Clinical Study Protocol	
Drug Substance	Benralizumab (Medi-563)
Study Code	D3254C00001
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EudraCT/EU CT Number	2019-002039-27

A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 24-Week Phase III Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients with Hypereosinophilic Syndrome (HES)

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EudraCT Number: 2019-002039-27

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 Standard - Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 8 – CSP Version 9	26 Sep 2024
Amendment 7 - CSP Version 8	12 Jun 2023
Amendment 6 - CSP Version 7	29 Jun 2022
Amendment 5 - CSP Version 6	16 Feb 2021
Amendment 4 - CSP Version 5	06 Aug 2020
Amendment 3 - CSP Version 4	27 Sep 2019
Amendment 2 - CSP Version 3	26 Aug 2019
Amendment 1 - CSP Version 2	13 Aug 2019
Original Protocol V 1.0	17 Jul 2019

CSP version 9 (26 Sep 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment

The primary reason for this amendment is to modify the timing of the primary analysis, which will be implemented once all randomised patients have completed the 24-week DB period, rather than when the flare target is achieved. This change is being made to ensure complete DB period follow-up is available for all patients at the time of the primary analysis, in line with Health Authority feedback.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
All applicable sections	Timing of the primary analysis to be implemented once all randomised patients have completed the 24-week DB period, rather than when the flare target is achieved	Change made to ensure complete DB period follow up is available for all patients at the time of the primary analysis, in line with Health Authority feedback
1.1 Synopsis (Overall Design synopsis, Statistical Methods) 1.3 Schedule of Activities 4.1 Overall Design 9.2 Sample Size Determination 9.4.2 Efficacy Analyses	Change to state that the primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period	As above

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.2 Schema	Footnote updated to reflect the change to the timing of the primary DBL	As above
4.1 Overall Design	Text on blinding after the primary DBL during the DB period removed	No longer applicable given the change in timing of the primary analysis
9.4.1 General Considerations	Removal of text relating to the binary endpoints being analysed in a subset of patients who have completed the 24-week DB period	All patients will now complete the 24-DB period before the primary analysis
9.4.5 Methods for Multiplicity Control	Removal of text stating that the updated analysis of the DB treatment period will not be multiplicity protected	An updated analysis of the DB treatment period will now no longer be required

DB = double blind; DBL = database lock; HES = hypereosinophilic syndrome.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis	New text added in italics: The primary analysis of efficacy endpoints will include all data captured during the DB treatment period ***for patients included in the full analysis set regardless of occurrence of intercurrent events such as treatment discontinuation or changes in background medications*** (intention-to-treat approach, ***treatment policy strategy***)	Clarification of the efficacy analysis set to be used. Previous wording could be misinterpreted
1.1 Synopsis	Study design figure updated to reflect the fact that approximately 60 patients are to be recruited per arm, instead of exactly 60 patients	To correct an error
1.1 Synopsis (number of patients, statistical methods) 4.1 Overall Design 9.2 Sample Size Determination	Change to state that recruitment may continue beyond 120 patients to achieve the target number of events	Modification of existing wording for clarity
1.1 Synopsis (number of patients) 4.1 Overall Design	Changed to say that approximately 4 to 6 adolescent patients are targeted to be randomised, rather than expected to be randomised	Change made based on observed recruitment rates in this age group
1.3 Schedule of Activities Table 1, Table 2, Table 3, and Table 4	Added (T and I) to the row for troponin central laboratory assessments	To clarify that both should be assessed
1.3 Schedule of Activities Tables 1 and 2	Added (2 samples) to the row for haematology, WBC w/ differential central laboratory assessments	To clarify that 2 samples should be taken
1.3 Schedule of Activities Table 2, Table 3, and Table 4	'Where permitted' added to footnote b (footnote c in Table 4) Cross-reference to this footnote added to brief physical examination and vital signs rows Cross-reference to this footnote also added to 'administer open-label benralizumab' rows	Not all countries permit self-administration To clarify that these can be skipped when visits are performed remotely To clarify that this can be performed remotely
1.3 Schedule of Activities Table 3	Footnote h removed	To correct an error introduced in CSP v8
1.3 Schedule of Activities Table 4	Footnote i removed	To correct an error introduced in CSP v8

