Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3252C00002
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A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Benralizumab in Patients with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps (ORCHID)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2021-000267-72

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VERSION HISTORY

Version 5.0 20Mar2024
The main purpose of the Version 5 protocol is to include relevant CSP wording to transition to EU CTR and align with new AstraZeneca CSP template. Additional CSP clarifications have been implemented at the same time. The main changes are summarized below: 1.2 Synopsis study period-last patient completed was updated from Q2 2024 to Q4 2025 to align with date of last subject randomized into the study. 1.2 Synopsis Objectives and Endpoints During the Double-Blind Treatment Period, Table 4 and Section 9.4.1.1 - Included “Time to first NP surgery and/or SCS use for NP” as a non-key secondary endpoint. To align list of secondary endpoints with section 9.4.1.1 which was already in CSP V4. 1.2 Synopsis: Objectives and Endpoints During the Open-Label Extension and Table 5 Objectives and Endpoints During the Open-Label Extension – remove “as compared to placebo” from “To assess the safety and tolerability of benralizumab as compared to placebo in subjects with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps” to make the description accurate since no placebo group in OLE. Table 2 Schedule of Activities – Updated foot note n. "Samples can be collected at any time from Week 0 (V3) after genetic consent is obtained" was changed to “Samples can be collected at any time from Week 0 (V3) after genetic consent is signed”. Section 5.5.1 - “For second rescreening, the patient will use the same E-code as initial screening.” was changed to “For second rescreening, the patient will be assigned new E-code.” to clarify the process how to assign E-code for subject with second re-screening caused by COVID-19 impact. Table 3 Schedule of Activities – For the Open-label Extension and Follow-up: Delete “Brief physical examination and vital signs will not be performed in the case of a telephone/virtual visit” of foot note b to make it consistent between table 3 and footnote n regarding to PE and vital signs. Section 4.4 - Clarified definition of the end of study according to European Union and Food and Drug Administration requirements.

Section 8.4.5 - Added Drug Abuse and Drug Misuse definition due to CSP template update.

Section 8.4.6 - Added Reporting of Overdose due to CSP template update.

Appendix A1 - Added sub-heading “Regulatory Reporting Requirements for Serious Breaches” due to CSP template update.

Appendix A6 - Updated information about timelines for submission of trial results summaries to EU CTR due to CSP template update.

Appendix A7 - Updated information about retention timelines of records and documents to “25 years after study archiving or as required by local regulations” due to CSP template update.

Appendix B8 - Added detailed Drug Abuse and Drug Misuse definition and examples due to CSP template update.

Section 4.1 Overall design and Section 9.6 Analyses of Data from the Open-Label Extension - Added OLE result analysis related wording.

Section 9.4.2.2 Analyses of safety variables - Updated “An additional table will present number and percentage of patients with most common AEs (frequency of ≥5%)” to “An additional table will present number and percentage of patients with most common AEs (frequency of ≥3%)”.

Table 4 Objectives and Endpoints During the Double-Blind Treatment Period - Population of Primary objective was updated from “Primary full analysis set” to “severe CRSwNP patients with asthma”.

Section 9.3 Populations for analyses - Moved “Primary full analysis set” from “Full analysis set” to a separate line.

Section 9.4.1 Efficacy analyses- Clarified the scope of analysis at the primary DBL and also added estimands for key secondary objectives.

Section 9.4.1.2 Methods for efficacy analyses – Clarified the planned analysis (i.e. the CMH test) for each individual component (i.e. proportion of patients who had CRSwNP surgery, and proportion of patients who had SCS for CRSwNP) will be repeated for the proportion of patients who had CRSwNP surgery and/or SCS for CRSwNP.

Section 8.4.3 Overdose – Added definition of overdose in the study.

Table4 Objectives and Endpoints During the Double-Blind Treatment Period – Deleted repeated content shown in secondary and exploratory objective /endpoints to correct formatting error.
Version 4.0 16 Mar 2021
SOA Table2 and Table3, ADA and nAb wording was changed to “immunogenicity”. Section 8.6 Immunogenicity: wording was changed accordingly.
Version 3.0 12 Feb 2021
The main purposes of the Version 3 protocol changes include: augmenting the eligibility criteria to enrol a population who will be benefit from Benralizumab; providing the eligible patients with additional around one-year treatment with open-label benralizumab; adding intranasal corticosteroid spray (INCS) as background treatment which is align with global standard of care for nasal polyps; increasing the sample size since western cohort has been included. Additional changes made to the protocol include multiple minor improvements. The main changes are summarized below and the reason for the same change category will be listed: Cover page: Regulatory Agency Identifying Number; The EudraCT number was added. Section 1.1: Schedule of activities (SoA) was updated. The overall study design description was added: adding optional OLE period, adding INCS as background medication and two separate database locks for DB treatment and OLE. The rational for adding OLE is to aid recruitment and to assess long term safety. The rational for adding INCS is to align to global standards of care in severe CRSwNP. Table 1 Schedule of Activities: The week number of Visit 1 was updated from W-5 to W-6 to allow for at least 4 weeks of background INCS before V2; The asthma exacerbation assessment was moved to "HRU assessments" and the terminology ClinRO was revised to ePRO changed from At site ePRO to align with global OSTRO study; INCS distribution and accountability was added for clarity; and foot notes a, e and f were updated. Table 2 Schedule of Activities - Randomization, treatment period and follow up: Table was updated to remove the previous follow-up periods; terminology for EOT updated to EoDB; visits after V11/W56 were removed; Column UNS was updated; Columns “FU first up to 74 pts”, “FU/FUD first up to 74 pts” and “FU Remining pts” were removed; Patient-reported outcome and Clinician-reported outcome assessments were updated to Patient-reported outcome assessments; “asthma patient only” for ACQ-6 and asthma exacerbation were removed as all patients will be asthmatics; asthma exacerbation assessment was moved to "HRU assessments" and the terminology ClinRO was revised to ePRO; INCS distribution and accountability were added for clarity; foot notes were updated.

Table 3 Schedule of Activities - For the open-label extension and follow-up: added.

Section 1.2 Synopsis - Background information in the rationale section: updated with literature support that comorbid asthma is associated with more severe eosinophilic nasal polyposis; Objective and endpoints during the open-label extension was added to provide safety oversight during OLE.

Section 1.2 Synopsis - Overall design section: Patient number was updated from 148 to 250; CCI was added as a factor for patient stratification, and country was updated for region; Information about how to take background medication INCS and Mometasone Furoate (MFNS) was added; The week number of Benralizumab dosing was updated; OLE dosing information was added; Follow-up section was removed. The rationale for sample size change is to achieve adequate power in the study.

Section 1.2 Synopsis: Study period section; First patient enrolment time was updated from Q4 2019 to 25Nov2019 and the estimated last patient completion time was updated from Q4 2022 to Q2 2024. These changes are according to changes of the study design.

Section 1.2 Synopsis - Number of patients section: The number of study countries was changed from 4 to 12, the number of study sites changed from 50 to 115 and the number of patients changed from 148 to 250.

Section 1.2 Synopsis - Treatment and Treatment duration section: Dosing information of Benralizumab and placebo in the double blind treatment period was updated; Follow-up period was removed; Dosing information of Benralizumab in OLE period was added; Dosing information of INCS in double blind treatment period was added. The rationale for this change was to add visit 12 (V12) to allow for 3 QW4 dosing with Benra (loading dose) to patients randomized to placebo in the DB period (dummy injection for those on Benra during DB). Restrictions on co-medication during OLE (e.g. SCS usage and INCS requirement) have been reduced, as only safety but no efficacy evaluation during OLE.

Section 1.2 Synopsis - Statistical methods section: One DBL was added, and the primary DBL and final DBL were clarified; Analysis method was updated; Patient stratification was updated.

Figure 1 Study Flow Chart: updated; OLE and week numbers were updated.

Section 2.2 Background: updated. Remove the description of JESREC score and ECRS. Add the references which emphasize the relation between asthma and CRSwNP. In addition, add the point that comorbid asthma is associated with more severe eosinophilic nasal polyposis.

Section 2.3 Benefit/Risk assessment: The total radiation dose estimated was changed from 3 milli Sievert to 2. The CT scan at week 24 was removed.

Table 4 Objective and Endpoints During the Double-Blind Treatment Period: Endpoints/variables including population, Co-primary endpoints, Intercurrent event strategy

and summary were added for primary objectives. Endpoint/variable "change from baseline in sinus severity score by Quantitative CT analysis" and "Change from baseline in Zinreich score" were added as secondary objective Sinus opacification by CT scan; Secondary objective Sense of Smell was added; endpoint/variable "number of courses of SCS for CRSwNP" and "Total SCS dose used and total duration of SCS use for CRSwNP" were added for secondary objective Systemic corticosteroids use for relief of nasal symptoms; Foot notes a and b were added. The rationale for this change is because DSS (smell) is considered the most clinically relevant symptom (per KEE feedback), therefore it was elevated to be the first key secondary endpoint followed by LMS.

Table 5 Objective and Endpoints During the Open-Label extension: added.

Section 4.1 Overall design: OLE added; Patient number was changed from 148 to 250; novel CCI criteria was added and country was changed to region for patient stratification; Addition of a stable INCS dose for 4 weeks prior to V1 and MFNS at 400 mcg, or equivalent, for 4 weeks prior to V2 and until EoDB was added; Addition that an ePRO device will be provided throughout the study; Week 112/FU was added after completing the OLE; CT scan frequency was changed to reduce radiation exposure; Timeline when will the primary DBL and final DBL be performed was added.

Section 4.2 Scientific rationale for study design: sample size and OLE was added.

Section 4.4 End of study definition: Eligibility for entering the OLE period was added.

Section 5.1 Inclusion Criteria: updated;

Criteria 6: A documented physician-diagnosed asthma was added; The rational is that comorbid asthma is associated with more severe eosinophilic nasal polyposis.

Criteria 7: updated with Asia only (Japan, China Mainland, China Taiwan, Vietnam and Thailand) and V2 was added for the CT Lund Mackay Score.

Criteria 8: Blood Eosinophil Count was changed to ">2% or ≥150/µL at V1, as determined by central lab" to ensure capture of eosinophilic patients.

Criteria 9: INCS was removed.

Criteria 15: was Updated to capture at least 70% INCS compliance during run-in with no monitor for LTRA usage on the ePRO device"

Criteria 15 in version 2.0 for weight was removed. Updated according to the PSSR.

Criteria 17 and 18 was updated to align with current PSSR.

Criteria 19 was removed.

Section 5.2 Exclusion criteria:

Criteria 8 History of Guillain-Barré syndrome was removed to align with the current PSSR.

Criteria 22: Criteria 23 in version 2.0 was updated to Criteria 22 in version 3.0 as "Receipt of herbal remedies or traditional Chinese medicines that may impact nasal polyps or its symptoms as per investigators judgement" and indicated that this criteria was applied to Asia only. To specify the herbal remedies and tradition Chinese medicines which need to be excluded and to clarify this criteria will not be checked for western patients.

Section 5.3 Added criteria to be confirmed prior to commencing OLE at Visit 11.

Section 5.4 Lifestyle restrictions: updated; Females added for sexually active patients; The time for effective contraceptive methods was updated from 12 to 16 weeks after the last dose of IP. Updated according to the PSSR.

Section 5.5.1 Re-screening: updated; Rescreened patients will use the same E-code as the initial screening.

Section 6.2.2, 6.2.3, 6.2.4 were added for self admin as mitigation to disruption, self admin OLE and optional remote visit.

Section 6.3.1 Methods for assigning treatment groups: CCI was added together with region for patient stratification.

Section 6.3.2 Methods for ensuring blinding: OLE was added.

Section 6.3.4 Open-Label Extension Period: Benralizumab Administration only added.

Section 6.4 Treatment compliance: updated to assure fewer protocol deviations with regards to IP administration and IP discontinuation.

Section 6.5 Concomitant therapy:

Table 5 in version 2.0 is now Table 7 in version 3.0; The restricted medication list was changed accordingly since OLE period has been added.

Table 6 in version 2.0 was updated to Table 8 in version 3.0; The Prohibited medication list was changed accordingly since OLE period has been added.

Section 6.5.1 Background medication: INCS and the INCS standardization (MFNS or equivalent) were added.

Section 6.7 Treatment after the end of the study: updated.

Section 7.1.1 Procedure for discontinuation of study treatment; “If patient decides to discontinue IP during OLE, he/she need to complete the IPD visit at 8 weeks after the last dose of IP, and no further follow-up visit is required.” added.

Section 8.1.1.1 Nasal Symptom Diary: updated; how to calculate the TSS was added.

Section 8.1.1.1.2 Difficulty with sense of smell: added (prioritized key secondary endpoint).

Section 8.1.1.3 Short Form 36-item Health survey, version 2: updated to highlight SF-36 threshold (rationale is included in SAP).

Table 9: Table 7 in version 2.0 was updated to Table 9 in version 3.0; The group difference was removed from the table as not included in study analysis.

Section 8.1.1.4 Patient Global Impression of Severity and Change: Grading of the PGI-S was added for correct response option.

Section 8.1.1.5 Asthma Control Questionnaire: Background information of ACQ-6 was updated to standardize protocol information.

Section 8.1.1.6 Asthma Exacerbations: “Asthma exacerbation is defined by a worsening of asthma” was updated to “The start date of an exacerbation is defined as the start date of systemic corticosteroid administration or date of hospital admission due to asthma. The end date of an exacerbation is defined as the last day of systemic corticosteroids or date of hospital discharge. A subsequent exacerbation must be proceeded by at least 7 days in which neither criteria is fulfilled”. The rationale is to ensure consistent capture of asthma exacerbations.

