever is longer prior to randomization.

22. Receipt of systemic corticosteroid 4 weeks prior to V1, or a scheduled systemic corticosteroid treatment during the study period.

    NOTE: Sustained release steroids (e.g. Kenalog [Triamcinolone acetonide]) or depot injections require minimum 6 weeks washout prior to V1.

23. Receipt of leukotriene antagonist/modifiers for patients who were not on a continuous stable dose for ≥30 days prior to V1.

Prior/concurrent clinical study experience

24. Concurrent enrolment in another clinical drug interventional trial.

Diagnostic assessments

25. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 3 times the upper limit of normal (ULN) confirmed during screening period.

Other exclusions

26. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site or immediate family members of such individuals).

27. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

28. Previous randomization in the present study.

29. Planned major surgical procedures or scheduled NP surgery at the time of the study enrolment and randomization.

30. Initiated or is being maintained on an aspirin desensitization regimen for the management of AERD at the time of study enrolment or during the run-in period.

31. History of alcohol or drug abuse within 12 months prior to V1, based on Investigator's assessment.

32. For women only – currently pregnant (or intend to become pregnant), breastfeeding or lactating.

5.3 Lifestyle restrictions

1. Fertile and sexually active patients or their partners should use effective contraceptive methods throughout the study and 16 weeks after last dose of the IP. Male patients should refrain from fathering children or donating sperm from the time of informed consent, to 16 weeks after last dose of the IP (see Inclusion criterion 15).

2. Patients must abstain from donating blood and plasma from the time of informed consent, to 16 weeks after last dose of the IP.

5.4 Screen failures

Screen failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomized and must not be assigned to the study treatment. These patients must be withdrawn from the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries form regulatory authorities (RAs). Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

These patients should have the reason for study withdrawal recorded in the electronic case report form (eCRF) as “Incorrect Enrolment” (ie. Patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized patients).

5.4.1 Re-screening

Re-screening is allowed only once for a patient.

Rescreening and/or up to 14 days extension of the screening period, is allowed for transient reasons (including but not limited to equipment/procedure failure, e.g. problems with the ePRO device impacting availability of data or documenting compliance with INCS, or unforeseen personal events that result in a missed visit).

For patients who require SCS and/or antibiotics for an asthma exacerbation or worsening of nasal polyp symptoms during the screening period (prior to V2), the screening period may be extended for up to 6 weeks, provided the treatment duration with SCS and/or Ab is ≤ 14 days. The next regular study visit (Visit 2) will be delayed and may proceed no sooner than 4 weeks after the last dose of SCS and/or Ab.

If the duration of treatment with SCS and/or Ab is >14 days, or asthma exacerbation/ worsening of nasal polyp symptoms occurred after V2, patients should be screen failed, but can be considered for re-screening.

Patients who fail to meet the required total NP score at V1 or V2, may be considered for re-screening once an appropriate time interval, as deemed by the investigator, has elapsed.

Patients may not be re-screened or have an extended screening period for failure to meet minimum symptom severity or SinoNasal Outcome Test (SNOT-22) requirements.

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

Re-screened patients should re-sign informed consent. All procedures from the screening/run-in period should be repeated. Re-screening should be documented so that its effect on study results, if any, can be assessed.

6. STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to benralizumab 30 mg or matching placebo, 1 mL.

6.1 Treatments administered

6.1.1 Investigational products

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

Table 3 Study Treatments

	Treatment 1	**Treatment 2**
Study treatment name:	Benralizumab	Placebo
Dosage formulation:	30 mg/mL solution for injection in accessorized pre-filled syringe, 1 mL fill volume	Matching placebo solution for injection in accessorized pre-filled syringe, 1 mL fill volume
	Clear to opalescent, colourless to yellow solution.	Clear to opalescent, colourless to yellow solution.
Route of administration	subcutaneously	subcutaneously
Dosing instructions:	Benralizumab active solution will be administered subcutaneously to patients by health care professionals in this clinical study using an accessorized prefilled syringe (APFS).	Placebo solution will be administered subcutaneously to patients by health care professionals in this clinical study using an accessorized prefilled syringe (APFS).

	Treatment 1	Treatment 2
	Each prefilled syringe is designated for single use only and is not to be administered to more than one patient.	Each prefilled syringe is designated for single use only and is not to be administered to more than one patient.
Packaging and labelling	Study treatment will be provided in accessorized pre-filled syringe. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Label text will be translated into local language as required. The label will include the following information: • study code • Investigational product/study treatment dosage form, route of administration, and quantity of dosage units • kit ID • P Lot ID • Expiry date • Investigator Name (to be written on the label) • E-code (to be written on the label) • Sponsor name and contact details • Directions for use • Storage condition • Standard statements required by regulatory authorities	Study treatment will be provided in accessorized pre-filled syringe. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Label text will be translated into local language as required. The label will include the following information: • study code • Investigational product/study treatment dosage form, route of administration, and quantity of dosage units • kit ID • P Lot ID • Expiry date • Investigator Name (to be written on the label) • E-code (to be written on the label) • Sponsor name and contact details • Directions for use • Storage condition • Standard statements required by regulatory authorities
Provider	AstraZeneca	AstraZeneca

6.2 Preparation/handling/storage/accountability

6.2.1 Preparation and handling

The investigational product will be administered at the study site on treatment visits and within visit windows as specified in the SoA.

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

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment.

Before investigational product administration

Prior to each IP administration:

- Investigator/authorized 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.

[redacted]

Further details on IP administration are described in the IP Handling Instruction provided to study sites. Investigational product administration must be carried out in line with the Instruction.

After investigational product administration

After IP administration, the patient should be observed for a minimum of 1 hour in case of any acute drug reactions.

Conditions requiring investigational product administration rescheduling

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

- The patient has an intercurrent illness, that in the opinion of the Investigator may compromise the safety of the patient in the study (e.g. viral illnesses);
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation;
- The patient is febrile (≥38°C; ≥100.4°F) within 72 hours prior to the IP administration.

6.2.2 Storage

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

The investigational product must be kept in the original outer container and under conditions specified on the label (between 2 to 8°C (36 to 46°F), protected from the light).

In the following cases, the site staff should not use affected IP and should immediately contact an AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study;
- Damaged kit upon receipt;
- Damaged syringe/cartridge.

Damaged IP should be documented via Interactive Web Response System/ Interactive Voice Response System (IWRS/IVRS; refer to IWRS/IVRS manual for further details).

6.2.3 Accountability

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

An AstraZeneca site monitor will account for all study treatments received at the site, for unused study treatments, and for appropriate destruction or return of unused study treatments. Certificates of delivery, destruction, and/or return should be signed.

In the case of a malfunctioning accessorized prefilled syringe (APFS), the site should contact the study monitor to initiate a product complaint process according to applicable guidelines.

Further guidance and information for the final disposition of unused study treatment are described in the Pharmacy Manual provided to the sites.

6.3 Measures to minimise bias: randomization and blinding

6.3.1 Methods for assigning treatment groups

Patients will be stratified by region (US vs non-US) and by baseline comorbid asthma status (yes vs no). It is expected that at most 50% of the randomized patients will not have comorbid asthma. The corresponding strata will be closed for randomization (see Section 7.3.1 Withdrawal due to recruitment completion in a randomization stratum).

All patients will be centrally assigned to randomized study treatment using an IWRS/IVRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

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

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule.