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities Table 4	X added to show that Visit 48 can be done remotely X removed from the brief HES physical examination row	To correct errors
1.3 Schedule of Activities Table 4	Updates to Year 3 visit numbers/weeks in footnote a	To correct an error
6.1 Study Intervention(s) Administered, Table 7	Removal of the formulation details of the IPs	Removal of commercially confidential information
8.4.7 Reporting of SAEs	Addition of statement regarding the reporting of SUSARs in the EU	Update required to comply with regulatory requirement (eg, EU-CTR) and global company requirement
9.4.2.1 Calculation or Derivation of Variable for Efficacy Analyses	For the key secondary endpoint of proportion of patients with a HES worsening/flare, the analysis has been updated such that patients who withdraw from the study without having had a flare will be considered as if they had a flare event	Patients who withdraw from the study without having had a flare will not count as flare-free, ensuring that missing data are handled in a conservative manner, in line with Health Authority feedback
Appendix A 1 Regulatory and Ethical Considerations	Addition of EU-CTR regulation details 536/2014	Update required to comply with regulatory requirement (eg, EU-CTR) and global company requirement
Appendix K Protocol Amendment History	Summary of CSP v8.0 modifications (Amendment 7) was moved to Appendix K	Updated in align with current AstraZeneca CSP template requirements/guidelines

CSP = clinical study protocol; EU = European Union; EU-CTR = European Union-Clinical Trial Regulation; HES = hypereosinophilic syndrome; IP = investigational product; SUSAR = Suspected Unexpected Serious Adverse Reaction; WBC(s) = white blood cell(s).

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA(s)	Anti-drug antibody(ies)
ADE(s)	Adverse device effect(s)
ADCC	Antibody dependent cell-mediated cytotoxicity
AE(s)	Adverse event(s)
AEC(s)	Absolute eosinophil count(s)
ALT	Alanine aminotransferase
APFS	Accessorised prefilled syringe
AST	Aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
CAPA	Corrective and preventive actions
CFR	Code of Federal Regulations
CI(s)	Confidence interval(s)
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
EDC	Electronic data capture
EU CTIS	European Union Clinical Trial Information System
DB	Double-blind
DBL	Database lock
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
DUS	Disease under study
ECG(s)	Electrocardiogram(s)
eCRF	Electronic case report form
eCOA	Electronic clinical outcomes assessments
EOT	End of treatment
ER	Emergency room
EU CT	European Union clinical trial
EU-CTR	European Union-Clinical Trial Regulation
FcγR	Fc-gamma receptor
FEV_1	Forced expiratory volume in one second

Abbreviation or special term	Explanation
FIP1L1	FIP1-like-1
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HCP	Health care professional
HES	Hypereosinophilic syndrome
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IATA	International Airline Transportation Association
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IFN-α	Interferon-α
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5Rα	Alpha chain of the IL-5 receptor
IM	Intramuscular(ly)
IP(s)	Investigational product(s)
IPD	IP discontinuation
IRB(s)/IEC(s)	Institutional Review Board(s)/Independent Ethics Committee(s)
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MCS	Mental component summary
MMRM	Mixed-effect model repeat measurement
nAb(s)	Neutralising antibody(ies)
OCS	Oral corticosteroid(s)
OLE	Open-label extension
PBMC(s)	Peripheral blood mononuclear cell(s)
PCR	Polymerase chain reaction
PCS	Physical component summary
PD	Pharmacodynamic(s)

Abbreviation or special term	Explanation
PDGFRA or *PDGFRB*	Platelet-derived growth factor receptor alpha or beta
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PN	Predicted normal
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PROMIS®	Patient-reported Outcomes Measurement Information System
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RNA	Ribonucleic acid
SADE(s)	Serious adverse device effect(s)
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous(ly)
SF-36v2	36-Item Short Form Health Survey version 2
SoA	Schedule of activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TPV	Third-party vendor
ULN	Upper limit of normal
US	United States
USADE(s)	Unanticipated serious adverse device effect(s)
WBC(s)	White blood cell(s)
WOCBP	Woman/Women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

International Coordinating Investigator:

PPD

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Protocol Title:

A Multicentre, Randomised, Double-blind, Parallel-group, Placebo-controlled, 24-Week Phase III Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab in Patients with Hypereosinophilic Syndrome (HES)

Short Title:

NATRON

Rationale:

Hypereosinophilic syndrome (HES) is a group of rare diseases with persistent blood eosinophilia, defined as > 1500 cells/μL, and evidence of eosinophil-mediated end-organ damage or dysfunction. Other potential causes for the organ damage or dysfunction must be excluded in order for HES to be diagnosed. Although any organ system can be involved, HES commonly involves the skin, heart, lungs, gastrointestinal tract, or central nervous system.