Section 8.1.3 Sinus Computed Tomography: EOT was updated to EoDB V11/week 56 and now reads: “In case of surgery during the double-blind part of the study, the CT scan should be done prior to surgery instead of at week 56 if at least 16 weeks passed since the previous CT scan.” The rationale for that CT should be performed before surgery is because the anatomy of sinus structures on CT may be completely altered after surgery, and LMS is not interpretable. Also, a CT scan prior to surgery will allow for use of actual data point which may improve robustness of study results and data interpretation. Worst possible score is still intended to be imputed in the primary analysis for patients undergoing surgery.

Table 12 Zinreich Score: Osteomeatal complex was added.

Section 8.1.4 Nasal Polyp Surgery: Clarification of the text to emphasize the necessity to perform assessment of NP severity before patients have nasal polyps surgery: “If the patient is scheduled for CRSwNP surgery, an unscheduled visit should be performed prior to the surgery to assess safety and efficacy (including total NPS, SNOT-22, CT [if at least 16 weeks since the previous CT scan], SF-36v2, PGI-S, PGI-C, ACQ-6 and UPSIT).” instead of “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)."

Section 8.1.5 SCS use for CRSwNP: "Safety and efficacy (including total NPS, SNOT-22, SF-36 v.2, PGI-S, PGI-C, ACQ-6 [for asthma patients only] and UPSIT) assessment should ideally be performed prior to the SCS use for NP." was updated to "Safety and efficacy (including total NPS, SNOT-22, SF-36v2, PGI-S, PGI-C, ACQ-6 and UPSIT) assessment should be performed prior to the SCS use for CRSwNP." to emphasize the necessity to perform the assessments before SCS use.

Section 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." was removed; 16 week was updated to 12 weeks after the last dose of IP.

Section 8.4.4 Management of investigational product-related reaction: updated according to recommendations from DRAC.

Section 8.5.1 Determination of drug concentration: clarified PK samples collected from the placebo group will not be analysed during DB period, while all samples will be analysed during the OLE.

Section 8.5.2 Storage and destruction of Pharmacokinetic samples: "or local requirement" was added.

Section 8.6 Immunogenicity: "or local requirement was added".

Section 8.6.1 Clarification that all ADA samples will be analysed.

Section 8.6.2 Neutralizing antibodies: removed.

Section 8.9 Biomarkers: CCI will be reported in the CSR; CCI is the only exploratory biomarker to be collected in China mainland.

Section 8.11 Other Assessments and Procedures: removed.

Section 9.1 Statistical hypotheses: Clarification that no hypothesis testing will be conducted for the OLE data. "Data collected from OLE will be summarized descriptively. No statistical hypotheses will be evaluated for OLE data based on formal statistical tests".

Section 9.2 Sample size determination:

Revised sample size from 148 to 250 to reflect inclusion of western countries in the study;

Updated model specification from MMRM to ANCOVA with WP/WOCF and MI.

Section 9.3 Populations for analysis: Primary full analysis and OLE analysis sets were added

Section 9.4 Statistical analyses was updated: Updated model specification to ANCOVA with WP/WOCF and MI; Added CCI and removed baseline eos from model covariates to reflect updates in the stratification factors for randomization; Updated primary estimand to impute worst possible after NP surgery and WOCF after SCS for NP; Updated list of key secondary endpoints to be DSS, LMK, and SNOT-22; Baseline CCI and atopic status (determined by CCI test) were added as subgroups; Removed subgroup analysis by baseline asthma status and by baseline INCS/LTRA status; Included DSS and SNOT-22 in multiplicity control to reflect updates in key secondary endpoints. Section 9.6 New section for "Analyses of Data from the Open-Label Extension" was added.
Version 2.0, 17 September 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 primary rationale for this amendment is to 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. Other updates: Table 1. Footnote b was updated. Table 2. Schedule of Activities – Randomisation, treatment period and follow-up - location from where ePRO questionnaires will be completed has been updated. Except for the NP Symptom Daily Diary, all other ePRO questionnaires will be completed on-site. Table 2. Footnote m was updated from "will not be collected in China" to "will be collected in Japan, Vietnam and Thailand".

Section 4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster or Public Health Crisis and Appendix F– New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity. Section 5.1 Inclusion Criteria – update the wording for inclusion criteria 7 to state that EOS may be repeated once based on the Investigators medical judgement. Section 5.2 Exclusion Criteria – updated wording for exclusion criteria 13 and 25 to align with the PSSR. Section 5.4.1 Re-screening – updated to allow 2nd re-screening if the 1st re-screening was failed due to civil crisis, natural disaster, or public health crisis. Section 6.4 Treatment Compliance and Section 7.1 Discontinuation of Study Treatment – remove the restriction of discontinuing the patient from study treatment if two IP doses were missed. Section 8.1.1 Clinical Outcome Assessments – updated to afford flexibility on the part of the site on their frequency of follow-up to the patient with regards to ePRO compliance. Section 8.1.3 Sinus Computed Tomography – updated to align with Footnote i. Section 8.1.5 SCS use for NP added.
Version 1.0, 12 July 2019
Initial creation

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

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

This study comprises 2 distinct periods: A 56-week double-blind (DB) treatment period, during which patients will be randomised to receive either benralizumab or placebo, on top of stable Intranasal corticosteroids (INCS), and an open-label extension (OLE) treatment period, during which all patients will receive benralizumab. The primary database lock (DBL) will occur after all randomised patients have been followed up for the 56-week DB treatment period.

The schedule of assessments (SoA) for the DB treatment period and for the OLE treatment period are provided in Table 2 and Table 3, respectively.

Patients may have the opportunity to participate in the OLE treatment period and receive benralizumab for about 1 year following completion of the DB period (see Section 4.1).

Table 1 Study of Assessments - Screening (run-in)

Study period	**Enrolment/ Screening (run-in)**		**Refer to section**
Visit	**V1**	**V2** [a)]	
Week	**w-6**	**w-2**	
Visit window (days)	**±7**	**+7**	
General Procedures			
Informed Consent[b)]	X		5.1, Appendix A 3
Inclusion/Exclusion criteria review	X	X	5.1, 5.2
Demographics	X		5.1
Medical and surgical history (including respiratory and CRSwNP) [c)]	X		5.1
Patient-reported Outcome Assessments			
At-site ePROs:			
Provide ePRO diary instructions	X		8.1.1
NP Symptom Screening Assessment (2 Week Recall) [d)]	X		8.1.1.1
SNOT-22 [d)]	X		8.1.1.2
Confirm that all PRO assessments have been completed [d)]	X	X	8.1.1
Review compliance of at-home PRO assessments		X	8.1.1
At-home ePROs completed by patients			
NP Symptom Diary (AM) [e)]	X	X	8.1.1.1

Study period	**Enrolment/ Screening (run-in)**		**Refer to section**
Visit	**V1**	**V2** [a)]	
Week	**w-6**	**w-2**	
Visit window (days)	**±7**	**+7**	
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
Local ECG	X		8.2.4
Adverse events	X	X	8.3, Appendix B
Concomitant medications	X	X	6.5
HRU Assessment			
HRU	X		8.10
Assess asthma exacerbations	X	X	8.1.1.6
Nasal polyps Assessments			
Nasal endoscopy	X	X	8.1.2
Sinus CT- scan		X	8.1.3
Assess nasal surgery or/and SCS use[f)]	X	X	8.1.4, 5.5.1, 6.5
Laboratory Assessments			
Clinical chemistry	X		8.2.1
Haematology	X		8.2.1
Serum pregnancy test [g)]	X		5.1, 8.2.1.1
Urine pregnancy test, dipstick [g)]		X	5.1, 8.2.1.1
Serology (HepB, HepC, HIV1, HIV2)	X		8.2.1.2
FSH [h)]	X		8.2.1.1
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 other study activities/procedures.
c. Nicotine use will be collected at V1.
d. Patients to complete available assessments in-clinic prior to other interventional study procedures (e.g. lab tests, endoscopy, sinus CT-scan).
e. Patient will start to complete NP Symptom Diary at home after the ePRO device is dispensed.
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 5.5.1.
g. This analysis will be only applicable for women of childbearing potential (WOCBP).
h. FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for ≥12 months.

CT- Computed tomography; ECG- Electrocardiogram; FSH- Follicle stimulating hormone; HRU - Healthcare resource utilization; CRSwNP - Chronic rhinosinusitis with nasal polyps ; (e)PRO- (electronic) Patient-reported outcome; SCS- Systemic corticosteroids; SNOT-22- SinoNasal Outcome Test, 22 item

Table 2 Schedule of Activities – Randomisation, Treatment Period

Study period	Treatment								EoDB[b]/IPD [c]	UNS [d]	Refer to section
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 [e]**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**		
Visit window (days) [a]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
General Procedures											
Inclusion/Exclusion criteria review	X										5.1, 5.2
Patient-reported Outcome Assessments											
At-site ePRO:											
Confirm that all PRO assessments have been completed [f]	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		8.1.1
UPSIT smell test [g]	X		X	X	X		X		X		8.1.1.7
SNOT-22	X		X	X	X	X	X	X	X		8.1.1.2
SF-36v2 (standard recall)	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	X		X	X	X	X	X	X	X		8.1.1.5
At-home ePROs completed by patients											
NP Symptom Diary (AM)	X	X	X	X	X	X	X	X	X		8.1.1.1
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

Study period	**Treatment**								**EoDB[b]/IPD [c]**	**UNS [d]**	**Refer to section**
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 [e]**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**		
Visit window (days) [a]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
Vital signs	X	X	X	X	X	X	X	X	X		8.2.3
Local ECG					X				X		8.2.4
Adverse events	X	X	X	X	X	X	X	X	X	X	8.3, Appendix B
Concomitant medications	X	X	X	X	X	X	X	X	X	X	6.5
HRU Assessment											
HRU	X	X	X	X	X	X	X	X	X		8.10
Assess asthma exacerbations	X	X	X	X	X	X	X	X	X		8.1.1.6
Nasal polyps Assessments											
Nasal endoscopy			X	X	X		X		X		8.1.2
Sinus CT- scan									X [h]		8.1.3
Assess nasal surgery or/and SCS use	X	X	X	X	X	X	X	X	X		8.1.4, 8.1.5, 6.5
Laboratory Assessments											
Clinical chemistry	X [i]				X				X		8.2.1
Haematology	X [i]			X	X		X		X		8.2.1
Urine pregnancy test, dipstick [j]	X	X	X	X	X	X	X	X	X		5.1, 8.2.1.1
CCI	X										8.2.1.3
CCI	X										8.2.1.3

Study period	**Treatment**								**EoDB[b)]/IPD [c)]**	**UNS [d)]**	**Refer to section**
Visit	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11 [e)]**		
Week	**w0**	**w4**	**w8**	**w16**	**w24**	**w32**	**w40**	**w48**	**w56**		
Visit window (days) [a)]	**±0**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**		
PK [j)]	X			X	X		X		X		8.5
Immunogenicity [j)]	X			X	X		X		X		8.6
Exploratory biomarkers - blood for serum proteins [k)]	X				X				X [l)]		8.9
Exploratory biomarkers - blood for plasma proteins [k)]	X				X				X [l)]		8.9
Exploratory biomarkers - blood for transcriptomic profiling [k)]	X				X				X [l)]		8.9
Exploratory biomarkers - nasal secretion [k)]	X				X				X [l)]		8.9
CCI	X				X				X [l)]		8.9
DNA sample (optional) [k)]	X [n)]										8.8
Randomisation, Investigational Product Administration											
Randomization [o)]	X										4.1
Investigational Product dispensed and administration [p)]	X	X	X	X	X	X	X	X	X [q)]		6.1, 6.2
Other											
INCS distribution and accountability	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. For patients who will not enter the OLE, V11 will be EoDB.
c. For patients who prematurely discontinue IP should return to the study site and complete the procedures described within 8 weeks after the last dose of IP.
d. Unscheduled visits may be initiated as needed, and additional assessments may be performed at these visits as indicated.
e. Visit 11 is the last double-blind visit and the first OLE visit. Only patients who enter OLE will receive IP (first dose of open-label Benralizumab) at this visit. All assessments at Visit 11 to be performed before administration of open-label benralizumab.
f. Patients to complete available assessments in-clinic prior to other study procedures.

g. UPSIT smell test will be performed in all countries which have validated version of the test.
h. Assessed at EoDB. For IPD patients only do assessment if at least 16 weeks since the previous CT scan. In case of surgery during the double-blind part of the study, the CT scan should be done prior to surgery instead of at week 56.
i. Results will only be used as baseline data. Will not be used for eligibility check.
j. At dosing visits, must be collected pre-dose.
k. Additional exploratory biomarker samples (excluding CCI and DNA sample (optional) will be collected in all participating countries except for China Mainland. DNA sample will not be collected in China Taiwan.
l. Assessed at EoDB. For IPD patients only do assessment if the time period between randomization and IPD visit is ≥24 weeks.
m. CCI is the only exploratory biomarker collected in China Mainland.
n. Samples can be collected at any time from Week 0 (V3) after genetic consent is signed.
o. All V3 procedures and assessments must be performed prior to randomization/IP dosing.
p. IP administration should be the last activity of the visit. All visit procedures should be done prior to dosing.
q. IP administration will be applied to patients who enter the OLE.

ACQ-6- Asthma Control Questionnaire-6; CRSwNP- Chronic rhinosinusitis with nasal polyps; CT- Computed tomography; CCI ; EoDB- End of double-blind; HRU- Healthcare resource utilization; CCI IPD- Investigational product discontinuation; 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.