If a randomized patient withdraws from the study, then his/her enrolment/randomization code cannot be reused. Withdrawn patients will not be replaced.

6.3.2 Methods for ensuring blinding

This is a double-blind study. AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of patients or in their clinical evaluation will not be aware of treatment allocation.

Placebo solution will be visually matched with benralizumab solution. Both benralizumab and placebo will be provided in an APFS.

6.3.2.1 Maintaining the blind to the patient's blood eosinophil counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower blood eosinophil counts than patients on placebo. In order to mitigate potential unblinding on this basis, per protocol haematology will be run by the central laboratory. After Visit 3, eosinophil, basophil and monocyte counts will be redacted from any central laboratory reports sent to investigative sites to prevent the Principal Investigator (PI)/designee from possibly deducting the 'eosinophil + basophil + monocyte' contribution to the complete blood count (CBC).

If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if haemoglobin (Hb) is desired the Investigator should avoid ordering a complete blood cell count with differential.

6.3.2.2 Handling of labs obtained during the study period but ordered outside of the clinical trial.

Site staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports. To help ensure this, each investigational site will designate an individual (e.g. administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil and monocyte results prior to the report being handed over to the site staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with AstraZeneca.

In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases, but should not be informed about lab results.

6.3.3 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or Pharmacists at the study site from the IWRS/IVRS. Further detail on how to unblind a patient's treatment allocation will be described in the IWRS/IVRS user manual provided to each study site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient 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 (RAs). Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.4 Treatment compliance

The administration of all study treatments (including IPs) should be recorded in the appropriate section of the eCRF.

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 on treatment visits and within visit windows as specified in the SoA.

In cases where a treatment visit needs to be re-scheduled, 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.

If 2 doses of the IP are missed during course of the study the patient should be discontinued from the study treatment.

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

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

6.5 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF, 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 medication can be found in the Table 4 and Table 5, provided below:

Table 4 Restricted medications

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Inactive/killed vaccinations (e.g. inactive influenza)	Not allowed within the 7 days before or within 7 days after any IP dosing study visit
Any Immunosuppressives – topical	Topical administration of Immunosuppressive medication may be allowed at the discretion of the Investigator

Medication/class of drug:	**Usage (including limits for duration permitted and special situations in which it's allowed):**
Allergen Immunotherapy	Allowed if on stable therapy started 30 days prior to V1; no change during the treatment period
Systemic corticosteroids (SCS)	A short course of SCS (3-14 days), allowed at PI's discretion to relieve symptoms of nasal polyposis worsening or asthma exacerbations
Decongestants (topical or systemic)	Only allowed for endoscopic procedure

Table 5 Prohibited medications

Prohibited medication/class of drug:	
Intranasal Medication including intranasal corticosteroids drops	Only study provided MFNS is allowed.
Any immunosuppressive treatment including but not limited to: methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxylchloroquine, 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 desensitization	Use of aspirin as a desensitization regimen for the management of aspirin exacerbated respiratory disease (AERD) is not allowed; all other uses of aspirin is allowed for any other medical conditions.
Any marketed or investigational biologic (monoclonal or polyclonal antibody)	Not allowed within 6 months or 5 half-lives (whichever is longer) prior to V1; during the study period 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 to randomization; and during the study period.
Live attenuated Vaccines	Not allowed within 30 days prior to randomization; 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 within 30 days prior to V1 and during the study period.

6.5.1 Background medication

If a patient is using an alternative INCS product other than MFNS prior to visit 1, the Investigator will switch the INCS to MFNS at visit 1. All patients will receive study provided standardized MFNS for a minimum of 4 weeks prior to V2, continued throughout the screening and study period.

Mometasone furoate (50 micrograms/actuation) nasal spray is contained in a bottle that contains 120 actuations for US and 140 actuations for all other countries. Two doses (50mcg/actuation) in each nostril twice daily (total daily dose of 400 mcg) will be administered, unless there is a medical rationale to use the lower dose (QD) regimen.

Each patient will receive enough background medication to cover the need until the next on site visit. Intranasal corticosteroids dispensation will be performed according to the SoA table (Table 1).

Intranasal corticosteroid compliance will be recorded by the patient in the ePRO diary and should be checked by Investigators during the study period. If a subject cannot tolerate MFNS during screening period, the subject should be screen failed.

The Principal Investigator should ask patients about SCS (oral, parenteral) use for NP at each visit and record in the eCRF. If medically justified, a short course of SCS (3-14 days) is allowed for NP worsening during the study, at PI's discretion, according to local standard of care. If SCS is used for ≤ 14 days between V1 and V2, the screening may be extended for maximum 6 more weeks. Otherwise, patient should be screen failed, but can be considered for rescreening once (please refer to section 5.4.1 Re-screening).

6.5.2 Other concomitant treatment

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

6.6 Dose modification

N/A

6.7 Treatment after the end of the study

After the end of the study, the patient should be given standard of care therapy, at the discretion of the Investigator, per local practice.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from IP in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
2. AE that, in the opinion of the Investigator, contraindicates further dosing.
3. Severe non-compliance with the CSP.
4. Risk to patient as judged by the Investigator or AstraZeneca.
5. Pregnancy.
6. IP unblinding (PI).
7. Development of any study specific criteria for discontinuation:
    - Anaphylactic reaction to the IP requiring administration of epinephrine;
    - Development of helminth parasitic infestations requiring hospitalization;
    - If 2 doses of the IP are missed during course of the study;
    - A respiratory-related event requiring mechanical ventilation.

7.1.1 Procedures of discontinuation of study treatment

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient that decides to discontinue IP should always be asked about the reason(s) and the presence of any AEs.

All patients who prematurely discontinue IP should return to the study site and complete the procedures described for premature IPD visit within 8 weeks after the last dose of IP. At that visit, although no longer on IP, patients should be encouraged to remain in the study to complete all subsequent study visits, procedures, and assessments. Data collection should continue according to the study protocol. Note that in this case, the IPD visit replaces the nearest regular visit while the following visits continue as possible.

If the patient does not agree to complete all subsequent visits and procedures, the patient should be encouraged to stay in the study, keep the daily diary (ePRO device), and continue selected visits until Week 56.

If the patient does not agree to continue in-person study visits, telephone visits should be performed to ensure the collection of endpoints and safety information. Patients will be encourage to keep the ePRO device and do assessments, participate in the telephone visits, and return ePRO handheld device at the end of the study. If a patient is not willing to complete ePRO procedures, device should be returned at the IPD visit and the telephone FU should be continued. A patient that agrees to modify FU is not considered to have withdrawn consent or to have withdrawn from the study.

If a patient is not willing to participate further in the study after the IPD visit, the ePRO will be returned at the IPD visit. The patient should be asked to return for a FU visit 12 weeks after the last dose of IP for final study-related assessments.

The reason for premature discontinuation of IP should be recorded in the eCRF.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Lost to follow-up

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

The patient 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; or 1 unsuccessful effort to check the vital status of the patient using publicly available sources, if allowed, by local regulations.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule;
- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by e.g. repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record;
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (e.g. withdraw consent), at any time (IP and assessments) at his/her own request, without prejudice to further treatment.

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

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

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up patients as medically indicated. The patient will return ePRO devices to the site staff.

See SoA (Table 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All Study treatment should be returned by the patient.