Eosinophilic diseases are in large part driven by interleukin-5 (IL-5), a cytokine produced by type-2 T helper cells, innate lymphocyte type-2 cells, and mast cells and a key mediator in eosinophil activation. Benralizumab is a monoclonal antibody (mAb) that binds to the alpha chain of the IL-5 receptor (IL-5Rα). This receptor is expressed not only by mature eosinophils but also by eosinophil progenitor cells and basophils. Benralizumab is a humanised, recombinant immunoglobulin (Ig)G, subclass 1, κ isotype mAb. The antibody has been engineered to be afucosylated, or without a fucose sugar residue, which enhances the interaction of benralizumab with the Fc-gamma receptor (FcγR)IIIa, which is expressed on immune effector cells on natural killer cells and macrophages. This results in enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). Benralizumab targets eosinophils and other cells expressing IL-5Rα in the circulation and residing in tissues for ADCC, which results in depletion of eosinophils in the circulation, bone marrow, and tissues. Benralizumab also targets eosinophil precursors in the bone marrow for ADCC. Thus, the direct eosinophil-depleting ability of benralizumab is effective in eosinophilic asthma and in steroid-dependent asthma.

The central role of eosinophilia in the pathophysiology of HES suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of HES. Benralizumab was shown in a Phase II study to significantly reduce absolute eosinophil count (AEC) over 12 weeks of treatment (30 mg subcutaneously [SC] given every 4 weeks [Q4W]) compared with placebo in patients with symptomatic HES. Benralizumab was well tolerated in patients who remained on open-label treatment through Week 48. The purpose of this Phase III study is to build on the Phase II findings and confirm the use of benralizumab as an effective and well tolerated option for FIP1-like-1 (*FIP1L1*)-platelet-derived growth factor receptor alpha (*PDGFRA*) fusion tyrosine kinase translocation-negative HES.

Objectives and Endpoints

Objectives and Endpoints – DB Treatment Period

Objectives	Endpoints
Primary	
To evaluate the effect of benralizumab on the time to first HES worsening/flare	Time to first HES worsening/flare [a] • Population [b]: Full analysis set • Intercurrent event strategy [b]: Included in analysis regardless of treatment discontinuation (treatment policy) • Population-level summary: Hazard ratio
Secondary	
To evaluate the effect of benralizumab on the proportion of patients who experience an HES worsening/flare	Key: Proportion of patients who experience an HES worsening/flare during the DB period [a, c]
To evaluate the effect of benralizumab on the number of HES worsenings/flares	Key: Number of HES worsenings/flares (annualised rate/year) during the DB period [a, c]
To evaluate the effect of benralizumab on the time to first haematological relapse	Key: Time to first haematologic relapse (AEC ≥ 1000 cells/µL) during the DB period [c, d]
To evaluate the effect of benralizumab on patient-reported measure of fatigue	Key: Fatigue severity (PROMIS fatigue short form 7a) at Week 24 [c]
To evaluate the effect of benralizumab on the proportion of patients with haematologic relapse	Proportion of patients who have haematologic relapse during the DB period [d]
To evaluate the effect of benralizumab on the number of patients who maintain AEC < 500 cells/µL for 24 weeks	Proportion of patients who have AEC < 500 cells/µL for 24 weeks
To evaluate the effect of benralizumab on corticosteroid use	Proportion of patients who require an increase in corticosteroid dose from baseline at any point in the DB period
To evaluate the effect of benralizumab on health status/HRQoL measures	HRQoL (SF-36v2, PGIS, and PGIC)
To evaluate the PK and immunogenicity of benralizumab in patients with HES	Serum benralizumab concentrations