Table 3 Schedule of Activities – For the Open-label Extension and Follow-up

Study period	Open-label treatment period							FU/IPD [c]	UNS [d]	Refer to section
Visit	**V12**	**V13** [b]	**V14** [b]	**V15**	**V16** [b]	**V17** [b]	**V18** [b]	**V19**		
Week	**W60**	**W64**	**W72**	**W80**	**W88**	**W96**	**W104**	**W112**		
Visit window [a]	±7 days									
Safety Assessments										
Brief physical examination [b]	X			X				X		8.2.2.2
Vital signs [b]	X			X				X		8.2.3
Adverse events	X	X	X	X	X	X	X	X	X	8.3, Appendix B
Concomitant medications	X	X	X	X	X	X	X	X	X	6.5
HRU Assessment										
Asthma exacerbation	X	X	X	X	X	X	X	X		8.1.1.6
Nasal polyps assessments										
Assess nasal surgery or/and SCS use	X	X	X	X	X	X	X	X		8.1.4, 8.1.5, 6.5
Laboratory Assessments										
Urinary pregnancy test [e]	X	X	X	X	X	X	X	X		5.1, 8.2.1.1
Clinical chemistry				X				X		8.2.1
Haematology				X				X		8.2.1
PK [e]				X				X		8.5
Immunogenicity [e]				X				X		8.6
Investigational Product Administration										
Investigational Product dispensed and administration [f]	X[g]	X	X	X	X	X	X			6.1, 6.2

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. Visit 13, 14, 16, 17 and 18 can optionally be performed via telephone/virtual system based upon the judgement of the PI and patient. This includes self-administration of IP at home.
c. For patients who prematurely discontinue IP should return to the study site and complete the procedures described within 8 weeks after the last dose of IP.
d. Unscheduled visits may be initiated as needed, and additional assessments may be performed at these visits as indicated.

e. At dosing visits, must be collected pre-dose.
f. IP administration should be the last activity of the visit. All visit procedures should be done prior to dosing.
g. Patients who are assigned to benralizumab arm will have a placebo injection.

FU- Follow-up; HRU- Healthcare resource utilization; IPD- Investigational product discontinuation; PK- Pharmacokinetics; SCS- Systemic corticosteroids; UNS- Unscheduled.

1.2 Synopsis

International co-ordinating investigator

PPD
Beijing TongRen Hospital, Capital Medical University
No1, Dongjiaominxiang, Beijing, China Mainland

Protocol Title:

A Multicentre, Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Efficacy and Safety Study of Benralizumab in Patients with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps (ORCHID).

Rationale:

Chronic rhinosinusitis with nasal polyps (CRSwNP) 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. The etiology of CRSwNP is currently unknown, though the role of eosinophils and basophils are considered important to the pathology of nasal polyps, especially in the eosinophilic phenotype. Furthermore, severe sinonasal disease has been linked to patients with comorbid asthma. Both diseases are thought to have high levels of T2 and eosinophilic inflammation. It is hypothesized that patients with eosinophilic nasal polyps and comorbid asthma may benefit from depletion of eosinophils and reduction of eosinophilic inflammation.

The aim of this study is to investigate the use of benralizumab in patients with eosinophilic CRSwNP, and comorbid asthma, whose severity is consistent with a need for surgery (total nasal polyps score [NPS] ≥5 and moderate to severe nasal blockage) despite ongoing treatment with INCS and a history of treatment with systemic corticosteroids (SCS) or prior surgery for CRSwNP. The 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 During the Double-Blind Treatment Period

Primary objective:	**Estimand Description / Endpoints:**
To evaluate the effect of benralizumab on nasal polyp burden and patient-reported nasal blockage (NB)	• Population[a] : severe CRSwNP patients with asthma • 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 (included in analysis regardless of treatment discontinuation) CRSwNP Surgery – composite (Worst Possible Carried Forward) SCS for CRSwNP – composite (Worst Observation Carried Forward) • Summary Measure: differences in least squares mean change from baseline in NPS and NBS between benralizumab and placebo. Week 56 is the primary timepoint.
Secondary Objective:	**Endpoint/Variable:**
To evaluate the effect of benralizumab on:	
Sense of smell	• Change from baseline in mean difficulty with sense of smell (DSS) score[b] • Change from baseline in the University of Pennsylvania Smell Identification Test (UPSIT) score
Sinus opacification by CT scan	• Change from baseline in Lund Mackay Score[b] (LMS) • Change from baseline in sinus severity score by Quantitative CT analysis • Change from baseline in Zinreich score (modified LMS)
Disease specific health-related quality of life (HRQoL)	• Change from baseline in SinoNasal Outcome Test (SNOT-22) score[b]
Nasal polyp surgery and/or systemic corticosteroids (SCS) use for relief of nasal symptoms	• Time to first NP surgery and/or SCS use for CRSwNP • Proportion of patients with NP surgery and/or SCS use for CRSwNP

Nasal polyp surgery	• Time to first CRSwNP surgery • Proportion of patients with surgery for CRSwNP
Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for CRSwNP • Time to first SCS course for CRSwNP • Number of courses of SCS for CRSwNP • Total SCS dose used and total duration of SCS use for CRSwNP
Symptoms associated with nasal polyps	• Change from baseline in nasal symptom score(s) as captured in the NP Symptom Diary (NPSD)
Patient-reported general health status	• Change from baseline in Short Form 36-item Health survey, Version 2 (SF-36v2) Physical Component Summary (PCS), Mental Component Summary (MCS) and domains
To characterize the PK and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity: anti-drug antibodies
Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of benralizumab as compared to placebo in subjects with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG • Assessments related to AEs cover - Occurrence/Frequency - Relationship to IP as assessed by investigator - Intensity - Seriousness - Death - AEs leading to discontinuation of IP • Vital signs parameters include systolic and diastolic blood pressure, and pulse. Assessments cover - Observed value - Absolute change from baseline values over time • Laboratory variables • ECG
Exploratory objectives:	**Endpoint/Variable:**
To assess the effect of benralizumab on asthma control	• Asthma Control Questionnaire (ACQ-6) • Asthma exacerbation rate (AER)
To assess the effect of benralizumab on patient recognition for improvement	• Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C)
To assess the effect of benralizumab on exploratory biomarkers of inflammation and nasal polyps disease and investigate biomarkers for predicting response to benralizumab	• Exploratory biomarker parameters • Serum and plasma for protein biomarkers • Whole blood for transcriptomic profiling • Nasal secretions for protein biomarkers

To assess the effect of benralizumab on CCI CCI as a biomarker of inflammation and nasal polyps disease and for predicting response to benralizumab	• CCI
To assess the effect of genetic variation on subject's response to therapy, susceptibility to, and severity and progression of disease	• A blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic exploratory analysis component of the study
To evaluate the effect of benralizumab on unplanned health care resource utilization	• Hospitalisations, emergency room and urgent care visits
a Treatment condition for primary estimand: Treatment with benralizumab versus placebo, regardless of compliance, where rescue with CRSwNP surgery and/or SCS for CRSwNP represents failure. b Key secondary efficacy endpoints. A similar estimand as outlined for the co-primary endpoints will be used for analyses of repeated measures secondary endpoints. Co-primary and key secondary endpoints are multiplicity protected.	

Objectives and Endpoints During the Open-Label Extension

Primary objective:	**Endpoint/Variable:**
To assess the safety and tolerability of benralizumab in subjects with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps	Safety and tolerability will be evaluated in terms of AEs, Vital signs and Clinical laboratory • Assessments related to AEs cover - Occurrence/Frequency - Relationship to IP as assessed by investigator - Intensity - Seriousness - Death - AEs leading to discontinuation of IP • Vital signs parameters include systolic and diastolic blood pressure, and pulse. Assessments cover - Observed value - Absolute change from baseline values over time • Laboratory variables
Secondary Objective:	**Endpoint/Variable:**
To characterize the PK and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity : anti-drug antibodies
Exploratory objectives:	**Endpoint/Variable:**
Nasal polyp surgery	• Proportion of patients with surgery for CRSwNP
Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for CRSwNP • Number of courses of SCS for CRSwNP • Total SCS dose used and total duration of SCS use for CRSwNP
Effect of benralizumab on asthma control	• Asthma exacerbations

Overall design:

This is a randomised, double-blind with placebo-controlled, parallel-group, multicentre, 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 eosinophilic CRSwNP. Following completion of the double-blind period, patients have the option to enter an OLE.

Approximately 250 patients will be randomised to receive benralizumab 30 mg SC or matching placebo.

Patients will be stratified by region and baseline CCI

After enrolment, and prior to entering a screening/run in period, eligible participants will have their current daily INCS therapy standardized to Mometasone Furoate (MFNS), total daily dose of 400 mcg or equivalent (highest local approved dose for CRSwNP), which should be maintained throughout the study until the last DB visit (V11). Patients who meet eligibility criteria will be randomised 1:1 at Week 0 (Day 0) to receive 8 doses of either placebo or benralizumab 30 mg administered SC every 4 weeks for the first 3 doses and every 8 weeks thereafter.

All patients who complete the 56-week DB treatment period on investigational product (IP) may be eligible to continue into around one year OLE, during which all patients will receive 8 doses of benralizumab 30 mg. The last study visit will occur at 8 weeks after the last dose of IP (Week 112/FU). Patients who do not enter OLE, will have their last study visit at Week 56 (EoDB) for follow-up and without administration of IP.

Study Period:

First patient enrolled 25 Nov 2019
Estimated date of last patient completed Q4 2025

Number of Patients:

This study will be conducted in approximately 12 countries at approximately 115 sites. The target is to randomize approximately 250 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). Matching placebo will be administered SC at the same time points.

All patients who enter the OLE period will receive 8 doses of benralizumab 30 mg administered SC every Q4W for the first 3 doses (Weeks 56, 60, 64) and Q8W thereafter (Weeks 72, 80, 88, 96 and 104). Patients randomized to the benralizumab arm during DB period, will receive one dose of placebo (dummy) injection at Visit 12 (week 60) in order to maintain the blind.

All participants will have their current INCS therapy standardized to MFNS at V1 for a minimum of 4 weeks prior to V2 continued throughout the screening and study period until Visit 11 (week 56). Equivalent dose should refer to the highest approved country INCS dose for CRSwNP. Note: Patients in Japan will follow the requirement regarding to INCS use as indicated in the country protocol.

Statistical methods

The primary database lock will occur after all randomised patients have been followed up for the 56-week DB treatment period. The study will remain blinded until the primary database lock. The final database lock will occur after the last patient completes the OLE. The primary analysis of efficacy endpoints will include all data captured during the double-blind-treatment period (intention-to-treat approach).

The primary analysis will compare the effect of benralizumab versus placebo on the change from baseline in total NPS at Week 56 (V11) and the change from baseline in bi-weekly mean NBS at Week 56 using a hybrid method of the worst-possible/worst-observation carried forward and multiple imputation, followed by an analysis of covariance (ANCOVA) with treatment arm, baseline scores of corresponding endpoint, region, and baseline CCI status CCI CCI as covariates. Analyses for key secondary endpoints (i.e. change from baseline in DSS, LMS, and SNOT-22 at week 56) will be analysed using ANCOVA in a similar manner to co-primary endpoints.

A hierarchical fixed-sequence testing strategy will be used to control the overall type I error rate at the 0.05 level to account for multiplicity in testing for the co-primary endpoints and the 3 key secondary endpoints in the primary population.

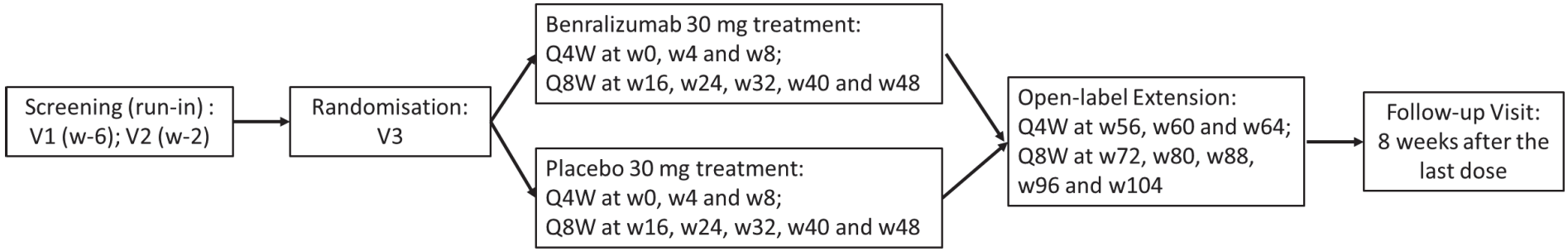
Approximately 250 patients will be randomised to benralizumab or placebo in a 1:1 ratio. Assuming a population standard deviation of 2 in total NPS and 1 in NBS, this sample size will provide at least 80% power to detect a true mean (population) treatment difference of 0.85 units in total NPS and a difference of 0.4 in NBS with a two-sided 0.05 alpha level.

All safety parameters will be analysed descriptively. Data collected from the OLE will be analysed descriptively.

1.3 Schema

The study design schema is summarized in Figure 1 Study Flow Chart.

Figure 1 Study Flow Chart



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 CRSwNP. Benralizumab is a monoclonal antibody (mAb) directed against the interleukin-5 receptor alpha subunit (IL-5Rα) on eosinophils and basophils, and the activation leads to efficient eosinophil and basophil depletion. Thus, depletion of eosinophils and basophils by SC-administered benralizumab in this randomised, double-blind, placebo-controlled Phase 3 study is hypothesized to reduce localized inflammation subsequently resulting in reduced polyp size, an improvement in symptoms and quality of life, and a reduced need for surgery.

2.2. Background

CRSwNP is a chronic inflammatory disease of the nasal mucosa. 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 greatly impact a patient's quality of life. Patients with CRSwNP have been observed to have worse symptoms (as evidenced by higher Sino-Nasal Outcome Test [SNOT]-20 scores), more severe disease by imaging (as demonstrated by Lund-Mackay computed tomography [CT] scores), and require more frequent surgical revision than patients with chronic rhinosinusitis without nasal polyps (Hull and Chandra 2017; Fokkens et al 2012).