7.3.1 Withdrawal due to recruitment completion in a randomization stratum

When a specific stratum is full, patients in the completed stratum will not be randomized and will be withdrawn from the study. The reason of the withdrawal should be documented in the source and eCRF as a development of study specific criterion for discontinuation. Same as with screen failures, no further study related follow-up of these patients is required.

The no-comorbid asthma stratum will be closed when the total number of patients in the stratum reaches approximately 200.

7.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study treatment. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and an agreement should be made between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Team must ensure all decisions are appropriately documented.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

The Investigator will ensure that data are recorded on the eCRF. Medidata Rave Web Based Data Capture system will be used for data collection and query handling.

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.

Immediate safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Additional data to assess the impact of study disruption caused e.g. by COVID-19 pandemic will be collected in additional eCRF modules. For more information please refer to the recent version of eCRF instruction.

8.1 Efficacy assessments

8.1.1 Clinical outcome assessments

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

The Investigator will ensure that patients 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 patient does not meet the screening requirements, the device will be deactivated and retained at the site. If eligible to continue, the patient 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 patient needs as required. The patient will be required to complete a training module before taking the device home. If a patient fails to meet eligibility criteria after V1 (for example regarding total NPS), the patient 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 patient adherence with the daily diary and follow-up as necessary to minimize missing data. Patient compliance should be checked weekly (at minimum) to ensure that the patient is completing the assessments as scheduled. Monitoring of patient adherence to the diary is critical during the baseline period (Study day -13 to Day 0) to ensure that the patient meets applicable criteria for randomization. Continued weekly monitoring of adherence throughout the study and follow-up with patients via phone and at the visits is required to ensure sufficient data is available for supporting the co-primary endpoint of this study.

All PRO assessments should be completed prior to any other interventional study procedure (e.g. laboratory tests, endoscopy, CT-scan) with the exception of informed consent at Visit 1. 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.

8.1.1.1 Nasal Polyposis Symptom Diary

The patient will complete an 11-item NP symptom diary (NPSD) each morning throughout the screening, treatment and follow-up periods. The patient is asked to consider their experience with NP / nasal polyps over the past 24 hours when responding to each question. Patients are asked to report their experience with NP symptoms (nasal blockage, nasal congestion, runny nose, postnasal drip (mucus 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). Patients 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 (Nasal Polyposis Symptom Screening Assessment) 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; otherwise concepts measured are the same as the daily diary.

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

8.1.1.1.1 Nasal Blockage Score

One of the co-primary endpoints of the study is the change from baseline in the bi-weekly mean of NBS at Week 40 (change from baseline at Week 56 is a key secondary endpoint). NBS is captured by an item in the NPSD asking patients to rate the severity of their worst nasal blockage 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 NBS 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.

8.1.1.1.2 Difficulty with Sense of Smell (DSS) score

One of the key secondary endpoints of the study is the change from baseline in the bi-weekly mean of DSS at Week 40 (change from baseline at Week 56 is also a key secondary endpoint). DSS is captured by an item in the NPSD asking patients 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 DSS 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.

8.1.1.2 SinoNasal Outcome Test 22 item

One of the key secondary endpoints of the study is the change from baseline in SNOT-22 total score at Week 40 (change from baseline at Week 56 is also a key secondary endpoint). The SNOT-22 is a condition-specific HRQoL assessment which captures patient-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 device per the SoA.

8.1.1.3 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 patients 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).

Table 6 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 Component Summary; MH Mental Health; PCS Physical Component Summary; PF Physical Functioning; RE Role Limitations due to Emotional Problems; RP Role Limitations due to Physical Health; SF Social Functioning; VT Vitality

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

[redacted]

8.1.1.7 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 standardized odor-impregnated test booklets (Doty et al, 1984). Four booklets each with 10 odorants each are used for the test. Patients are asked to identify the odor using multiple choice format which lists different possibilities. The test is forced-choice; i.e., the patient is required to mark one of the four alternatives even if no smell is perceived. Scores are based on number of correctly identified odors (score range 0 to 40).

Please note that the UPSIT smell test will be performed in all countries participating in the study except Denmark. No Danish version of the test is available.

8.1.2 Nasal Polyp Score

One of the co-primary endpoints of the study is the change from baseline in bilateral endoscopic total NPS at week 40 (change at week 56 is a key secondary endpoint). The score (maximum 8) is the sum of the right and left nostril scores, 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 sent to centralized reader. Centralized imaging data assessments and scoring by an independent physician reviewer for the imaging data will be performed for all endoscopies. To confirm eligibility at V3, the V1 and V2 central reading results will be made available to the site.

The sites will remove patient-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 also 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 nasal polyp score

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

Polyp score	Polyp size
3	Large polyps reaching the lower border of the inferior turbinate or large polyps of score 2 with additional large polyps medial to the middle turbinate
4	Large polyps causing complete or near-complete obstruction of the inferior nasal cavity i.e. touching the floor of the nose

8.1.3 Sinus Computed Tomography

Computed tomography will be performed in up to 200 patients at selected sites. Baseline CT will be performed at V2 or V3 and a final CT will be performed at EOT (or IPD if 24 weeks passed since baseline CT).

Baseline CT should be performed after the nasal polyp biopsy (biopsy and CT can be performed on separate days) and before nasal polyp biopsy at EOT/IPD.

Sinus CT images will be used to derive LMSs based on the visual assessment by independent central readers (see Section 8.1.3.1 Lund-Mackay score), and for quantitative estimation of a sinus severity score (see Section 8.1.3.2 Quantitative measurement of sinus disease burden on sinus computed tomography), which is representative of sinus disease burden.

The sites will remove patient-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 also 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.

8.1.3.1 Lund-Mackay score

The Lund-Mackay score scoring system (see Table 8 below) is used to provide a semi-quantitative assessment of nasal sinuses on sinus CT scans (Lund et al 1993). Based on the sinus CT images, the five sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) on each side are scored by central radiologist as follows:

Table 8 Lund-Mackay score

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

The osteomeatal complex is scored for right and left sides:

Table 9 Osteomeatal complex score

Score	CT scan assessment
0	Not occluded
2	Occluded

The change in score between baseline and EOT will be analyzed (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 and baseline and EOT will be compared.

8.1.4 Nasal polyp surgery

Nasal polyposis surgery is defined as any procedure involving instruments resulting in incision and removal of tissue (e.g. polypectomy, endoscopic sinus surgery).

Surgery procedures performed for NP during the study, including reason for surgery and information whether the surgery was performed as an outpatient or inpatient (i.e. including an overnight stay in the hospital) procedure, should be recorded in the Nasal Polyp Surgery eCRF.

Administration of IP post NP surgery is discretionary and subject to assessment by the Investigator. If the patient is scheduled for NP surgery, an unscheduled visit, should ideally be performed prior to the surgery to assess safety and efficacy (including total NPS, SNOT-22, SF-36v2, PGI-S, PGI-C, ACQ-6 [for asthma patients only] and UPSIT).

Note: protocol mandated nasal polyp biopsy sampling (see Section 8.9 Biomarkers) will not be regarded as NP surgery.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 10 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.

For information on methods of collection, assessment, labelling, storage, and shipment of samples, please refer to the separate Laboratory Manual.