Objectives and Endpoints – DB Treatment Period

Objectives	Endpoints
	Anti-benralizumab antibodies and nAbs
Safety	
To evaluate the safety and tolerability of benralizumab in patients with HES	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory assessments. Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by the investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
Exploratory	
To evaluate the effect of benralizumab on healthcare resource utilisation due to HES	Number of HES-related hospitalisations; length of the hospital stay; intensive care unit days; number of HES-related ER visits; number of HES-related outpatient visits (by type); number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on HES-related hospitalisation	Proportion of HES worsening/flare resulting in hospitalisation
To evaluate the effect of benralizumab on patient-reported measure of HES symptom severity	HES symptom questionnaire
To characterise the patient-reported experience and treatment benefits of benralizumab through patient interviews	Patient qualitative interview to characterise patient-reported experience and treatment benefits (sub-study)
To evaluate the effect of benralizumab on CRP	CRP levels
To evaluate the effect of benralizumab on biomarkers related to the mechanism of action of benralizumab, eosinophilic inflammation, and HES disease pathogenesis, as well as HES clinical subtypes and baseline predictors of response to benralizumab	Exploratory biomarkers in: • Serum • Plasma • Urine • Whole blood (including mechanistic sub-study) • Tissue biopsies
To assess effect of lymphocyte phenotype on responsiveness to benralizumab	Whole blood lymphocyte phenotyping

[a] For HES worsening/flare, see Section 8.2.1.

[b] The population and intercurrent event strategy also apply to the secondary endpoints.

[c] Key secondary endpoint (multiplicity protected)

[d] Haematologic relapse post-baseline: AEC ≥ 1000 cells/μL; baseline is the randomisation AEC.

AE(s) = adverse event(s); AEC = absolute eosinophil count; CRP = C-reactive protein; DB = double blind; ER = emergency room; HES = hypereosinophilic syndrome; HRQoL = health-related quality of life; IP = investigational product; nAbs = neutralising antibodies; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); PROMIS = Patient-reported Outcomes Measurement Information System; SF-36v2 = 36-Item Short Form Health Survey version 2.

Objectives and Endpoints – OLE Treatment Period

Objectives	Endpoints
To evaluate the effect of benralizumab on the proportion of patients who experience an HES worsening/flare [a]	Proportion of patients who experience an HES worsening/flare [b]
To evaluate the effect of benralizumab on the number of HES worsenings/flares [a]	Annualised rate of HES worsening/flare [b]
To evaluate the effect of benralizumab on patient-reported measure of fatigue [c]	Fatigue (PROMIS fatigue short form 7a)
To evaluate the effect of benralizumab on HRQoL [c]	HRQoL (SF-36v2)
To evaluate the safety and tolerability of benralizumab in patients with HES [a]	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory assessments. Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To evaluate the PK and immunogenicity of benralizumab in patients with HES [a]	Serum benralizumab concentrations Anti-benralizumab antibodies and nAbs
To evaluate the effect of benralizumab on healthcare resource utilisation due to HES [c]	Number of HES-related hospitalisations; length of the hospital stay; intensive care unit days; number of HES-related ER visits; number of HES-related outpatient visits (by type); number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on patient-reported measure of HES symptom severity [c]	HES symptom questionnaire
To evaluate the effect of benralizumab on CRP [a]	CRP levels
To evaluate the effect of benralizumab on biomarkers related to the mechanism of action of benralizumab, eosinophilic inflammation, and HES disease pathogenesis [c]	Exploratory biomarkers in: • Serum • Plasma • Urine • Tissue biopsies

Objectives and Endpoints – OLE Treatment Period

Objectives	Endpoints
To better characterise the early onset of eosinophil depletion to support extrapolation to build a relationship between adults, adolescents, and younger patients	PK: Benralizumab concentrations PD: Eosinophil counts

[a] Applicable to full duration of OLE

[b] For HES worsening/flare, see Section 8.2.1.

[c] Applicable to 1st year of OLE only

AE(s) = adverse event(s); CRP = C-reactive protein; ER = emergency room; HES = hypereosinophilic syndrome; HRQoL = health-related quality of life; IP = investigational product; nAbs = neutralising antibodies; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; PROMIS = Patient-reported Outcomes Measurement Information System; SF-36v2 = 36-Item Short Form Health Survey version 2.

Overall Design Synopsis

This is a multicentre, randomised, double-blind (DB), parallel-group, placebo-controlled, 24-week Phase III study to compare the efficacy and safety of benralizumab 30 mg versus placebo administered by SC injection Q4W in patients with HES.

This study comprises 2 distinct periods (together defined as the 'main study'): A 24-week DB treatment period, during which patients will be randomised to receive either benralizumab or placebo, in addition to their prior stable HES background therapy, and an open-label extension (OLE) period, during which all patients will receive benralizumab.

The primary database lock (DBL) will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period.

A patient must complete the 24-week DB treatment period on investigational product (IP) to be eligible to enter the OLE treatment period. The final DBL will occur after the last patient completes the OLE.