The etiology of CRSwNP is still considered unclear, but allergy, asthma, infection and aspirin sensitivity (AERD) have all been associated with this complex refractory disease in adults (Hull and Chandra 2017). Both CRSwNP and asthma are predominantly T2-driven disease processes characterised by an abundance of eosinophils. The inflammatory profile observed in bronchial asthma shares many features and similarities with the inflammation seen in patients with CRSwNP where eosinophils are the dominant inflammatory cell; the 'united airways concept' (Hakansson et al 2015).

The prevalence of comorbid asthma in CRSwNP ranges from 20% up to 60% (Klossek 2005; Khan et al 2019; Philpott et al 2018; Promsopa 2016; DeConde 2015; DeConde 2017; Batra 2013), indicative of high comorbid rates between these two diseases. Presence of asthma and elevated eosinophils in tissue are associated with more severe sinonasal diseases, greater symptoms recurrences and worse quality of life (Lou Ho et al 2015; Stevens et al 2019; Staudacher et al 2020; Laidlaw et al 2020), as compared with CRSwNP without comorbid asthma (Wang et al 2020).

Several studies have observed that there is a correlation between infiltrating eosinophils and severity of polyps as scored by Lund-Mackay score (LMS) on CT scans (Shah et al 2016;

Poznanovic and Kingdom 2007; Kuhar et al 2017) and eosinophil aggregates were associated with significantly worse disease (Kuhar et al 2017). Patients with eosinophilic inflammation in their nasal polyps also show longer duration of symptoms and higher symptoms scores as well as higher incidence of surgery and a greater risk of recurrence of nasal polyps after surgery (Sun et al 2017; Fokkens et al 2012; Mygind et al 2000; Brescia et al 2016). Similar observations have also been made with basophils where basophils correlate with CRSwNP severity by CT (Kagoya et al 2015) and nasal polyp (NP) recurrence post-surgery (Brescia et al 2015).

The profile of inflammatory cell infiltrate in biopsy tissue from polyps compared with bronchial mucosa in CRSwNP patients with and without asthma was similar (Ediger et al 2005). Furthermore, the profile of inflammatory cytokines and chemokines was correlated between the upper and lower airways in patients with CRSwNP with and without asthma suggesting that the inflammatory profile is similar throughout the airway in CRSwNP and CRSwNP with asthma. (Hakansson et al 2015). There is evidence of other shared pathogenic processes between these diseases such as disrupted epithelial barrier and airway remodelling (Samitas et al 2018; Langdon et al 2016; Wang et al 2019).

Interleukin-5 is a key cytokine essential for eosinophil trafficking and survival (Molfino et al 2012). Interleukin-5 has been found to be significantly raised in patients with CRSwNP compared with healthy controls (Gevaert et al 2009). The effect of Interleukin-5 (IL-5) inhibition by mepolizumab (a monoclonal antibody directed against IL-5), has been shown to reduce polyps size and symptoms in patients with severe CRSwNP refractory to corticosteroid therapy (Gevaert et al 2011; Bachert et al 2017).

Benralizumab is a humanized, afucosylated, mAb that binds specifically to the human IL-5Rα on the target cell, which is expressed on the surface of eosinophils and basophils (Takatsu et al 1994; Toba et al 1999**)**. Afucosylation confers enhanced antibody-dependent cellular cytotoxicity which results in highly efficient eosinophil depletion by apoptosis (Kolbeck et al 2010).

Clinical efficacy of benralizumab 30 mg SC in asthma was confirmed in Phase 3 global safety and efficacy trials in patients on high dose ICS/LABA (Bleecker et al 2016; Fitzgerald et al 2016; Nair et al 2017**)**. In patients with blood eosinophil counts ≥300 cells/μL, benralizumab, administered every 4 weeks or every 4 weeks for the first 3 doses followed by every 8 weeks thereafter for up to approximately 1 year, produced significant decreases in asthma exacerbations and improvements in lung function, reduction in OCS use and total daily asthma symptoms.

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

2.3. Benefit/risk assessment

CRSwNP represents an area of significant unmet medical need, especially for a subset of patients with CRSwNP who have exhausted current treatment options, which include medical interventions (INCS and SCS) and surgical interventions. Based on the high prevalence of eosinophilic inflammation in CRSwNP and preliminary clinical efficacy of IL-5 neutralization in this condition, benralizumab's anti-eosinophil mechanism of action (with resultant tissue eosinophil depletion) is expected to meaningfully reduce the disease burden in patients with severe CRSwNP by reducing polyp size, symptom burden, and the need for SCS or surgery.

Development of anti-drug antibodies (ADA) to benralizumab has been documented. Potential risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease). To date, no confirmed cases of immune complex disease have been observed and no appearance of a relationship between ADA and treatment emergent AEs has been established. There was no impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in asthma.

Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes observation in line with clinical practice at the clinical site following IP administration for the appearance of any acute drug reactions.

Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumours. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites, or negatively impact the natural history of certain malignant tumours. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

The overall safety profile of benralizumab in severe asthma patients (which included approximately 20% of patients with comorbid CRSwNP disease) was similar to placebo for exposures up to approximately 1 year. Fewer patients in the benralizumab groups reported any adverse event (AE) compared with placebo. The most commonly reported AEs included nasopharyngitis, asthma, and upper respiratory tract infections. The majority of AEs were mild to moderate in nature. Fewer patients in the benralizumab group reported serious adverse events (SAEs) compared with placebo.

Based on benralizumab’s mechanism of action, there is a potential for benefit in the CRSwNP population. In addition, given the extensive safety data already available, the benefit risk

profile in patients with severe CRSwNP is expected to be commensurate with that observed in the benralizumab asthma pivotal trials, i.e. a favourable benefit/risk profile.

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. The total radiation dose is estimated to be approximately 2 milli Sievert (mSv). This dose is within the accepted radiation dose range for biological research (1-10 mSv; Directorate-General – Environment, nuclear safety and civil protection 1998).

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

3. OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints During the Double-Blind Treatment Period

Primary objective:	**Estimand Description / Endpoints:**
To evaluate the effect of benralizumab on nasal polyp burden and patient-reported nasal blockage (NB)	• Population[a] : severe CRSwNP patients with asthma • Co-primary endpoints: Change from baseline in endoscopic total nasal polyp score (NPS) Change from baseline in mean NBS • Intercurrent event strategy: Treatment discontinuation - treatment policy (included in analysis regardless of treatment discontinuation) CRSwNP Surgery – composite (Worst Possible Carried Forward) SCS for CRSwNP – composite (Worst Observation Carried Forward) • Summary Measure: differences in least squares mean change from baseline in NPS and NBS between benralizumab and placebo. Week 56 is the primary timepoint.
Secondary Objective:	**Endpoint/Variable:**
To evaluate the effect of benralizumab on:	
Sense of smell	• Change from baseline in mean difficulty with sense of smell (DSS) score[b] • Change from baseline in the University of Pennsylvania Smell Identification Test (UPSIT) score
Sinus opacification by CT scan	• Change from baseline in Lund Mackay Score[b] (LMS) • Change from baseline in sinus severity score by Quantitative CT analysis • Change from baseline in Zinreich score (modified LMS)
Disease specific health-related quality of life (HRQoL)	• Change from baseline in SinoNasal Outcome Test (SNOT-22) score[b]

Nasal polyp surgery and/or systemic corticosteroids (SCS) use for relief of nasal symptoms	• Time to first NP surgery and/or SCS use for CRSwNP • Proportion of patients with NP surgery and/or SCS use for CRSwNP
Nasal polyp surgery	• Time to first CRSwNP surgery • Proportion of patients with surgery for CRSwNP
Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for CRSwNP • Time to first SCS course for CRSwNP • Number of courses of SCS for CRSwNP • Total SCS dose used and total duration of SCS use for CRSwNP
Symptoms associated with nasal polyps	• Change from baseline in nasal symptom score(s) as captured in the NP Symptom Diary (NPSD)
Patient-reported general health status	• Change from baseline in Short Form 36-item Health survey, Version 2 (SF-36v2) Physical Component Summary (PCS), Mental Component Summary (MCS) and domains
To characterize the PK and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity: anti-drug antibodies
Safety Objective:	**Endpoint/Variable:**
To assess the safety and tolerability of benralizumab as compared to placebo in subjects with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG • Assessments related to AEs cover - Occurrence/Frequency - Relationship to IP as assessed by investigator - Intensity - Seriousness - Death - AEs leading to discontinuation of IP • Vital signs parameters include systolic and diastolic blood pressure, and pulse. Assessments cover - Observed value - Absolute change from baseline values over time • Laboratory variables • ECG
Exploratory objectives:	**Endpoint/Variable:**
To assess the effect of benralizumab on asthma control	• Asthma Control Questionnaire (ACQ-6) • Asthma exacerbation rate (AER)
To assess the effect of benralizumab on patient recognition for improvement	• Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C)
To assess the effect of benralizumab on exploratory biomarkers of inflammation and nasal	• Exploratory biomarker parameters • Serum and plasma for protein biomarkers

polyps disease and investigate biomarkers for predicting response to benralizumab	• Whole blood for transcriptomic profiling • Nasal secretions for protein biomarkers
To assess the effect of benralizumab on CCI CCI as a biomarker of inflammation and nasal polyps disease and for predicting response to benralizumab	• CCI
To assess the effect of genetic variation on subject's response to therapy, susceptibility to, and severity and progression of disease	• A blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic exploratory analysis component of the study
To evaluate the effect of benralizumab on unplanned health care resource utilization	• Hospitalisations, emergency room and urgent care visits
a Treatment condition for primary estimand: Treatment with benralizumab versus placebo, regardless of compliance, where rescue with CRSwNP surgery and/or SCS for CRSwNP represents failure. b Key secondary efficacy endpoints. A similar estimand as outlined for the co-primary endpoints will be used for analyses of repeated measures secondary endpoints. Co-primary and key secondary endpoints are multiplicity protected.	

Table 5 Objectives and Endpoints During the Open-Label Extension

Primary objective:	Endpoint/Variable:

To assess the safety and tolerability of benralizumab in subjects with Eosinophilic Chronic Rhinosinusitis with Nasal Polyps	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory • Assessments related to AEs cover - Occurrence/Frequency - Relationship to IP as assessed by investigator - Intensity - Seriousness - Death - AEs leading to discontinuation of IP • Vital signs parameters include systolic and diastolic blood pressure, and pulse. Assessments cover - Observed value - Absolute change from baseline values over time • Laboratory variables
Secondary Objective:	**Endpoint/Variable:**
To characterize the PK and immunogenicity of benralizumab	• PK: Serum trough concentrations • Immunogenicity: anti-drug antibodies
Exploratory objectives:	**Endpoint/Variable:**
Nasal polyp surgery	• Proportion of patients with surgery for CRSwNP
Systemic corticosteroids (SCS) use for relief of nasal symptoms	• Proportion of patients with SCS use for CRSwNP • Number of courses of SCS for CRSwNP • Total SCS dose used and total duration of SCS use for CRSwNP
Effect of benralizumab on asthma control	• Asthma exacerbations

4. STUDY DESIGN

4.1. Overall design

This is a randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase 3 study to evaluate the efficacy and safety of repeat dosing of benralizumab 30 mg administered SC versus placebo in patients with severe eosinophilic CRSwNP. Following completion of the double-blind period, patients have the option to enter an OLE.

Approximately 250 patients will be randomised, to receive benralizumab 30 mg SC or matching placebo.

Patients will be stratified by region and baseline CCI Randomisation will be monitored to ensure that no more than CCI of the study population will have CCI When the target percentage of patients in a subgroup is reached, consideration will be given to closing the IWRS randomisation for that subgroup. Once a subgroup is closed, patients in the screening/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed.

After enrolment, and prior to entering the screening/run in period, eligible participants will have their current INCS therapy switched to MFNS (400 mcg daily) or equivalent (highest local approved for CRSwNP), which should be maintained throughout the study until the last DB visit (V11). Patients must have been on a stable daily dose of INCS for at least 4 weeks prior to V1. Patients will be provided with an electronic patient-reported outcome (ePRO) device to record symptoms throughout the study until V11 (week 56) (see section 8.1.1 Clinical outcome assessments).

Patients who continue to meet eligibility criteria will be randomised 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). All patients who complete the 56-week DB treatment period on IP may be eligible to continue into an OLE, during which all patients will receive 8 doses of benralizumab 30 mg every QW4 for the first 3 doses (Weeks 56, 60, 64) and Q8W thereafter (Weeks 72, 80, 88, 96 and 104). Patients randomized to the Benralizumab arm during DB period will receive one dose of placebo (dummy) injection at Visit 12 (week 60) in order to maintain the blind.

During the DB period, patients will return to the study site at dosing visits and at V11 (week 56) for evaluation of efficacy, safety, pharmacokinetics (PK), ADA, collection of blood sample and nasal secretion for exploratory biomarkers. Patients who enter the OLE period will receive their first OLE dose at V11, after completion of all visit-related assessments. Throughout the OLE, patients will mainly have assessments related to safety (see Table 3).

The last study visit will occur at 8 weeks after the last dose of IP (Week 112/FU). Patients who do not enter OLE, will have their last study visit at Week 56 (EoDB) for follow-up and without administration of IP. 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).

CT scanning will be performed at V2 (week -2) and EoDB V11 (week 56), or IPD if at least 16 weeks since the previous CT scan. In case of surgery during the double-blind part of the study, the CT scan should be done prior to surgery instead of at week 56 if at least 16 weeks since the previous CT scan. CT assessment at V2 will be used both for inclusion criterion 7 for Asian patients and as baseline (see Section 8.1.3 Sinus Computed Tomography).