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

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

Table 10 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Alkaline phosphatase (ALP)
B-Leukocyte count	S/P-Aspartate aminotransferase (AST)
B-Mean corpuscular volume (MCV)	S/P-Alanine aminotransferase (ALT)
B-Red blood cell (RBC)	S/P-Bilirubin, total
B-Platelet count	S/P-Blood urea nitrogen (BUN)
B-White blood cell (WBC) count with differential[a]	S/P-Calcium, total
	S/P-Creatinine
	S/P-Gamma-GT (gamma-glutamyl transpeptidaze)
	S/P-Glucose
	S/P-Potassium
	S/P-Sodium

[a] Eosinophils, basophils and monocytes counts will be redacted from central laboratory reports

The clinical chemistry and haematology analysis 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.

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

8.2.1.1 Pregnancy Test

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

- Serum beta-HCG: To be performed for all females at screening Visit 1except for those who are NOT of child bearing potential as defined in inclusion criterion 14. This test is to be sent to and analyzed at the central laboratory;
- FSH: To be performed at screening Visit 1 only, for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 months;
- Urine HCG: To be performed at the study site for all females at each treatment visit **before IP** administration using a dipstick except for those females who are NOT of child bearing potential as defined in inclusion criterion 14. A positive urine test result must be confirmed with serum beta-HCG.

8.2.1.2 Serology

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

In case of positive result of hepatitis B surface antigen or hepatitis C virus antibody, additional testing (e.g. hepatitis C RNA PCR test) may be performed to confirm eligibility.

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.

8.2.1.3 Serum immunoglobulin E and allergen-specific Immunoglobulin E (Phadiatop)

The levels of total immunoglobulin E (IgE) and a qualitative assessment for the presence of allergen-specific IgE (ImmunoCAP Phadiatop) will be evaluated by a central laboratory. These tests will be performed at Visit 3 according to the SoA.

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

8.2.2 Physical examinations

Physical examinations will be performed at timepoints as specified in the SoA. The Investigators should pay special attention to clinical signs related to previous serious illnesses as new or worsening abnormalities may qualify as AEs, see Section 8.3.7 Adverse events based on examinations and tests, for details.

8.2.2.1 Complete physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

8.2.2.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

8.2.3 Vital signs

Pre-dose vital signs are to be obtained in accordance with 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 while sitting, and will be assessed utilizing 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 patient in a quiet setting without distractions (eg, television, cell phones);
- Respiration rate will be obtained after patient has been resting for at least 5 minutes, by counting number of breaths (how many times the chest rises) for 1 minute.

8.2.4 Electrocardiograms

Electrocardiograms are to be performed at Visit 1 to assess eligibility for this study, and then as clinically indicated during the treatment period.

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, endoscopy, blood draw).

An independent reader will provide overall interpretation as normal or abnormal and assess the clinical significance of any potential ECG findings. A reassessment ECG may support evaluation of clinical significance, when uncertain.

A patient with a clinical significant abnormal finding on the ECG, assessed by PI, should be screen failed.

8.2.5 Other assessments

8.2.5.1 Weight and height

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

The patient'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.

8.3 Collection of adverse events

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

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

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

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

8.3.1 Method of detecting adverse events and serious adverse events

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

8.3.2 Time period and frequency for collecting adverse event and serious adverse event information

Adverse events (serious and non-serious) will be collected from time of signature of ICF throughout the treatment period and including the FU 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.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify AstraZeneca.

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

8.3.3 Follow-up of adverse events and serious adverse events

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

Any AEs that are unresolved at the patient'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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE;
- Date Investigator became aware of serious AE;
- AE is serious due to (specify the SAE criteria per definition in Appendix B);

- Date of hospitalization;
- Date of discharge;
- Probable cause of death;
- Date of death;
- Autopsy performed;
- Causality assessment in relation to Study procedure(s);
- Causality assessment to other medication.

8.3.5 Causality collection

The Investigator will assess causal relationship between IP and each 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 will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure* the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

*Note: NP surgery is not a planned study procedure.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient 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.

8.3.7 Adverse events based on examinations and tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the Clinical Study Report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

uses the clinical, rather than the laboratory term (e.g. anaemia versus low Hb value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated, clinically relevant, abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease-under study (DUS) (see Section 8.3.9 Disease-under study (DUS)).

8.3.8 Hy's Law (HL)

Cases where patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with TBL ≥ 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 HL.

8.3.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of NP or the nasal endoscopy procedure.

Events which are unequivocally due to disease under study should not be reported as an AE during the study unless there is a deterioration or worsening of the expected symptoms that led to discontinuation of the investigational product OR the events meet SAE criteria.

Hospital admissions and/or surgical operations due to NP planned during the study are not considered SAEs. If the condition unexpectedly deteriorated after NP surgery, the reported SAE term should be the reason for hospitalization/prolongation of hospitalization. NP surgery should not be reported as the SAE term.

NP surgery is a clinical endpoint and assessment of subject discontinuation from IP should not be based on the NP surgery. Refer to section 7.1 Discontinuation of study treatment for additional information.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day (i.e., immediately but **no later than 24 hours)** of when he or she becomes aware of it.

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

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

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

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

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

For further guidance on the definition of a SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study and before the subject has received any study treatment.

If a pregnancy is reported, the Investigator should inform AstraZeneca within 24 hours of learning of the pregnancy.

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

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital 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 patient was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure.

Male patients should refrain from fathering a child or donating sperm during the study and for 16 weeks (5 half-lives) following the last dose of IP.

Pregnancy of the patient's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 16 weeks (5 half-lives) after the last administration of IP. The Investigators must obtain the consent of the patient's partner prior to obtaining information on the pregnancy.

8.4.3 Overdose

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply (see Section 8.3.2 Time period and frequency for collecting adverse event and serious adverse event information). For other overdoses, reporting must occur within 30 days.

8.4.4 Management of investigational product-related reaction

Appropriate drugs (e.g. epinephrine, H1 and H2 antihistamines, and corticosteroids), and medical equipment to treat acute anaphylactic reactions must be immediately available at the

clinical research site where IP is administered. Study personnel must be trained to recognize 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 (minutes to hours) and that may result in death (Sampson et al 2006). Anaphylaxis to an IP that the patient has not been previously exposed to (such as benralizumab) 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 1 of the following: a) respiratory compromise or b) reduced BP or symptoms of end-organ dysfunction.

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient including: involvement of the skin/mucosal tissue, respiratory compromise, reduced BP or associated symptoms and/or persistent gastrointestinal symptoms.

3. Reduced BP after exposure.

Patients will have had a pre-assessment (i.e. vital signs) prior to IP administration and should be observed after IP administration for a minimum of 1 hour for the appearance of any acute drug reactions.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

8.4.5 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (i.e., immediately but no later than 24 hours) of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life Threatening or follow-up Fatal/Life Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2 Time period and frequency for collecting adverse event and serious adverse event information) and within 30 days for all other medication errors.

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

8.5 Pharmacokinetics

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

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

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and AstraZeneca. Instructions for the collection and handling (processing, storage and shipment) of biological samples can be found in the separate Laboratory Manual provided by AstraZeneca to the sites. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of benralizumab concentration in serum may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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

8.5.1 Determination of drug concentration

Samples for determination of benralizumab concentration in serum will be analysed by analytical test sites on behalf of AstraZeneca, using an appropriate bioanalytical method.

The following samples will be analysed:

- Baseline (Visit 3) PK samples from all patients who are subsequently randomised to either treatment group
- On-treatment PK samples from patients assigned to the benralizumab treatment group

Full details of the analytical method used will be described in a separate bioanalytical report.