The target patient population is male and female patients 12 years of age and older with symptomatic active HES (AEC ≥ 1000 cells/μL at Visit 1). Eligible patients must be negative for the *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation.

Potentially eligible patients with documented stable HES therapy for at least 4 weeks prior to Visit 1 will enter a 3-day screening period and will be required to have AEC ≥ 1000 cells/μL at local laboratory testing to proceed to the second day of the screening period. Patients will be assessed for corticosteroid responsiveness (defined as an AEC < 1000 cells/μL after 2 days of oral corticosteroids [OCS] [prednisone/prednisolone] 1 mg/kg/day given on top of the patient's background therapy for HES) prior to randomisation; other OCSs in equivalent doses

are permitted (Appendix I). Patients who are not corticosteroid responsive or fail any other eligibility criteria will be screen failed.

Brief Summary

The purpose of this study is to compare the efficacy and safety of benralizumab versus placebo in patients with HES. This study comprises 2 distinct periods (together defined as the 'main study'): a DB treatment period, during which patients will receive either benralizumab or placebo in addition to their prior stable HES background therapy, and an OLE treatment period, during which all patients will receive benralizumab in addition to their prior stable HES background therapy.

Study details include:

- Patients will receive either benralizumab or matching placebo for a 24-week DB treatment period. The OLE period is intended to allow each adult patient at least 1 year and each adolescent patient at least 2 years of treatment with open-label benralizumab.
- The final dose of IP during the DB treatment period will be given at Week 20, and the DB period will complete at Week 24. Following completion of the DB period on treatment, adult patients may have the opportunity to receive benralizumab during the OLE period for at least 1 year, while adolescent patients may have the opportunity to receive benralizumab for at least 2 years. The first dose of open-label benralizumab will be administered on Week 24 after all visit assessments are completed.
- The visit frequency will be Q4W.

Disclosure Statement

This is a randomised, DB, parallel-group, interventional study with 2 treatment arms (benralizumab versus placebo) that are blinded to patients, site-staff, and investigators.

Number of Patients

It is expected that approximately 120 eligible patients will be randomised at a 1:1 ratio to receive either benralizumab 30 mg or matching placebo, but recruitment may continue beyond 120 patients to achieve the target number of HES worsening/flares. Approximately 4 to 6 adolescent patients (aged 12 to 17) are targeted to be randomised.

Study Arms, Treatments, and Treatment Duration

Patients who meet the eligibility criteria at Visits 1, 2, and 3 will be randomised to a 24-week DB treatment period with IP (either benralizumab or placebo) Q4W by SC injection.

Patients will be encouraged to stay on stable dose(s) and regimen of background therapy during the screening period and throughout 36 weeks of treatment (up to Visit 12/Week 36 when therapy can be adjusted). Modifications in background therapy are allowed anytime if

required for a HES clinical worsening/flare or an adverse event (AE) thought to be due to background therapy.

All patients who complete the DB treatment period on IP may be eligible to continue into an OLE treatment period. The OLE is intended to allow each adult patient at least 1 year and each adolescent patient at least 2 years of treatment with open-label benralizumab 30 mg administered SC Q4W (earlier enrolled patients may therefore be in the OLE for longer than 1 year).

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be tasked with monitoring safe conduct of the study and overall patient safety. The DSMB will periodically review unblinded safety summary tables and listings. The committee will operate in accordance with the DSMB Charter.

Statistical Methods

The primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period. Treatment allocation will remain blinded until the primary DBL. The final DBL 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 for patients included in the full analysis set, regardless of occurrence of intercurrent events such as treatment discontinuation or changes in background medications (intention-to-treat approach, treatment policy strategy).

DB Period

The primary analysis population will be the full analysis set consisting of all patients who are randomised and receive at least one dose of IP. The treatment groups will be compared on the basis of randomised treatment, regardless of the treatment actually received.

The primary endpoint is time to first HES worsening/flare. The primary analysis is to compare the time to first HES worsening/flare in patients on benralizumab versus placebo. The null hypothesis is that the time to first HES worsening/flare is not different between benralizumab and placebo. The alternative hypothesis is that time to first HES worsening/flare is different between benralizumab and placebo. The primary endpoint will be tested at CCI level using a stratified log-rank test adjusting for region and HES flare status at screening. A similar stratified log-rank test will be used to compare the time to first haematologic relapse between the benralizumab group and placebo group.