The primary database lock will occur after all randomised patients have been followed up for the 56-week DB treatment period. The study will remain blinded until the primary database lock. The final database lock will occur after the last patient completes the OLE. The primary analysis of efficacy endpoints will include all data captured during the DB treatment period (intention-to-treat approach). Selected safety data from the OLE period will be reported in the CSR at primary DBL and additional data from the OLE period will be reported separately at the final DBL. For an overview of the study design see Figure1, Section 1.3. For details on treatments given during the study, see Section 6 Treatments Administered.

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

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

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the 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 a civil crisis, natural disaster, or public health crisis, 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:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).

- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

- ePRO visit confirmation via StudyWorks Portal: site personnel may perform the visit confirmation remotely to the patient's handheld device via the StudyWorks Portal if the patient cannot do an on-site visit.

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

4.2. Scientific rationale for study design

The DB portion of this study is designed to investigate the safety and efficacy of benralizumab to placebo in patients with severe bilateral eosinophilic CRSwNP and comorbid asthma who remain symptomatic despite standard of care therapy. The OLE is intended to allow patients to receive around one year of treatment with open-label benralizumab 30 mg.

The population is composed of patients with ongoing chronic symptoms of CRSwNP for at least 12 weeks prior to enrolment with moderate to severe patient-reported nasal blockage, endoscopic diagnosis of bilateral CRSwNP (NPS of at least 5 out of a maximum of 8) centrally read by an independent physician, despite treatment with standard of care, including a history of treatment with SCS or surgical interventions. The disease severity at enrolment and failure of standard pharmacological treatment likely constitute an accepted indication for surgery (despite regional variability in availability for surgical options) or for a targeted biologic therapeutic modality such as benralizumab.

The sample size (n = approximately 250) and 56-week DB treatment duration is considered appropriate to capture maintenance effects.

4.3. Justification for dose

The benralizumab dose and regimen proposed in the CRSwNP Phase 3 pivotal study will be consistent with the asthma dosing regimen, i.e. 30 mg by SC injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter. This proposal is based on consideration of mechanism of disease (similarity of the inflammatory profile between asthma and CRSwNP, see Section 2.2 Background), and all available safety, efficacy, and immunogenicity data from completed asthma trials, as well as population exposure-response modelling, and stochastic trial simulations from earlier phase benralizumab trials.

Both empirical and population-based analyses of asthma exacerbation rate (AER) data in Phase 2b and Phase 3 asthma patients confirmed 30 mg every 8 weeks (i.e. benralizumab 30 mg by SC injection every 4 week for the first 3 doses, and then every 8 weeks thereafter) as the optimal dose for efficacy, based on annualized AER. The efficacy plateau for pre-bronchodilator forced expiratory volume in 1 second (FEV1) was reached with benralizumab 30 mg every 8 weeks. This regimen demonstrated statistically significant reductions in the AERs, and statistically significant improvements in pulmonary function (FEV1) and total asthma symptom score. Compared with the 30 mg every 4 weeks regimen, the benralizumab 30 mg every 8 weeks regimen was more consistent across studies and endpoints, and no additional benefit was observed by dosing with benralizumab more frequently. Neither body weight nor ADA was found to impact the annualized AER or pre-bronchodilator FEV1.

In the Phase 3 asthma pivotal studies, approximately 20% of patients had CRSwNP in addition to severe asthma. Importantly, the patients with CRSwNP had similar pharmacokinetics (PK) exposure and eosinophil depletion to patients without CRSwNP.

In conclusion, the 30 mg every 8 weeks dosing regimen (including an additional dose at Week 4) is recommended to be used in the benralizumab CRSwNP Phase 3 program. No dose adjustment for CRSwNP is warranted based on the similarity of the inflammatory profile between asthma and CRSwNP, and considerations of PK variability, blood eosinophil count depletion, immunogenicity, exposure-response analysis of efficacy endpoints in patients with severe asthma, and the clinical safety profile of benralizumab.

4.4. End of study definition

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

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

Food and Drug Administration requirements defines two completion dates:

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

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

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 assigned/randomised 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, refer to section 5.5.

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

For procedures for withdrawal of incorrectly enrolled or randomised patients see Section 7.4.

5.1. Inclusion criteria

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

Informed consent

1. 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 prior to any mandatory study specific procedures, sampling, and analyses.
3. Provision of signed and dated written Genetic informed consent prior to collection of sample for genetic analysis.

   The ICF process is described in Appendix A 3.

Age

4. Subject must be 18 to 75 years of age inclusive, at the time of signing the informed consent form.

Type of patient and disease characteristics

5. Patients with bilateral sinonasal polyps that, despite treatment with a stable daily dose of INCS for at least 4 weeks prior to V1, in addition to a history of treatment with SCS (oral, parenteral) and/or prior surgery for CRSwNP 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 randomisation 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. A documented physician-diagnosed asthma.
7. Asia only (Japan, China Mainland, China Taiwan, Vietnam, and Thailand): CT Lund Mackay score for ethmoid ≥ maxillary at V2, as determined by the study Imaging Core lab .
8. Blood eosinophil count of >2% or ≥150/µL at V1, as determined by central lab. The test may be repeated once based on the Investigators medical judgement.
9. Patients who are on leukotriene receptor antagonists (LTRAs), need to be at stable dose for at least 30 days prior to V1.
10. Willingness to maintain all standard of care treatment for CRSwNP stable for the duration of the study.
11. SNOT-22 total score ≥20 at enrolment (V1).

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

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

13. At randomisation, a bi-weekly mean NBS ≥1.5.
14. SNOT-22 total score ≥20 at randomisation (V3).
15. Minimum 70% compliance with INCS during the run-in period based on daily diary.

Reproduction

16. Negative serum pregnancy test result at V1 and a negative urine pregnancy test at V2 and randomisation for female patients of childbearing potential.
17. Women of childbearing potential (WOCBP) must agree to use a highly effective method of birth control (confirmed by the Investigator) from enrolment, throughout the study duration and for 12 weeks after the last dose of IP. Highly effective methods (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation-oral, intravaginal, or transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable
    - Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Sexual abstinence, i.e. refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient)
    - Vasectomized sexual partner (provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success)
18. Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrheic for 12 months prior to the planned date of the randomisation 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. Until FSH is documented to be within menopausal range, treat the patient as WOCBP.
    - Women 50 ≥ years old are considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

5.2. Exclusion criteria

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 tumours

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 (e.g. allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangiitis [Churg-Strauss syndrome], hyper eosinophilic syndromes), granulomatosis with polyangiitis (Wegener's granulomatosis), Young's syndrome, etc.

4 Any disorder, including but not limited to: cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, autoimmune, 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 hospitalisation (>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 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.

9 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.

10 Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, 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.

11 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.

12 Current active liver disease
Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen (HBsAg) or hepatitis C antibody), or other stable chronic liver disease are acceptable if subject otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

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

14 Infection requiring systemic antibiotics (Ab) or systemic Ab for the treatment of CRSwNP within 14 days prior to V1.

Prior/concomitant therapy

15 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.

16 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.

17 Previous receipt of benralizumab.

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

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

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

21 Receipt of systemic corticosteroid within 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.

22 Asia only: receipt of herbal remedies or traditional Chinese medicines that may impact nasal polyps or its symptoms as per investigators judgement within 30 days prior to V1.

Prior / Concurrent clinical study experience

23 Concurrent enrolment in another clinical drug interventional trial.

Diagnostic assessments

24 Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 3 times the upper limit of normal (ULN), confirmed by repeated testing during screening period. Transient increase of AST/ALT level that resolves by the time of randomisation is acceptable if in the Investigator's opinion the subject does not have an active liver disease and meets other eligibility criteria.

Other exclusions

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

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

27 Previous randomisation in the present study.

28 Planned major surgical procedures or scheduled CRSwNP surgery at the time of the study enrolment and randomisation.

29 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.

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

31 For women only - currently pregnant (or intend to become pregnant), breastfeeding or lactating.

5.3. Criteria to be Confirmed Prior to Commencing OLE at Visit 11 criteria

Patients who complete the DB period of the study on treatment may be eligible to continue into the OLE.

5.4. Lifestyle restrictions

1. Fertile and sexually active female patients should use effective contraceptive methods throughout the study and 12 weeks after last dose of the IP.

2. Patients must abstain from donating blood, plasma, or platelets from the time of informed consent, to 12 weeks after last dose of the IP.

5.5. Screen failures

Screen failures are defined as patients who signed the informed consent form to participate in the clinical study but are not subsequently randomised 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 from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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

5.5.1. Re-screening

Re-screening is allowed only once for a patient. In case that patients are screening failed due to Civil Crisis, Natural Disaster, or Public Health Crisis at the first rescreening, second rescreening is allowed.

Rescreening and/or up to 6-week 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 unforeseen personal events that result in a missed visit).

For patients who require SCS for an asthma exacerbation or worsening of nasal polyp symptoms during the screening period (prior to V2), the screening period may be extended, provided the treatment duration with SCS is ≤17 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.

Extension of the screening period can be allowed if deemed necessary by the investigator and agreed with the AZ study physician/delegate (e.g. in case of acute events, or need to obtain additional evidence of the patient's eligibility).

If the duration of treatment with SCS is >17 days, or SCS is used at or 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. For second rescreening, the patient will be assigned new E-code.

Re-screened patients should re-sign informed consent. All procedures from the screening/run-in period should be repeated. CT will be repeated at rescreening if it has been more than 3 months since the previous scan at screening; or repeated earlier at the discretion of PI. 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 investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to benralizumab 30 mg or matching placebo, 1 mL.

6.1. Treatments administered

6.1.1. Investigational products

Table 6 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: Also refer to Section 6.2 of study specific handling instructions are required i.e. for IV preparation	Benralizumab active solution will be administered subcutaneously to patients by health care professionals, patients, or their caregivers using an accessorized prefilled syringe (APFS). Each prefilled syringe is designated for single use only and is not to be administered to more than one patient.	Placebo solution will be administered subcutaneously to patients by health care professionals in this clinical study using an accessorized prefilled syringe (APFS). 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)	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)

	• Sponsor name and contact details • Directions for use • Storage condition • Standard statements required by regulatory authorities	• 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

Up to and including on Visit 12, the investigational product will be administered at the study site on treatment visits and within visit windows as specified in the SoA. After Visit 12 , IP may be administered within the visit windows as described in Table 3, either on-site by an HCP or, optionally, at home or a remote location by the patient or their caregiver. Self-administration of the IP requires assessment and training by the Investigator (Section 6.2.1.X).

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.

Investigational product administration

The investigational product will be administered by the Investigator/authorized delegate. Investigational product should be administered into the upper arm, thighs, or the abdomen (see Figure 2).

It is recommended that the site of injection is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, or hardened.

Figure 2 Injection Sites Scheme

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 in case of any acute drug reactions in line with clinical practice.

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. Self-administration of Investigational Product as Mitigation to Disruption

At Visits 3 and 4, appropriate patients and/or their caregiver may be trained in self-administration of investigational product administration by the investigator or designee. If not

possible at Visits 3 and 4, this may occur at later visits. This training will be provided so that patients are prepared in case remote visits may be required secondary to study disruptions as described in Section 4.1.1. Patients may still participate in the study if they do not consent/assent to this training.

6.2.3. Optional At-home or Remote Location Self-administration

To reduce patient burden and to allow flexibility during the OLE, patients will have the option for at-home or remote location self-administration of IP, or at-home or remote location administration of IP by the patient's caregiver using the APFS. The investigator will first assess the patient and/or his/her caregiver to ensure they are appropriate for self-administration of IP, or caregiver administration of IP, and have received appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided.

If the IP is administered at the patient's home/remotely, the patient should administer the IP the same day as the Visit, after the visit assessments. It is strongly encouraged that the patient is contacted by the Investigator or qualified designee after the dose is administered in line with clinical practice. If the patient reports an injection site reaction or other AEs, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

Refer to the Study Instructions for At-home or Remote Location Administration of Benralizumab by the Patient and/or His/Her Caregiver for step-by-step guidance including Investigator assessment/training of patient and/or caregiver, drug accountability, and reconciliation requirements. The option of at-home or remote-location administration of IP will only be available in countries where allowed according to local regulations.

6.2.4. Optional Remote Visits for Patients Doing At-Home or Remote-Location

Investigational Product Administration

During the OLE, some visits (as specified in the SoA in Section 1.1) can optionally be done as remote visits by telephone contact for patients who are doing at-home/remote-location IP administration.

For these patients, IP kits and (for WOCBP) urine dipsticks for pregnancy testing for the optional remote visits will be dispensed at the prior, mandatory on-site visit during OLE. WOCBP should be asked if they are pregnant during the telephone visit.

6.2.5. 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 (IWRS; refer to IWRS manual for further details).

6.2.6. 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: randomisation and blinding

6.3.1. Methods for assigning treatment groups

Patients will be stratified by region and baseline CCI Randomisation will be monitored to ensure that no more than CCI of the study population will have CCI When the target percentage of patients in a subgroup is reached, consideration will be given to closing the IWRS randomisation for that subgroup. Once a subgroup is closed, patients in the screening/run-in period in the closed subgroup will not be allowed to be randomised and will be screen failed. A patient who does not qualify for the open subgroup cannot be rescreened.

All patients will be centrally assigned to randomised study treatment using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. The IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit. Routines for this will be described in the IWRS user manual that will be provided to each centre. Randomisation codes will be assigned PPD in each stratum as patients become eligible for randomisation.