8.5.2 Storage and destruction of pharmacokinetic samples

The PK samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of CSR to properly address potential questions from RAs.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 Immunogenicity

Instructions for immunogenicity (ADA and neutralizing antibody [nAb]) sample collection, processing, storage, and shipment can be found in the separate Laboratory Manual provided to the sites.

The immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 3 years following publication of the CSR to properly address potential questions from RAs.

A summary of the analysis will be presented in the CSR. Details of the analytical method used will be described in a bioanalytical report.

8.6.1 Anti-drug antibodies

Serum samples for analysis of ADA will be collected **pre-dose** at selected visits according to SoA.

The presence or absence of ADA will be determined in the serum samples using validated bioanalytical methods.

8.6.2 Neutralizing antibodies

In vitro nAb activity testing will occur for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

The presence or absence of neutralizing ADA will be determined using a validated bioanalytical method.

8.7 Pharmacodynamics Collection of samples

Pharmacodynamics' samples will be taken during the study prior to IP according to the SoA.

Samples for the analysis of the peripheral blood eosinophils will be performed in the central laboratory as part of the routine haematology assessment (CBC).

8.8 Genetics

8.8.1 Optional exploratory genetic sample

The blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

Samples can be collected at any time after the genetic consent form is signed.

See Appendix D for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the separate Laboratory Manual provided to the sites.

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

8.8.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15

years or as per local regulations from the date of the Last Patient's Last Visit, 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.

8.9 Biomarkers

The patient's consent to the use of donated biological samples is mandatory.

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.

8.9.1 Storage, re-use and destruction of exploratory biomarker samples

AstraZeneca or a designee will retain biomarker samples for investigation of research NP disease, the pharmacology of benralizumab and potential predictors of response for a maximum of 15 years following the Last Patient's Last Visit after which they will be destroyed.

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. If a patient does not allow samples to be used for future biomarker research they may continue with their samples being used for the main study.

8.10 Health Economics

Healthcare Resource Utilization (HRU) data outside of the scheduled study visits will be collected in the eCRF by the Investigator and study-site personnel for all patients throughout

the study, as shown in the SoA. The data may be used as input to cost analyses for example cost utility analysis or cost effectiveness analysis. Protocol-mandated procedures, tests, and encounters are excluded.

The following healthcare resource use variables will be collected at Visit 1 with a 1-year recall period and then at each visit after randomization. They measure the amount of unplanned/unscheduled healthcare resource use since the patient previous visit due to (a) nasal polyps, (b) asthma exacerbation (c) other reasons:

- General and intensive care hospitalizations and lengths of stay;
- Emergency room visits;
- Urgent care visits.

All hospitalizations, ER, and urgent care visits will be collected, even when an ER visit results in a hospital admission. All hospital admissions (including dates) will also be collected, even when readmission occurs within a short period of time.

Unplanned hospitalization for symptoms/diagnosis other than NP must be reported as an SAE.

Hospitalization due to NP surgery should only be reported as SAE, if the condition unexpectedly deteriorated after surgery.

For hospitalizations resulting from all other events should be reported as SAEs.

Refer to Appendix B4 for reporting hospitalization.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The co-primary efficacy endpoints are the change from baseline in total NPS at Week 40 and the change from baseline in bi-weekly mean NBS at Week 40. The primary analysis is to compare the changes from baseline in total NPS and in NBS of benralizumab with placebo (change from baseline for both endpoints at week 56 are included as key secondary endpoints).

The null hypothesis is that the change from baseline in total NPS and/or the change from baseline in NBS are similar between benralizumab and placebo. The alternative hypothesis is that both of the change from baseline in total NPS and the change from baseline in NBS are different between benralizumab and placebo.

The type I error will be controlled across co-primary and key secondary endpoints at 0.05 two-sided) statistical significance level. Both of the co-primary endpoints will be tested at 0.01 (two-sided) and the key secondary endpoints will be tested hierarchically at 0.05 (two-

sided) level (see section 9.4.4). The co-primary endpoints will be evaluated using a hybrid of WP/WOCF and MI, followed by an ANCOVA with treatment arm, baseline scores, region (US vs non-US), and baseline comorbid asthma status (yes vs no) as covariates.

9.2 Sample size determination

The primary analysis will compare the effect of benralizumab vs placebo on the change from baseline in total NPS at Week 40 and on the change from baseline in bi-weekly mean NBS at Week 40 using a hybrid of WP/WOCF and MI, followed by an ANCOVA with treatment arm, baseline scores, region (US vs non-US), and baseline comorbid asthma status (yes vs no) as covariates.

Approximately 400 patients will be randomized into SC benralizumab 30 mg or placebo in a 1:1 ratio.

Based on the assumptions above, the minimum observed mean difference that would be statistically significant at the 0.01 level is -0.52 in total NPS and –0.26 in NBS.

9.3 Populations for analyses

All efficacy analyses will be performed based on the full analysis set (FAS). The analyses of LMS and sinus severity score will be conducted in the patients randomized in the selected sites for CT assessment as mentioned section 8.1.3. The analyses of asthma exacerbation and ACQ-6 will be conducted in the patients who had comorbid asthma at baseline.

For consistency, demographic and baseline characteristics will be presented using the FAS. Safety objectives and the immunogenicity will be analyzed based on the Safety analysis set. Pharmacokinetic analyses will be conducted based on the PK analysis set.

9.3.1 All patients analysis set

This analysis set will comprise all patients screened for the study and will be used for reporting of disposition and screening failures.

9.3.2 Full analysis set (FAS)

All patients randomized and receiving any IP will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment. Patients who withdraw consent, and assent when applicable, to participate in the study will be included up to the date of their study termination.

9.3.3 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active.

9.3.4 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset.

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock.

The efficacy analyses will be based on FAS population. Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be prepared prior to first patient randomized and any subsequent amendments will be documented, with final amendments completed prior to database lock. This section is a summary of the planned statistical analyses. Details will be included in the SAP. Any deviations from this plan will be reported in the CSR.

9.4.1 Efficacy analyses

All analyses described below apply to the full analysis of all patients, through to IPD/EOT (Week 56) unless otherwise stated. Efficacy endpoints will also be summarized separately for the patients who entered the long-term FU, and summaries for this cohort of patients will be repeated over the entire FU period to characterize the durability of the treatment effect.
The primary estimand will be used for the primary analysis and quantifies the difference in outcomes for subjects randomized to the benralizumab and placebo arms at the planned timepoints of the study, regardless of the treatments that subjects actually received. It includes all the data collected during the study including data collected after discontinuation of study treatment except data collected after NP surgery and/or SCS use for NP. A composite strategy will be used for patients who undergo NP surgery and/or receive SCS for NP. Data collected post-SCS for NP will be set to missing, and the patient's worst observed

post-baseline value on or before the time of SCS use for NP will be imputed from that point through Week 56. Data collected post-surgery will be set to missing, and the worst possible value will be imputed from that point through Week 56. For patients who discontinue the study without NP surgery or SCS use for NP, missing data will be imputed using multiple imputation (MI) using all patients who did not have NP surgery or receive SCS for NP under a missing at random assumption. Further details of the primary analysis as well as sensitivity analyses will be included in the SAP.