To account for multiple testing for the primary endpoint (time to first HES worsening/flare during the DB period) and the key secondary endpoints (proportion of patients who

experience an HES worsening/flare during the DB period, number of HES worsenings/flares during the DB period, time to first haematologic relapse during the DB period, change from baseline in PROMIS fatigue score at Week 24), a hierarchical fixed-sequence testing strategy (testing endpoints in the order outlined above at the primary analysis) will be used to control the overall type I error rate at the CCI level.

Approximately 38 first HES worsening/flare events during the DB period are required to detect a statistically significant difference between treatment groups at the CCI CCI significance level with approximately CCI power if the true treatment effect is a hazard ratio of CCI (equivalent to CCI of patients on benralizumab experiencing an event by the end of the DB period compared to CCI of patients on placebo). It is expected that approximately 120 patients will need to be randomised to observe approximately 38 flare events, but recruitment may continue if needed to achieve the target number of events.

All safety parameters will be analysed descriptively. Safety analyses will be based on the safety analysis set.

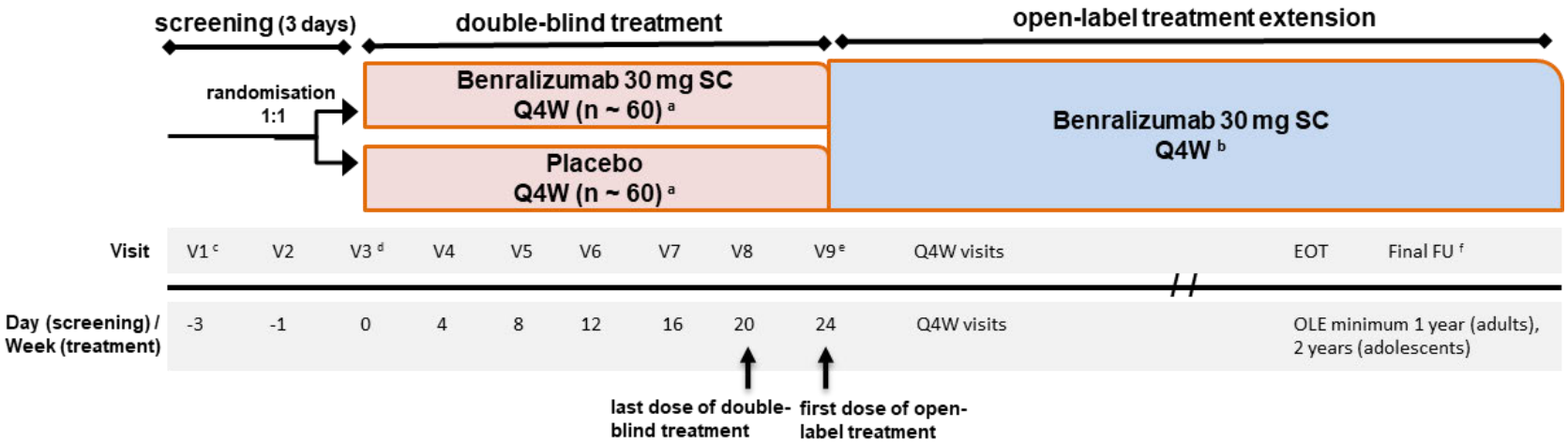
OLE Period

A further assessment of safety, tolerability, efficacy, pharmacokinetics, and immunogenicity during the OLE period will be presented in an addendum to the primary analysis clinical study report (CSR) and/or a separate OLE treatment period CSR.

1.2 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



[a] All patients remain on stable background HES medications during screening and throughout the DB treatment; background medications may be modified if a patient has an HES worsening/flare or an AE thought to be due to background therapy.

[b] Three months after entering the OLE (Week 36), background HES medication can be adjusted.

[c] Screening AEC will be assessed at Visit 1 in local laboratory; results must be available the same day. Potentially eligible patients (AEC ≥ 1000 µL) will receive 2 days of OCS to assess corticosteroid responsiveness (additional test for AECs at Visit 2).

[d] Visit 2 and Visit 3 (randomisation visit) can be performed the same day, if feasible, given that local laboratory results for corticosteroid responsiveness are obtained and all eligibility criteria confirmed prior to randomisation.

[e] Primary DBL. The primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period.

[f] The final DBL will occur after the last patient completes the OLE.