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

6.3.2. Methods for ensuring blinding

This study includes a 56-week double blind treatment period. AstraZeneca staff involved in the study, the patients, and the Investigators and site staff 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 and tissue eosinophil counts

While not entirely assured, patients on active benralizumab treatment are expected to have lower blood (or tissue) 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. From baseline (V3) until the second visit of the OLE (Week 60, V12), eosinophil, basophil and monocyte counts will be redacted from all 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, from baseline (V3) until the second visit of the OLE (Week 60, V12) 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 randomisation for each randomised patient, will be available to the Investigator(s) or Pharmacists/designee at the study site from the IWRS. Further detail on how to unblind a patient's treatment allocation will be described in the IWRS user manual provided to each study site.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. 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). Randomisation codes will not be broken for the planned analyses of data (i.e. the primary database lock) until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.3.4. Open-label Extension Period – Benralizumab Administration Only

Patients will keep the same E-code in the OLE as assigned in the double-blind period of the study. Open-label IP administration will begin at Week 56 (V11). The IWRS will continue to allocate IP kit number for each dosing visit of the OLE.

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.

If IP cannot be administered at a scheduled treatment visit, it can be postponed as necessary and administered as soon as possible (preferably within visit window). When IP dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for IP administration) are still performed within the visit window.

Re-scheduled IP dose can be then administered at an unscheduled visit. Physical exam and vital signs assessment are the minimum procedures to be performed at this visit. For WOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative. It may also include remaining visit procedures (not performed at the scheduled visit) and additional assessments as deemed necessary by the investigator.

If the visit procedures cannot be conducted within the window (e.g. the patient is unable to attend the study site), then the entire visit will be re-scheduled along with IP dosing.

If a dose is significantly delayed it is recommended to keep at least 2-4 weeks interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the postponed dose will be skipped, and the next dose of IP given at the regularly scheduled visit. The visit schedule will be always calculated from randomisation visit date.

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

The PI should make every effort to assure that no IP administrations are missed during the course of the study. If a patient misses more than 2 consecutive or non-consecutive doses of IP at any time within a calendar year, it is strongly recommended a conversation between the investigator and the AZ study physician to review the patient's adherence to treatment and decide on the patient's disposition. Before a decision to discontinue a patient from IP is instituted, the investigator should carefully consider whether continuation on IP or discontinuation of IP will be in the best interest of the patient, and whether the issue can be mitigated by postponing or skipping the dose. It is highly recommended that the AZ study physician be consulted before the IP discontinuation transaction takes place. In case of safety concerns IP administration may be immediately withheld until the final decision is made.

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

The site staff is responsible for managing the Investigational medicinal product (IMP) from receipt by the study site until the destruction or return of all unused IMP.

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. 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 Table 7 Restricted medications and Table 8 Prohibited medications , provided below:

Table 7 Restricted medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it's allowed):
LTRA (until V11 week 56)	LTRA is allowed if stable for minimum 30 days prior to V1 and maintained stable
Inactive/killed vaccinations (e.g. inactive influenza)	Not allowed within the 7 days before or within 7 days after any IP dosing study visit
Topical immunosuppressives (until V11 week 56)	Topical administration of Immunosuppressive medication may be allowed at the discretion of the Investigator
Allergen Immunotherapy	Allowed if on stable therapy started 30 days prior to V1; no change during the treatment period until the last study visit
Systemic corticosteroids (SCS) (until V11 week 56)	A short course of SCS (≤17 days), allowed at PI's discretion to relieve symptoms of nasal polyposis worsening or asthma exacerbations, but preferably not until 3-6 months after randomization. It is recommended not to use SCS for CRSwNP within the first 3-6 months after V3. Refer to Section 8.1.5 for details.
Decongestants (topical or systemic) (until V11 week 56)	Only allowed for endoscopic procedure

Table 8 Prohibited medications

Prohibited medication/class of drug:	
Intranasal medication including intranasal corticoids drops (until V11 week 56)	Only MFNS (400 mcg daily) or equivalent (highest local approved for CRSwNP) is allowed and should remain stable.
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 after last dose of the IP.
Aspirin desensitization (including OLE period)	Use of aspirin as a desensitization regimen for the management of aspirin exacerbated respiratory disease (AERD) is not allowed; all other uses of aspirin/NSAID is allowed for any other medical conditions.
Any marketed or investigational biologic (monoclonal or polyclonal antibody) (including OLE)	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 randomisation; and during the study period until the last study visit.
Live attenuated Vaccines	Not allowed within 30 days prior to randomisation; during the study period, and 12 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 until the last study visit.
Herbal remedies or traditional Chinese medicines that may impact nasal polyps or its symptoms as per investigators judgement (until V11 week 56) - for Asia only	Not allowed 30 days prior to V1 and during the treatment period.

6.5.1. Background medication

During the study, the background INCS will be MFNS. Patients not already using MFNS will be converted to MFNS at 400 mcg daily or equivalent (highest dose locally approved for CRSwNP) if MFNS is not available locally at visit 1. All patients are required to be stable on background INCS for a minimum of 4 weeks prior to V2, continued throughout the screening and study period until V11 (week 56).

MFNS (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 (50 mcg/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. Any change in background medication should be discussed with the AZ study physician, the justification should be documented in the source and the change in the doses should be reflected in the eCRF.

Each patient will receive enough background medication to cover the need until the next on site visit. INCS dispensation will be performed according to the SoA table (Table 1 and 2).

INCS compliance will be recorded by the patient on the ePRO device (using NPSD) and should be checked by Investigators during the study period until V11 (week 56). If a subject cannot tolerate MFNS during screening period, the subject should be screen failed.

Patients in Japan will follow the requirement regarding to INCS use as indicated in the country protocol.

The Principal Investigator should ask patients about SCS (oral, parenteral) use for CRSwNP at each visit and record in the eCRF. If deemed necessary and medically justified, a short course of SCS (≤17 days) is allowed for CRSwNP worsening during the study, at PI's discretion but adequately documented, according to local standard of care. If SCS is used for ≤17 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 5.5.1 Re-screening).

6.5.2. Other concomitant treatment

Medications other than that 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 Case Report Form.

6.6. Dose modification

N/A

6.7. Treatment after the end of the study

At the end of the study, the patient should be provided with 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

Subjects may be discontinued from investigational product (IP) in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- AE that, in the opinion of the Investigator, contraindicates future dosing.
- Severe non-compliance with the Clinical Study Protocol.
- Risk to patient as judged by the Investigator or AstraZeneca.
- Pregnancy for study female subjects.
- Development of any study specific criteria for discontinuation:
  - Anaphylactic reaction to the IP requiring administration of epinephrine;
  - Development of helminth parasitic infestations requiring hospitalisation;
  - A respiratory-related event requiring mechanical ventilation.

7.1.1. Procedures for 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 during DB period 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 continues until V11 week 56.

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 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 encouraged to keep the ePRO device and do assessments, participate in the telephone visits, and return the ePRO device at the end of the DB period (Week 56). If a patient is not willing

to complete ePRO procedures, device should be returned at the IPD visit and the telephone follow-up visit should be continued. A patient that agrees to a modified follow-up visit is not considered to have withdrawn consent or to have withdrawn from the study. The decision on the selected follow-up option needs to be documented in the patients' medical records.

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. No further follow up visit is required after the IPD visit.

If patient decides to discontinue IP during OLE, he/she needs to complete the IPD visit at 8 weeks after the last dose of IP, and no further follow-up visit is required.

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.

To prevent patients being lost to FU, it is recommended that the study sites maintain up-to date patients' contact details, including next of kin or other emergency contacts (if allowed by national regulations).

The Investigator should educate the patient on the importance of maintaining contact with the investigator study site throughout the study.

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.
- Repeated attempts must be made to regain contact with the patient or next of kin by e.g. repeat telephone calls, emails, certified letter. 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.

A patient will be classified as lost to FU only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study, despite all of the above listed efforts.

7.3. Withdrawal from the study

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

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options described in section 7.1.1.

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

If a 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 adverse events (AE). The Investigator will follow up subjects as medically indicated. The patient will return the ePRO device to the site staff.

See SoA, Table 2 and 3, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.4. Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised 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 randomised or initiated on treatment, and must be withdrawn from the study.

If a patient does not meet all the eligibility criteria but is randomised in error, the investigator should inform the AZ study physician immediately to discuss potential safety concerns and the best interests of the patient, and decide on further patient's disposition.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the eCRF. Medidata 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.

Safety concerns should be discussed with the sponsor 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.

8.1. Efficacy assessments

8.1.1. Clinical outcome assessments

Patients will complete all patient-reported outcome (PRO) assessments using a handheld ePRO device.

An 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 Polyps 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 usage.

The ePRO device will be programmed at Visit 1 with reminder alarms for the daily diary (NPSD). 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. 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 randomisation. Continued weekly monitoring of adherence throughout the study and follow-up with patients via phone and at the visits may be done, as needed, 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 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 Polyps Symptom Diary

The patient will complete a 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 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 or LTRA compliance (yes or no) will be administered after the symptom and symptom impact items.

A 2-week recall version of the diary (Nasal Polyps 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 medication compliance item; otherwise concepts measured are the same as the NPSD.

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 at Week 56 in the bi-weekly mean of NBS as 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 (randomisation visit). 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

One of the key secondary endpoints of the study is the change from baseline at Week 56 in the bi-weekly mean of DSS as 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 (SNOT) 22 item

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 Importance Difference (MID) of 8.90 has been established (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.

The SF-36 threshold is suitable for interpreting change at the individual level and is referred to as the responder threshold (Table 9) or responder definition (QualityMetric 2011).

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

Table 9 Threshold values for the SF-36v2 scale and summary measures

	SF-36v2 score									
Threshold	**PCS**	**MCS**	**PF**	**RP**	**BP**	**GH**	**VT**	**SF**	**RE**	**MH**
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

8.1.1.4. Patient Global Impression of Severity and Change

The PGI-S is a single item designed to capture the patient's perception of overall symptom severity at the time of completion using a 6-point categorical response scale (0–no symptoms; 1–very mild; 2–mild; 3–moderate; 4–severe; and 5–very severe). The PGI-C captures the patient's overall evaluation of response to treatment. The patients are asked to report the degree to which they have changed since entering the treatment period using a 7-point scale (1–much better; 2–moderately better; 3–a little better; 4–about the same; 5–a little worse; 6–moderately worse; and 7–much worse).

The PGI-S and PGI-C will be completed on the ePRO device per the SoA.

8.1.1.5. Asthma Control Questionnaire

The ACQ-6 was developed for self-administration by adults and adolescents by omitting the forced expiration volume in 1 second (FEV1) % predicted question (Juniper et al 1999). Patients are asked to record their experience with 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and use of short-acting β2 agonist (SABA) over the previous week using a 7-point scale (0 = no impairment; 6 = maximum impairment). The ACQ-6 score is calculated by taking the mean of the 6 equally weighted items. The ACQ-6 score range is 0 (well controlled) to 6 (extremely poorly controlled). Individual score change of at least 0.5 is meaningful and is used to support the responder definition (Juniper et al 2005, Juniper et al 2006). Mean ACQ scores ≤0.75 indicate well-controlled asthma, scores between 0.75 and 1.5 indicate partly controlled asthma, and a score ≥1.5 indicates poorly controlled asthma (Juniper et al 2006).

The ACQ-6 will be completed on the ePRO device per the SoA.

8.1.1.6. Asthma exacerbations

Asthma exacerbation is defined by a worsening of asthma requiring:

- Use of systemic corticosteroids for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids,

- An emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an Emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per above),

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

- Use of systemic corticosteroids (oral, parenteral), an emergency room/urgent care visit or a hospitalisation due to asthma should be recorded in the corresponding eCRF. A hospitalisation should also be reported as an SAE.

The start date of an exacerbation is defined as the start date of systemic corticosteroid administration or date of hospital admission due to asthma. The end date of an exacerbation is defined as the last day of systemic corticosteroids or date of hospital discharge. A subsequent exacerbation must be proceeded by at least 7 days in which neither criteria is fulfilled.

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 odour-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 odour 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 odours (score range 0 to 40).

UPSIT will be completed using paper booklets and the test results will be added to the appropriate eCRF.

UPSIT smell test will be performed in all countries which have validated version of the test.

8.1.2. Nasal Polyp Score

One of the co-primary endpoints of the study is the change from baseline at Week 56 in bilateral endoscopic total NPS. 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 10.

Table 10 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
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

Polyp score	Polyp size
4	Large polyps causing complete or near-complete obstruction of the inferior nasal cavity i.e. touching the floor of the nose

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 the imaging core lab. Centralized imaging data assessments and scoring by independent physician reviewers 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 how the nasal endoscopy should be performed as well as equipment requirements will be available in a separate Nasal Endoscopy Video Acquisition Guideline provided to the sites. The imaging core lab will follow an Independent Review Charter (IRC), which defines the logic and basis for the independent analysis methodology including the assessments to be recorded and corresponding assessment criteria to be used by the reviewers conducting the analysis.

8.1.3. Sinus Computed Tomography

CT scanning will be performed at V2 (week -2), and V11 (week 56), or at IPD if at least 16 weeks passed since the previous CT scan. In case of surgery during the double-blind part of the study, the CT scan should be done prior to surgery instead of at week 56 if at least 16 weeks passed since the previous CT scan. CT assessment at V2 will be used both for inclusion criterion 7 and as baseline, while V11 (or IPD) will be used to estimate efficacy as calculated as change from baseline.

The CT images will be used to derive Lund-Mackay Score (LMS) and Zinreich (modified Lund Mackay) score, based on the visual assessment by independent central readers (see Section 8.1.3.1 Lund-Mackay score and section 8.1.3.3 Zinreich 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 how sinus CT images should be obtained will be available in a separate Image Acquisition Guideline (IAG) provided to the sites. The imaging core lab will follow an

Independent Review Charter (IRC), which defines 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 11 below) is used to provide a semi-quantitative assessment of nasal sinuses on sinus CT scans (Lund et at 1993). Based on the sinus CT images, the five sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) and osteomeatal complex on each side are scored by central radiologist as follows:

Table 11 Lund-Mackay score

Sinuses	**Score**
Maxillary	0 No abnormality 1 Partial opacification 2 Total opacification
Anterior ethmoid	
Posterior ethmoid	
Sphenoid	
Frontal	
Osteomeatal complex	0 Not occluded 2 Occluded

The maximum total score of LMS and Osteomeatal complex score is 24.