9.4.1.1 Calculation or derivation of variables for efficacy analyses

The changes from baseline in total NPS and NBS at Week 40 are co-primary endpoints. The change from baseline in SNOT-22 total score at Week 40, time to the earlier of first NP surgery and/or SCS use for NP by Week 56, time to first NP surgery by Week 56, change from baseline in DSS score at Week 40, change from baseline in total NPS at Week 56, change from baseline in NBS at Week 56, change from baseline in SNOT-22 total score at Week 56, change from baseline in DSS score at Week 56, and change from baseline in LMS at EOT/IPD are the 9 key secondary endpoints.

Total nasal polyps score (Co-primary endpoint and key secondary endpoint)

The change from baseline in total NPS at Week 40 is one of the co-primary endpoints and at Week 56 is one of the key secondary endpoints. The total NPS is the sum of the bilateral NPS, which will be evaluated centrally. The total scores and the corresponding changes from baseline at each visit will be calculated. In addition, the proportion of NPS responders, which is defined as patients with at least 1 point improvement (reduction) in total NPS will be a supportive variable to the primary objective.

Nasal blockage score (Co-primary endpoint and key secondary endpoint)

The change from baseline in NBS at Week 40 is the other co-primary endpoint and at Week 56 is one of the key secondary endpoints. The NBS will be summarized bi-weekly (14-day periods). The bi-weekly mean and the changes from the baseline will be calculated.

Disease specific health-related quality of life: SNOT-22 (Key secondary endpoint)

Disease specific health-related quality of life will be evaluated by SNOT-22. The changes from baseline in SNOT-22 total score at Weeks 40 and 56 are key secondary endpoints. The observed values and the changes from baseline in SNOT-22 total score at each timepoint will be calculated.

Time to first NP surgery and/or SCS use for NP (Key secondary endpoint)

The time to the first NP surgery and/or SCS use for NP by Week 56 is another key secondary endpoint. The time will be calculated based on the earliest occurrence of NP surgery and/or SCS use for NP and will be calculated as follows:

Earlier of (Start date of first NP surgery, Start date of first SCS use for NP) - date of randomization +1

For patients who do not experience any surgery or SCS use for NP, the time to will be censored at the date of their last visit for the 56-week treatment period, or at the time point after which a surgery or SCS use could not be assessed (for lost to follow-up patients).

Time to first NP surgery (Key secondary endpoint)

The time to the first NP surgery by Week 56 is another key secondary endpoint and will be evaluated for all patients. The time to first NP surgery is calculated as follows:

Start date of first NP surgery - date of randomization +1

For patients who do not experience any surgery, the time to first NP surgery will be censored at the date of their last visit for the 56-week treatment period, or at the time point after which a surgery could not be assessed (for lost to follow-up patients).

Difficulty with Sense of Smell (DSS) score (Key secondary endpoint)

The changes from baseline in DSS score at Weeks 40 and 56 are key secondary endpoints. The DSS score will be summarized bi-weekly (14-day periods). The bi-weekly mean and the changes from the baseline will be calculated.

Lund Mackay (key secondary endpoint) and sinus severity score

Only the data from blinded central reader will be used for analysis. Both LMS (key secondary endpoint) and sinus severity score as described in Section 8.1.3.2 will be evaluated centrally. The observed values and the change from baseline at EOT/IPD will be calculated.

University of Pennsylvania Smell Identification Test (UPSIT)

Sense of smell will be evaluated by UPSIT. The observed values and changes from baseline at each timepoint will be calculated. The proportion of patients with different thresholds of smell impairment or normal smell abilities will be calculated overall as well as by sex. The thresholds will be pre-specified in the SAP.

SCS use for NP and proportion of NP surgery

The proportion of patients who had NP surgery, the proportion of patients who use SCS for NP, and the proportion of patients who had surgery or use SCS for NP will be calculated by Week 56 for all patients.

In addition, the number of courses of SCS for NP, total SCS dose used and total duration of SCS use for NP, will also be summarized by Week 56.

Nasal polyps associated symptom scores

Individual components of the NPSD as well as the TSS will be summarized bi-weekly (14-day period). The bi-weekly mean and the corresponding changes from baseline at each timepoint will be calculated.

Patient-reported general health status: SF-36

The observed values and the changes from baseline in SF-36v2 PCS, MCS, and domain scores at each timepoint will be calculated.

Other patient reported outcomes-related variables

The following variables will be calculated at each visit for all patients in the FAS.

- Change from baseline in PGI-S;
- PGI-C scale will be summarized categorically (proportion).

In addition, mean ACQ-6, the changes from baseline in ACQ-6 and ACQ-6 responders, which is defined as change from baseline≤ -0.5, will also be calculated for the patients who have comorbid asthma at baseline.

Asthma exacerbations

In the patients with comorbid asthma at baseline, the number of exacerbations and the annual exacerbation rate will be calculated. The number of exacerbations related to ER/urgent care/hospitalization/SCS will be summarized.

9.4.1.2 Methods for efficacy analyses

Analyses of the co-primary endpoints

The primary estimand will be applied to the co-primary endpoints, the change from baseline in total NPS and the change from baseline in NBS, using a hybrid method of WP/WOCF and MI followed by ANCOVA with treatment arm, baseline score, region (US vs non-US), and baseline comorbid asthma status (yes vs no) as covariates. The estimates of the treatment effects at Week 40 and Week 56 will be based on contrasts from this ANCOVA model. The analyses will use the data collected up to Week 56 visit regardless of whether patients remained on treatment or not except data collected after NP surgery and/or SCS use for NP. A composite strategy will be used for NP surgery and SCS use for NP. If a patient had any NP surgery before Week 56, the data will be censored after the first NP surgery and the worst possible value will be imputed in its place. If a patient had any course of SCS use for NP before Week 56, the data will be censored after the time of having the first course of SCS use for NP and the patient's previously worst observed value will be imputed in its place.

Sensitivity analyses will be conducted based on different estimands and different missing data mechanism assumptions, including those expected to be more conservative such as missing not at random, to explore the robustness of any treatment effect, utilizing multiple imputation approaches. Specifically, a sensitivity analysis will be conducted in which the worst possible value is imputed after NP surgery and a treatment policy strategy is used for both treatment discontinuation and use of SCS for NP. Full details of the sensitivity analyses will be pre-specified in the SAP.

Analyses of secondary endpoints

All secondary continuous efficacy endpoints will be summarized by visit and treatment group. In addition, the changes from baseline at scheduled visits in total NPS, NBS, SNOT-22 total score, DSS score, TSS, UPSIT, SF-36v2 (PCS, MCS, and domains), ACQ-6, will be analyzed under the primary estimand using ANCOVA, in a similar manner to that outlined for the co-primary endpoints above.

The changes from baseline at EOT/IPD in CT-scores will be analyzed under a similar estimand to that used for the primary and other secondary endpoints, but with a treatment policy rather than composite strategy for SCS use for NP. The analyses will use the data collected up to Week 56 visit regardless of whether patients remained on treatment or received SCS for NP except data collected after NP surgery. A composite strategy will be used for NP surgery. If a patient had any NP surgery before Week 56, the data will be censored after the first NP surgery and the worst possible value will be imputed in its place. The composite strategy of imputing WOCF after SCS use for NP will not be used for CT-scores because there is only one post-baseline assessment.

The estimates of the treatment effects at Week 40 and Week 56 for SNOT-22 total score and DSS score and at EOT/IPD for LMS for the analyses of key secondary endpoints will be based on contrasts from the respective ANCOVA models.

Time to first NP surgery up to Week 56, time to first course of SCS use for NP up to Week 56, and the Time to first NP surgery and/or first course of SCS use for NP up to Week 56 will be analyzed using a Cox proportional hazard model with treatment, region (US vs non-US) and baseline comorbid asthma status (yes vs no), as covariates.

The proportions of responders at selected timepoints in total NPS, in SNOT-22 total score and in ACQ-6, will be analyzed using logistic regression with treatment arm, baseline scores, region (US vs non-US), and baseline comorbid asthma status (yes vs no) as covariates.

The proportion of patients who had NP surgery and the proportion of patients who had courses of SCS for NP up to Week 56 will be analyzed using a Cochran–Mantel–Haenszel test controlling for region (US vs non-US) and baseline comorbid asthma status (yes vs no). The total number of courses of SCS_NP will be analyzed using a negative binomial model adjusting for region (US vs non-US), baseline comorbid asthma status (yes vs no), and prior use of SCS for NP (yes vs no).

9.4.1.3 Subgroup analysis

To explore the uniformity of the detected overall treatment effect on the efficacy endpoints, subgroup analyses will be performed for the co-primary endpoints, SNOT-22 total score, and DSS score. The subgroups will include, but may not be limited to the following:

[redacted] hese analyses are to be considered as exploratory (as the study has not been designed or powered to assess treatment effect in any individual subgroup) and will be performed on the FAS.

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Analysis Set. Treatment-emergent AEs/SAEs will be summarized over the FU period common to all patients (date of first dose through to Week 60). In addition, exposure adjusted summaries covering the entire post-treatment (first dose date through to last safety follow-up) will be considered for all patients. Separate presentation of AEs may be considered for the extended post-Week 60 FU period for patients entering this FU period.

9.4.2.1 Calculation or derivation of Safety Variables

The following safety data will be collected: vital signs, physical examination, haematology, clinical chemistry and reported AEs. The observed values and the corresponding changes during the study will be calculated for relevant measurements.

9.4.2.2 Analyses of safety variables

Both AEs and SAEs will be summarized. Adverse events will be listed for each patient and summarized by System Organ Class and Preferred Term assigned to the event by MedDRA.

Laboratory data for haematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges during the study will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given.

9.4.3 Other analyses

9.4.3.1 Analysis of immunogenicity variables

Anti-drug antibodies status and the titers will be summarized using descriptive statistics. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety and efficacy will also be evaluated.

9.4.3.2 Analysis of pharmacokinetic variables

Benralizumab serum concentrations will be summarized using descriptive statistics. The population PK analysis and pharmacodynamic analyses will be presented separately from the main CSR.

9.4.3.3 Analyses of biomarkers

Biomarkers will be summarized using standard summary statistics. Limited exploratory biomarkers may be reported in the CSR. These analyses will be detailed in the SAP.

The remaining exploratory biomarkers will be reported outside of the CSR.
Details of the remaining exploratory biomarker analyses will be described in the exploratory analyses plan, which will be finalized before the database lock.

9.4.4 Methods for multiplicity control

To account for multiplicity to test the co-primary endpoints (change from baseline in total NPS at Week 40 and change from baseline in NBS at Week 40) and the 9 key secondary endpoints (the change from baseline in SNOT-22 total score at Week 40, time to first NP surgery and/or SCS use for NP by Week 56, time to first NP surgery by Week 56, the change from baseline in DSS score at Week 40, the change from baseline in total NPS at Week 56, the change from baseline in NBS at Week 56, the change from baseline in SNOT-22 total score at Week 56, the change from baseline in DSS score at Week 56, the change from baseline in LMS at EOT/IPD), the type I error will be controlled across co-primary and key secondary endpoints at 0.05 (two-sided) statistical significance level. Both of the co-primary endpoints will be tested at a 0.01 (two-sided level) and the key secondary endpoints will be tested hierarchically at a 0.05 (two-sided) level. The testing strategy will be as follows:

- Step 1: Perform the 2 tests of co-primary endpoints at a significance level of 0.01. If both p-values are less than 0.01, and the treatment effect favours benralizumab, then proceed to Step 2. Otherwise no null hypothesis is rejected.
- Step 2: Test the 9 key secondary endpoints at a significance level of 0.05 using a hierarchical fixed sequence testing approach following the order below.
  - Change from baseline in SNOT-22 total score at Week 40.
  - Time to first NP surgery and/or SCS use for NP up to Week 56.
  - Time to first NP surgery up to Week 56
  - Change from baseline in DSS score at Week 40.
  - Change from baseline in NPS at Week 56.
  - Change from baseline in NBS at Week 56.

- Change from baseline in SNOT-22 total score at Week 56.
- Change from baseline in DSS score at Week 56.
- Change from baseline in LMS at EOT/IPD.

9.5 Interim analyses

No interim analysis is planned for this study.

9.6 Data monitoring committee (DMC)

No data monitoring committee (DMC) is planned for this study.

9.7 Independent adjudication committee

No independent adjudication committee is planned for this study.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) Guidelines;
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients. Where applicable as per relevant laws and regulations, amendments will also be submitted to, reviewed and approved by regulatory authorities/national competent authorities.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and Sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate Regulatory Authorities (RAs). 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 patient and answer all questions regarding the study.

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

The medical record must include a statement that written informed consent was obtained before the patient 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.

Patients 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 patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

Patients who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional future exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the future exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for future exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

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

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

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from RAs.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All patient data relating to the study will be recorded on printed or electronic case report form (eCRF) unless transmitted to AstraZeneca 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.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of 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 patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on 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.

A 9 Study and Site closure

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. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.
In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests

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.

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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.

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

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

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

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

B 2 Definitions of serious adverse event

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

- Results in death;
- Is immediately life threatening;
- Requires in-patient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor 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 hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

B 3 Life threatening

'Life threatening' means that the patient 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 patient'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).

B 4 Hospitalization

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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient 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 (e.g. neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization;
- Development of drug dependency or drug abuse.

B 6 Intensity rating scale:

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

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

B 7 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

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

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

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study treatment 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 recognize that could have led to an error.

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

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

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

- Errors related to or resulting from IWRS/IVRS - including those which lead to one of the above listed events that would otherwise have been a medication error;
- Participant accidentally missed drug dose(s) e.g. forgot to take medication;
- Accidental overdose (will be captured as an overdose);
- Participant failed to return unused medication or empty packaging;
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product.

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

Appendix C Handling of Human Biological Samples

C 1 Bicustody of biological samples

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

The Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate).

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

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

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

If a patient does not allow samples to be used for future biomarker research they may continue with their samples being used for the main study.

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

C 2 Withdrawal of Informed Consent for donated biological samples

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

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

The Investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories

(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).
For transport purposes, the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g. Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g. Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B;
- are to be packed in accordance with UN3373 and IATA 650.

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations;
- Clinical trial samples will routinely be packed and transported at ambient;
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm);**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content;**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable;
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a patient'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 Institutional Review Board/Independent Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting patients.

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

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

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

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

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

The samples will be retained while research on study treatment continues but no longer than 15 years or other period as per local requirements from the date of the Last Patient Last Visit (LPLV), after which they will be destroyed.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

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

Inclusion criteria

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

Exclusion criteria

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

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

Withdrawal of consent for genetic research:

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

Collection of samples for genetic research

The blood sample for genetic research may be obtained from the patients at any time after randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

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

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the patient enrolment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix B.