8.1.3.2. Quantitative measurement of sinus disease burden on sinus computed tomography

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

This is defined as:
Sinus severity score = sinus mucosal volume / (sinus mucosal volume + sinus air volume) *100%.
The following parameters used to calculate the sinus severity score:

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

Image analysis will be performed centrally.

8.1.3.3. Zinreich (modified Lund Mackay) score

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

All five sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid and frontal) on each side will be scored based on the percentage of opacification from mucosal thickening according to Table 12.

Table 12 Zinreich score

Score	Percent opacification
0	0%
1	1%-25%
2	26%-50%
3	51%-75%
4	76%-99%
5	100%
Osteomeatal complex	0 Completely patent 1 Partially obstructed 2 Completely obstructed

The maximum total Zinreich score is 50 (54 when including the Osteomeatal complex score.

Scoring will be performed centrally by the imaging core lab.

8.1.4. Nasal polyp surgery

Patients who have a scheduled CRSwNP surgery at the time of the study enrolment and randomisation should not be randomised in the study (please refer to exclusion criterion 29). After randomisation, surgery should not be planned for the first 3 to 6 months unless emergent or deemed necessary by the PI. These cases should be discussed with the AZ study physician.

If the patient is scheduled for CRSwNP surgery, an unscheduled visit should be performed prior to the surgery to assess safety and efficacy (including total NPS, SNOT-22, CT [if at least 16 weeks since the previous CT scan], SF-36v2, PGI-S, PGI-C, ACQ-6 and UPSIT).

Nasal polyps 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 CRSwNP 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 CRSwNP surgery is discretionary and subject to assessment by the Investigator.

8.1.5. SCS use for CRSwNP

Patients who have a scheduled SCS use at the time of the study enrolment and randomisation should not be randomised in the study (please refer to exclusion criterion 22). After randomisation, patients are not recommended to use SCS for CRSwNP for the first 3 to 6 months unless emergent or deemed necessary by the PI. These cases should be discussed with the AZ study physician. Investigators need to record the medical justification for SCS use in source data. Safety and efficacy (including total NPS, SNOT-22, SF-36v2, PGI-S, PGI-C, ACQ-6 and UPSIT) assessment should be performed prior to the SCS use for CRSwNP.

8.2. Safety assessment

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

8.2.1. Clinical safety laboratory assessments

See Table 13 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA. Clinical chemistry assessments should be collected under fasting conditions (fasting starts at least 8 hours before sample collection).

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 centre 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.

Table 13 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-Leukocyte differential count and percentage	S/P-Calcium, total
	S/P-Creatinine
	S/P-Gamma-GT (gamma-glutamyl transpeptidaze)

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
	S/P-Glucose
	S/P-Potassium
	S/P-Sodium

[a] Eosinophils, basophils and monocytes counts and percentage after V3 will be redacted from central laboratory reports

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

8.2.1.1. 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 1 except for those who are NOT of child bearing potential as defined in inclusion criterion 23. This test is to be sent to and analysed at the central laboratory;

- FSH: To be performed at screening Visit 1 only, at the central laboratory, 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. Serum pregnancy test could be used to replace Urine HCG, per local site/lab practice.
  WOCBP who are doing optional remote visits with IP self-administration (after Visit 12) will be provided with urine pregnancy dipstick test and advised to perform the test prior to IP self-administration. If the urine pregnancy test result is positive, the patient should contact the site and should not administer IP.
  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, additional testing may be performed to check eligibility at the discretion of the Investigator. In case of a positive result for hepatitis C virus antibody, hepatitis C RNA PCR test will be performed by central lab.

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. CCI [redacted]

The levels of total CCI [redacted] and a qualitative assessment for the presence of allergen-specific CCI [redacted]) 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 examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 Adverse events based on examinations and tests, for details.

For the physical examination, only information on whether the assessment was performed or not is to be recorded.

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.

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 IP administration, and if possible, before blood draw.

- Body temperature, pulse rate, respiratory rate and blood pressure will be assessed
- Body temperature will be measured in Celcius 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 (e.g. 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 at V7 (week 24) and V11 (week 56). In all patients, the printouts of the ECG will be collected and signed, dated and stored at the study centre along with a signed and dated copy (if the printouts are not on archive-quality paper).

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 (e.g. endoscopy, blood draw). Patients with any ECG abnormalities should be evaluated by the Investigator or qualified delegate to determine if each abnormality is clinically significant. It is highly recommended that the same machine is used for assessment throughout the patient's participation in the study.

The overall evaluation of the ECG will be recorded into eCRF. For abnormal ECG, the reason and clinical significance should also be recorded.

A patient with a clinical significant abnormal finding on the ECG at V1, assessed by PI, should be screen failed.

8.2.5. Other safety assessments

8.2.5.1. Weight and height

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

The 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.

AE 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.

8.3.1. Method of detecting AEs and SAEs

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

8.3.2. Time period and frequency for collecting AE and SAE information

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

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study 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 the sponsor.

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

8.3.3. Follow-up of AEs and SAEs

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 are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any 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 Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(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 hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

8.3.5. Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

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

Note: CRSwNP surgery is not part of study procedure. The Investigator should assess the causal relationship based on the Investigational product and the adverse event. Refer to Section 8.3.8 on disease under study.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

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 CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7. Adverse events based on examinations and tests

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.8.

8.3.8. Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of CRSwNP 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 CRSwNP planned before or during the study are not considered SAEs. If the condition unexpectedly deteriorated after surgery, the reported SAE term should be the reason for hospitalisation and not the surgical procedure.

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 investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

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

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

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

Once the Investigators or other site personnel indicate an AE is serious in the 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 Clinical Study Protocol.

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 patient has received any study drug.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenitalanomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1. Maternal exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.2.2. Paternal exposure

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 12 weeks 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

No clinical data regarding overdose are available. Single doses of up to 200 mg were administered SC in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities. For management of IP-related reaction, see Section 8.4.4.

For this study, any dose of benralizumab greater than 200 mg will be considered an overdose.

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

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 should be available at the study site, and study personnel should be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix E.

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

1. The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, AND AT LEAST 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: 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 the appearance of any acute drug reactions in line with clinical practice.

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, Drug abuse and Drug Misuse

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.1) and **within 30 days** for all other events.

8.4.5.1. Medication Error

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

The full definition and examples of medication error can be found in Appendix B 8.

8.4.5.2. Drug Abuse

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

The full definition and examples of drug abuse can be found in Appendix B 8.

8.4.5.3. Drug Misuse

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

The full definition and examples of drug misuse can be found in Appendix B 8.

8.4.6. Reporting of Overdose

Refer to **Section 8.4.3** for definition and treatment of overdose.

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.3) and **within 30 days** for all other overdoses.

8.4.7. Device Constituent Deficiencies

In a combination drug-device IMP (e.g. APFS), the Device Constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer. Serious Adverse Device Effect (SADE) is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not

been taken, intervention had not occurred, or circumstances had been less fortunate.

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

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

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

8.4.7.1. SADE Reporting

NOTE: There are additional reporting obligations for device constituent deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to device constituents being used in clinical studies.

Any device constituent deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device constituent deficiency.

The sponsor will review all device constituent deficiencies and determine and document in writing whether they could have led to an SAE. These device constituent deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

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. Full details of the analytical method used will be described in a separate bioanalytical report. The following samples will be analysed:

- During DB period, all PK samples from patients assigned to the benralizumab treatment group
- During OLE period all PK samples

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 or local requirement 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, if applicable according to local regulation, 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

Blood samples for determination of ADA in serum will be collected pre-investigational product administration as detailed in Table 2 and Table 3 and assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

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

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

8.7. Pharmacodynamics

Not applicable.

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. Exploratory genetic samples will be collected in participating countries, except China Mainland.

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. Mandatory collection of samples for biomarker research is also part of this study. Biological samples will be collected for exploratory analyses to investigate the effect of benralizumab on biomarkers of inflammation, CRSwNP disease, pharmacology of benralizumab and for potential predictors of response.

Whole blood for transcriptomic profiling (RNA profiling), preparation of serum and plasma samples for analysis of proteins and inflammatory markers and nasal secretions for proteins and inflammatory markers will be collected according to the SoA. Blood samples and nasal secretions should be collected pre-dose at the pre-specified scheduled visit in the SoA.

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

The results of the CCI analyses will be reported in the CSR. The results of all the additional exploratory biomarkers (not collected in China Mainland) will be reported separately from the CSR in a scientific report or publication.

Additional exploratory biomarkers samples will be collected in participating countries, except China Mainland. CCI is the only exploratory biomarker to be collected in China Mainland.

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

AstraZeneca or a designee will retain biomarker samples for investigation of research CRSwNP disease, the pharmacology of benralizumab and potential predictors of response for a maximum of 15 years (or as per local regulation) 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 randomisation. 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 hospitalisations and lengths of stay;

- Emergency room visits;
- Urgent care visits.

All hospitalisations, 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.

Note: Unplanned hospitalisation for all other symptoms/diagnosis other than CRSwNP must also be reported as an SAE. Hospitalisation due to CRSwNP surgery should only be reported as SAE if the condition unexpectedly deteriorated after surgery. For CRSwNP related hospitalisation refer to Appendix B 4.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical hypotheses

The co-primary efficacy endpoints are the change from baseline in total NPS at Week 56 and the change from baseline in bi-weekly mean NBS at Week 56. The primary analysis is to compare the changes from baseline in total NPS and in NBS of benralizumab with placebo.

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 0.05 (two-sided) and the key secondary endpoints will be tested hierarchically at 0.05 (two-sided) level if the null hypothesis is rejected for both co-primary endpoints. The co-primary endpoints will be evaluated using a hybrid method of the worst-possible/worst-observation carried forward and multiple imputation, followed by an analysis of covariance with treatment arm, baseline scores of corresponding endpoint, region, and baseline CCI status CCI as covariates.

Data collected from OLE will be summarized descriptively. No statistical hypotheses will be evaluated for OLE data based on formal statistical tests.

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 56 and on the change from baseline in bi-weekly mean NBS at Week 56 using a hybrid method of the worst-possible/worst-observation carried forward and multiple imputation, followed by an analysis of covariance with treatment arm, baseline scores of corresponding endpoint, region, and baseline CCI status CCI) as covariates.

Approximately 250 patients will be randomised into SC benralizumab 30 mg or placebo in a 1:1 ratio.

The sample size was estimated based on a two-sided t-test at a significance level of 0.05. Assuming a population standard deviation of 2 in total NPS and 1 in NBS, this sample size will provide an overall 80% power to detect a true mean (population) treatment difference of 0.85 units in total NPS and a difference of 0.4 in NBS with a two-sided 0.05 alpha level.

Based on the assumptions above, the minimum observed mean difference that would be statistically significant at the 0.05 level is – 0.50 in total NPS and – 0.25 in NBS.

9.3. Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
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.
Full analysis set	All patients randomised and receiving any IP will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised 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.
Primary full analysis set	Primary full analysis set consists of all CRSwNP patients with asthma in the FAS.
Safety analysis set	The safety analysis set consists of all patients who have received at least one dose of investigational product. Erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received IP is classified as active.
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 measurable serum PK observation post first dose will be included in the PK analysis dataset.

OLE analysis set	The OLE analysis set will include all patients who enter the OLE part of the study and who receive at least 1 dose of IP during the OLE treatment period.

Unless otherwise stated, all efficacy analyses will be performed based on the primary full analysis set (PFAS). For consistency, demographic and baseline characteristics will be presented using the PFAS. Safety objectives and the immunogenicity will be analysed based on the safety analysis set. Pharmacokinetic analyses will be conducted based on the PK analysis set.

9.4. Statistical analyses

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

The efficacy analyses will be based on PFAS unless otherwise stated. Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be finalised before primary database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Analyses for the OLE are described in Section 9.6. Any deviations from this plan will be reported in the CSR.

9.4.1. Efficacy analyses

All analyses described below apply to the primary full analysis set (PFAS), through to IPD/EoDB (Week 56) unless otherwise stated. The primary database lock will occur after all randomised patients have been followed up for the 56-week double-blind treatment period. The study will remain blinded until the primary database lock. The final database lock will occur after the last patient completes the OLE. All available data captured during the DB period and selected safety data from the OLE period will be reported at the primary DBL, while remaining data from the OLE period will be reported separately at the final DBL. Unblinding and data analysis will occur after the primary database lock.

The primary estimand for co-primary endpoints will quantify the difference in change from baseline between patients randomized to benralizumab and placebo at the planned timepoints, regardless of the treatments that patients actually received, where rescue by CRSwNP surgery and/or SCS_NP indicates failure. It includes all the data collected during the study including data collected after discontinuation of study treatment except data collected after CRSwNP surgery and/or SCS_NP. A composite strategy will be used for patients who undergo CRSwNP surgery or receive SCS for CRSwNP. Data collected post-SCS_NP will be set to missing, and the patient's worst observed post-baseline value on or before the time of SCS_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 surgery or SCS_NP, missing data will be imputed using multiple imputation using all patients who did not have surgery or receive SCS_NP. Details of the primary analysis as well as sensitivity analyses will be included in the SAP.