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study site. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, 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 patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory Authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

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

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can

only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual patient 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 cases of Hy's Law (HL). 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 patient meets potential Hy's Law (PHL) criteria at any point during the study.

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

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

Hy's Law

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

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

E 3 Identification of potential Hy's Law cases

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

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

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

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

- Notify the AstraZeneca representative;
- Request a repeat of the test (new blood draw) by the central laboratory;
- Complete the appropriate unscheduled laboratory electronic case report form (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 patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative;
- Determine whether the patient meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits;
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

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

- Inform the AstraZeneca representative that the patient 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 patient does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting Study treatment (see Section 8.4 Safety reporting and medical management)

- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated;
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL lab kit should be used;
- Complete the three Liver eCRF Modules as information becomes available;
- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

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.

No later than 3 weeks 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. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

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

If 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, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes.

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

- Report an 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 3 weeks 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above;
- 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 met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the patients' condition compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required;

- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5;

- A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (e.g. chronic or progressing malignant disease, severe infection or liver disease),

If **No**: Follow the process described in Appendix E 4.1.

If **Yes**: Determine if there has been a significant change in the patient's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix E 4.

A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Anaphylaxis: signs and symptoms, management

F 1 INTRODUCTION

As with any antibody, allergic reactions to dose administration are possible. The clinical criteria for defining anaphylaxis for this study are listed in Section 2 Introduction. A guide to

the signs and symptoms and management of acute anaphylaxis is provided in Section 3 Objectives and Endpoints. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

F 2 CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

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

   AND AT LEAST 1 OF THE FOLLOWING

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

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

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

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

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

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

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

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

Immune Complex Disease

Immune complex disease or Hypersensivity Type III is evoked by the deposition of antigenantibody or antigen-antibody-completed 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 edema;
- Hypotension;
- Cardiac arrhythmias;
- Feeling of impending doom;
- Unconsciousness;
- Shock.

Other earlier or concomitant signs and symptoms can include:

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

- Headache;
- Uterine cramps;
- Generalized warmth.

F 4 MANAGEMENT OF ACUTE ANAPHYLAXIS

F 4.1 Immediate intervention

1. Assessment of airway, breathing, circulation, and adequacy of mentation.
2. Administer epinephrine intramuscular (IM) 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.

F 4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place patient 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.

F 4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion;

(b) Consider H1 and H2 antihistamines;

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

(d) Consider systemic corticosteroids;

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

(f) Consider glucagon for patient 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 Sampson et al 2006.

F 5 REFERENCES

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 Study Conduct Mitigation in the event of evolving SARS-Cov-2 (COVID19) pandemic or other study disruption

Note: The changes below should be implemented only during study disruptions caused by COVID-19 or similar pandemic (e.g. during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2), during which patients may not wish to or may be unable to visit the study site for study visits.

These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor. Instructions on how to perform these procedures will be provided at the time of implementation.

G 1 Obtaining verbal consent (where applicable)

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g. remote visits. Patient's consent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the following sections. Local and regional regulations and/or guidelines regarding consent of study patients should be checked and followed. As a minimum requirement patients verbal consent obtained for the alternative means of carrying out visits and assessments in the OSTRO study should be documented in the patient source data.

G 2 Telemedicine Visit to Replace On-site Visit (where applicable)

During the COVID-19 pandemic or other study disruption, visits to sites and collection of study assessments should only be performed if the Investigator considers it to be safe for the patient and personnel.

On-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. A telemedicine contact will allow for collection of adverse events and concomitant medication, verification of background medication compliance, completion of ePRO questionnaires and UPSIT assessments and where applicable, evaluation of pregnancy test results.

Missing assessments, which cannot be performed via remote visit or are omitted due to safety precautions, may be performed outside of visit window.

G 3 Study procedures may be postponed/omitted (where applicable)

Study procedures (e.g. nasal endoscopy, nasal biopsy and nasal secretion) which may represent a safety risk to patients or site staff if performed during the peak period of the COVID-19 pandemic or other study disruption may be postponed based on Sponsor´s recommendation, Investigator's clinical judgement and local, international or professional guidance and recommendations.

G 4 Remote completion of on-site ePRO assessments (where applicable)

During the COVID-19 pandemic or other study disruptions, ePRO questionnaires (SNOT-22, ACQ-6, SF-36v2, PGI-S, and PGI-C) may be completed remotely at the patient's home using the handheld ePRO device, without the need of in-office visit confirmation.

G 5 Patients' Home delivery of study supplies (where applicable)

To secure continuity of background medication intake and compliance, collection of UPSIT and safety pregnancy assessments, home delivery of these study items may be introduced, where applicable and allowed per local regulations

G 6 Data Capture During Telemedicine Visit (where applicable)

Site staff and/or designated HCP should always refer to the CSP and conduct all study procedures that can be performed/collected remotely for that study visit.

Data collected during a telemedicine visit should be captured by a qualified HCP from the study site and recorded in the source documents and in the electronic data capture (EDC) system.

Appendix H Abbreviations

Abbreviation or special term	Explanation
Ab	Antibiotics
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-drug antibodies
AE	Adverse event
AER	Asthma exacerbation rate
AERD	Aspirin exacerbated respiratory disease
AFS	Allergic fungal sinusitis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
APFS	Accessorized prefilled syringe
AST	Aspartate aminotransferase
BP	Blood pressure
CBC	Complete blood count
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
DILI	Drug induced liver injury
DMC	Data monitoring committee
DSS	Difficulty with sense of smell
DUS	Disease-under study
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EU	European Union
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone

Abbreviation or special term	Explanation
FU	Follow-up
FUD	Follow-up discontinuation
GCP	Good Clinical Practice
GH	General health perceptions
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HIV	Human immunodeficiency virus
HL	Hy's law
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgE	Immunoglobulin E
IL-5	Interleukin-5
IL-5Rα	IL-5 receptor alpha subunit
IM	Intramuscular
IMP	Investigational medicinal product
INCS	Intranasal corticosteroids
IP	Investigational product
IPD	IP discontinuation
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRC	Independent review charter
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LMS	Lund-Mackay score
LPLV	Last patient last visit
mAb	Monoclonal antibody
MCID	Minimal clinical importance difference
MCS	Mental component score

Abbreviation or special term	Explanation
MFNS	Mometasone furoate nasal spray
MH	Mental health
MI	Multiple Imputation
nAb	Neutralizing antibody
NB	Nasal blockage
NBS	Nasal blockage score
NP	Nasal polyposis
NPS	Nasal polyp score
NPSD	Nasal Polyposis Symptom Diary
PCS	Physical component score
PF	Physical functioning
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHL	Potential Hy's law
PI	Principal investigator
PK	Pharmacokinetics
PPE	Personal protective equipment
PRO	Patient-reported outcome
RA	Regulatory authority
RBC	Red blood cell
RE	Role limitations due to emotional problems
RP	Role limitations due to physical health
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneously
SCS	Systemic corticosteroids
SF	Social functioning
SF-36v2	Short Form 36-item Health Survey, Version 2
SNOT-22	SinoNasal Outcome Test, 22 item
SoA	Schedule of activities
TBL	Total bilirubin

Abbreviation or special term	Explanation
TSS	Total Symptom Score
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
WBC	White blood cell
WOCBP	Women of childbearing potential
WOCF	Worst Observation Carried Forward
WP	Worst Possible

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