Estimands for key secondary endpoints are the same as described for co-primary endpoints, except for LMS where treatment policy strategy will be used for rescue SCS use. In order to limit the radiation exposure, there is only one post-baseline CT scan assessed at the End of Treatment (or IP discontinuation or prior to surgery). The composite strategy for rescue SCS with worst observation carried forward is considered to be less appropriate as for co-primary endpoints. Therefore, treatment policy strategy will be applied instead, and the analysis will use observed data collected after rescue SCS use. The composite strategy for CRSwNP surgery with the worst possible score imputation will apply to all key secondary endpoints including LMS.

9.4.1.1. Calculation or derivation of variables for efficacy analyses

The changes from baseline in total NPS and NBS at Week 56 are co-primary endpoints. The change from baseline in DSS, Lund Mackay score, and SNOT-22 at Week 56 are the key secondary endpoints.

Total nasal polyp score (Co-primary endpoint)

The change from baseline in total NPS at Week 56 is one of the co-primary 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)

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

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

The change from baseline in DSS score at Weeks 56 is one of 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 score (Key secondary endpoint)

The change from baseline in Lund Mackay score at Week 56 is one of key secondary endpoints. Lund Mackay score as described in Section 8.1.3.1 will be evaluated centrally. Only the data from blinded central reader will be used for analysis. The observed values and the changes from baseline at EoDB/IPD will be calculated.

Health-related-quality of life: SNOT-22 (Key secondary endpoint)

The change from baseline in SNOT-22 total score at Week 56 is one of the 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 CRSwNP surgery and/or SCS use for CRSwNP

The time to the first CRSwNP surgery by Week 56 will be evaluated for all patients in the PFAS. The time to first CRSwNP surgery is calculated as follows:

- Start date of first CRSwNP surgery - date of randomisation +1

For patients who do not experience any surgery, the time to first CRSwNP 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).

Time to first SCS use for CRSwNP and time to first CRSwNP surgery and/or SCS use for CRSwNP will be evaluated using the similar approach as time to first CRSwNP surgery.

SCS use for CRSwNP and proportion of CRSwNP surgery

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

In addition, the number of courses of SCS for CRSwNP, total SCS dose used and total duration of SCS use for CRSwNP, 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.

University of Pennsylvania Smell Identification Test

The UPSIT score, the change from baseline and the proportion of patients with different thresholds of smell impairment or normal smell abilities, will be calculated overall as well as by gender. The thresholds will be pre-specified in the SAP.

Sinus severity score and Zinreich (modified Lund Mackay) score

Sinus severity score and Zinreich (modified Lund Mackay) score, as described in Section 8.1.3.2 and Section 8.1.3.3, respectively, will be evaluated centrally. Only the data from blinded central reader will be used for analysis. The observed values and the changes from baseline at EoDB/IPD will be calculated.

Patient-reported general health status: SF-36v2

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 PFAS.

- 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.

Asthma exacerbations

The number of exacerbations and the annual exacerbation rate will be calculated in the PFAS. The number of exacerbations related to ER/urgent care/hospitalisation/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 the worst-possible/worst-observation carried forward and multiple imputation, followed by an analysis of covariance with treatment arm, baseline scores of corresponding endpoint, region, and baseline CCI status CCI) as covariates. The estimates of the treatment effects at Week 56 will be based on a contrast 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 CRSwNP surgery and/or SCS use for CRSwNP. A composite strategy will be used for CRSwNP surgery and SCS use for CRSwNP. If a patient had any CRSwNP surgery or course of SCS use for CRSwNP before Week 56, the data will be censored before the first CRSwNP surgery and/or the time of having the first course of SCS use for CRSwNP, and the patient's worst-possible/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. 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 DSS score, SNOT-22 total score, Lund Mackay scores, sinus severity score, Zinreich score, individual NPSD scores, TSS, UPSIT, SF-36v2 (PCS, MCS, and domains), will be analysed using a ANCOVA, which is similar to the model used for the co-primary endpoints.

Time to first CRSwNP surgery up to Week 56, time to first course of SCS use for CRSwNP up to Week 56, and the time to first CRSwNP surgery and/or first course of SCS use for CRSwNP up to Week 56 will be analysed using a Cox proportional hazard model with treatment, region, and baseline CCI status CCI) as covariates.

The proportions of responders at selected timepoints in total NPS and SNOT-22 total score will be analysed using logistic regression with treatment arm, baseline scores of corresponding endpoint, region, and baseline CCI status CCI) as covariates.

The proportion of patients who had CRSwNP surgery, the proportion of patients who had SCS for CRSwNP, and the proportion of patients who had CRSwNP surgery and/or SCS for CRSwNPup to Week 56 will be analysed using a Cochran–Mantel–Haenszel test controlling for region, and baseline CCI status CCI).

Analyses of pharmacokinetic variables

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

Analyses 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.

9.4.1.3. Subgroup analysis

To explore the uniformity of the detected overall treatment effect on efficacy endpoints, subgroup analyses will be performed for the co-primary endpoints and key secondary endpoints. The subgroups will include, but may not be limited to the following: sex (male vs female), age (18-65 vs ≥65 years), region, and baseline CCI prior CRSwNP surgery history (yes vs no), number of prior CRSwNP surgeries (0, 1, 2 or more), prior SCS use (yes vs no), baseline AERD status (yes vs no), atopic status by CCI (positive vs negative), quartiles of baseline CCI quartiles of baseline eosinophil (EOS) counts. Additional subgroup analyses using different cumulative eosinophil thresholds may be considered. Further details will be provided in the SAP. These analyses are to be considered as exploratory and will be performed on the PFAS.

9.4.2. Safety analyses

Safety analyses will be performed on the Safety Analysis Set. Treatment-emergent AEs/SAEs will be summarized over the study. 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.

9.4.2.1. Calculation or derivation of Safety Variables

The following safety data will be collected: vital signs, ECG, 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

Safety data will be presented using descriptive statistics unless otherwise specified. In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP. Details will be described in the SAP.

Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AZ/designee. AEs will be presented for each treatment group by SOC and/or PT covering number and percentage of patients reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. Separate AE tables will be provided taken into consideration

relationship as assessed by the investigator, intensity, seriousness, death and events leading to discontinuation of IP. An additional table will present number and percentage of patients with most common AEs (frequency of ≥3%). Key patient information will be presented for patients with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. An AE listing for the safety analysis set will cover details for each individual AE. Full details of AE analyses will be provided in the SAP.

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of IP
- Worsening of pre-existing events on or after first dose of IP

Vital signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, Min, median, and Max. For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline. Details of vital sign analyses will be provided in the SAP.

Clinical Laboratory Measurements

Laboratory data will be summarized per treatment group by presenting shift tables using normal ranges (baseline to most extreme post-baseline value) and by presenting summary statistics of observed and change from baseline values. Details of laboratory data analyses will be provided in the SAP.

ECG

Summary statistics for the overall evaluation of ECG will be tabulated per treatment group. Details of ECG analyses will be provided in the SAP.

9.4.3. Other analyses

9.4.3.1. Effect of benralizumab on asthma control

The changes from baseline in mean ACQ-6 will be analysed using a similar ANCOVA model for the co-primary endpoints. The ACQ-6 responder at Week 56 will be analysed using a similar logistic regression model for other efficacy endpoints.

The annual exacerbation rate will be analysed using a negative binomial model. The logarithm of the patient's follow-up time will be used as an offset variable in the model to adjust for patients having different exposure times during which the exacerbations occur.

9.4.3.2. Patient recognition for improvement

Descriptive statistics will be provided for PGIS and PGIC responses over time. The proportion of PGIC responders will also be presented over time.

9.4.3.3. Analyses of biomarkers

Biomarkers will be summarized using standard summary statistics. Limited exploratory biomarkers may be reported in the CSR. This analysis 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. The results of the EAP will be reported outside the CSR.

9.4.3.4. Healthcare resource utilization

Unplanned healthcare resource use of hospitalisations, emergency room, and urgent care visits will be summarized using descriptive statistics. Details will be provided in the SAP.

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 56 and change from baseline in NBS at Week 56) and the 3 key secondary endpoints (the change from baseline in DSS, LMS, and SNOT-22 at Week 56), 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 and key secondary endpoints will be tested at 0.05 (two-sided) level. A testing strategy below will be as followed.

- Step 1: Perform the 2 tests of co-primary endpoints at a significant level of 0.05. If both p-values are less than 0.05, then proceed to Step 2. Otherwise no null hypothesis is rejected.
- Step 2: Test the 3 key secondary endpoints using a step-down approach following the hierarchical order DSS, LMS, and SNOT-22 at the significant level of 0.05.

9.5. Interim analyses

No interim analysis is planned for this study.

9.6. Analyses of Data from the Open-Label Extension

Descriptive statistics will be presented for endpoints evaluated during the OLE. Selected safety data from the OLE period will be reported in the CSR at primary DBL and additional data from the OLE period will be reported separately at final DBL.

9.7. Data monitoring committee (DMC)

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

9.8. 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 (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, 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.

The investigator will be responsible for the following:

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

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

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal

obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

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

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it. In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

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

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

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 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 or his/her legally authorised representative and answer all questions regarding the study.

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

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

If a patient's partner becomes pregnant during the study for 12 weeks following the last dose of IP, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Subjects" and provide information about the pregnancy accordingly.

Patients who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorised designee will explain to each patient the objectives of the 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 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 analysed 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 the sponsor. Any patient records or data sets transferred to the sponsor 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 the sponsor 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 the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

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

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

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

A 7 Data quality assurance

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

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

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of 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 25 years after study archiving or as required by local regulations. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in in the Source Data Agreement and/or the Clinical Study Agreement (CSA).

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 patients 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 patient 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 patients' 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 the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

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

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a 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 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 hospitalisation or prolongation of existing hospitalisation .
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the 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 fulfil the attributes for being assessed as Serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as Non-Serious;

examples 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 (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations due to CRSwNP planned before or during the study are not considered AEs or SAEs. If the condition unexpectedly deteriorated after surgery, the reported SAE term should be the reason for hospitalisation and not the surgical procedure

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the 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 hospitalisation
- 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, Drug Abuse, and Drug Misuse

- **Medication Error**

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

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

Medication error includes situations where an error.

- occurred
- **was identified and** participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

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

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

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

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) 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.

- **Drug Abuse**

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

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

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

- **Drug Misuse**

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

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

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person

- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

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

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

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

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

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

C 2 Withdrawal of Informed Consent for donated biological samples

If a 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 analysed, AstraZeneca is not obliged to destroy the results of this research.

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 (IATA) 6.2 Guidance Document

16.1 LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a 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 (except patients from China Mainland and China Taiwan) 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 randomisation. 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 or other period as per local requirements, 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/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix 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 the consent form for the main study and the genetic component of the study. Copy of the consent form 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 Anaphylaxis: signs and symptoms, management

E 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 E 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in E 3. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat anaphylactic reactions should 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.

E 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.

E 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

E 4 MANAGEMENT OF ACUTE ANAPHYLAXIS

E 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.

E 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

E 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.

E 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 F Changes related to mitigation of Study Disruptions Due to Cases of Civil Crisis Natural Disaster or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (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 or similar pandemic infection) 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 and instructions on how to perform these procedures will be provided at the time of implementation .

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

F 1 Reconsent of Study Patients During Study Interruptions

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. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 2 Rescreening of Patients To Reconfirm Study Eligibility

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

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 1.1 Table 1, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4.1. The procedures detailed in Sections 5.1 and 5.2 must be undertaken to confirm eligibility using

the same randomisation number for the patient. Patients re-screened for the third time will be assigned a new randomisation number. Refer to Section 5.4.1 for details.

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

A qualified HCP from the study site or TPV service may visit the patients' home / or other remote location as per local Standard Operating Procedure (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).
Refer to the guidance document for the study procedures that can be performed during home or remote visit.

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

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, add other information including efficacy data where relevant to be collected according to study requirements to be reported and documented.

F 5 At-home or Remote Location IP Administration Instructions

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

F 5.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

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

F 5.2 At-home or Remote Location IP Administration by the Patient or His/Her Caregiver

Prior to at-home or remote location IP administration the investigator must assess the patient or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the patient or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

F 6 Data Capture During Telemedicine or Home / Remote Visits

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

F 7 ePRO Remote Visit Confirmation via StudyWorks Portal

Site personnel may remotely confirm study visits on the patient's handheld device via the StudyWorks Portal if the patient cannot perform an on-site visit.

Appendix G 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
APFS	Accessorized prefilled syringe
AST	Aspartate aminotransferase
BP	Blood pressure
CBC	Complete blood count
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSA	Clinical study agreement
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTT	Clinical Trial Transparency
CTIS	Clinical Trial Information System
DB	Double blind
DES	Data Entry Site
DMC	Data monitoring committee
DUS	Disease-under study
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
CCI [redacted]	
EoDB	End of double-blind
EMA	European Medicines Agency

Abbreviation or special term	Explanation
ePRO	Electronic patient-reported outcome
EU	European Union
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
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
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Conference on Harmonisation
CCI	
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
JESREC	Japan Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis
LMS	Lund-Mackay score

Abbreviation or special term	Explanation
LPLV	Last patient last visit
LTRA	Leukotriene receptor antagonists
mAb	Monoclonal antibody
MCID	Minimal clinical importance difference
MCS	Mental component score
MH	Mental health
NERD	NSAID exacerbated respiratory disease
NB	Nasal blockage
NBS	Nasal blockage score
NSAID	Nonsteroidal anti-inflammatory drug
NP	Nasal polyp
NPS	Nasal polyp score
PCS	Physical component score
PF	Physical functioning
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient-reported outcome
RAs	Regulatory Authorities
RBC	Red blood cell
RE	Role limitations due to emotional problems
RP	Role limitations due to physical health
SADE	Serious Adverse Device Effect
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

Abbreviation or special term	Explanation
ULN	Upper limit of normal
UNS	Unscheduled
UPSIT	University of Pennsylvania Smell Identification Test
WOCBP	Women of childbearing potential

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