AE =adverse event; AEC(s) = absolute eosinophil count(s); DB = double-blind; DBL = database lock; EOT = end of treatment; FU = follow-up; HES = hypereosinophilic syndrome; n = number of patients in the treatment group; OCS = oral corticosteroids; OLE = open-label extension; Q4W = every 4 weeks; SC = subcutaneous(ly); V = visit.

1.3 Schedule of Activities

This study comprises 2 distinct periods (together defined as the 'main study'): A 24-week DB treatment period, during which patients will be randomised to receive either benralizumab or placebo in addition to prior stable HES background therapy, and an OLE treatment period, during which all patients will receive benralizumab. The primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period.

The SoA for the DB treatment period and for the first year of the OLE treatment period are provided in Table 1 and Table 2, respectively.

Patients may have the opportunity to participate in the OLE treatment period for at least 1 year for adults and at least 2 years for adolescents following completion of the DB treatment period on IP (Section 4.1). The SoA for the period after the end of Year 1 of the OLE reflects the variable duration of each patient's participation and is described in Table 3 and Table 4.

Table 1 Schedule of Activities for the DB Treatment Period

Study Procedures	Screening Period			DB Treatment Period									Details in CSP Sections or Appendix
Visit [a]	V1		V2 [b]	V3 (rand. visit) [b]	V4	V5	V6	V7	V8	V9 [c]	Flare visit [d]	IPD visit [e]	
Study Week (calculated from V3) Visit windows: ± 7 days for V4 – V9	Day -3 (Screening Day 1)	Day -2 (Screening Day 2)	Day -1 (Screening Day 3)	0	4	8	12	16	20	24			
General Procedures													
Informed consent/assent (main study) [f]	X												5.1
Optional genomics initiative informed consent	X												5.1
Inclusion/exclusion criteria	X		X	X [g]									5.1 and 5.2
Demography/medical and surgical history	X												5.1 and 5.2
History of HES [h] and treatment	X												5.1 and 5.2
Prior/concomitant medication	X		X	X	X	X	X	X	X	X	X	X	6.5
HES and PRO [i] Assessments													
HES worsening/flare evaluation	X			X	X	X	X	X	X	X	X	X	8.2.1
Complete HES physical examination	X									X			8.2.1.1 and Appendix H
Brief physical examination				X	X	X	X	X	X		X [j]	X	8.2.1.1 and Appendix H
Investigator-led HES symptom interview	X			X	X	X	X	X	X	X	X	X	8.2.1.2 and Appendix G
PROMIS fatigue short form 7a	X			X	X	X	X	X	X	X		X	8.2.3.1
SF-36v2	X			X			X			X		X	8.2.3.2
PGIS	X			X	X	X	X	X	X	X		X	8.2.3.3
PGIC					X	X	X	X	X	X		X	8.2.3.4
HES symptom questionnaire	X			X	X	X	X	X	X	X	X	X	8.2.3.5

Table 1 Schedule of Activities for the DB Treatment Period

Study Procedures	Screening Period			DB Treatment Period									Details in CSP Sections or Appendix
Visit [a]	V1		V2 [b]	V3 (rand. visit) [b]	V4	V5	V6	V7	V8	V9 [c]	Flare visit [d]	IPD visit [e]	
Study Week (calculated from V3) Visit windows: ± 7 days for V4 – V9	Day -3 (Screening Day 1)	Day -2 (Screening Day 2)	Day -1 (Screening Day 3)	0	4	8	12	16	20	24			
Vital Signs, AEs, and Instrumental Assessments													
Vital signs	X			X	X	X	X	X	X	X	X	X	8.3.2
ECG				X									8.3.4
Echocardiogram	X [k]										X [d]		8.3.5
Spirometry (prebronchodilator FEV_1 and FVC) [l]	X [l]									X [l]	X [d,l]		8.10.2
Height	X												8.3.1.1
Weight	X									X			8.3.1.1
AEs/SAEs	X		X	X	X	X	X	X	X	X	X	X	8.4 and Appendix B
Local Laboratory Assessments (always taken pre-dose at dosing visits)													
Clinical chemistry	X		(X) [m]								(X) [m]		8.3.3
Troponin	X										(X) [m]		8.3.3
Haematology, WBC w/ differential [n]	X		X										8.3.3
Urine pregnancy test (dipstick) in WOCBP [o]	X						X			X			8.3.3.1
Local express test for HIV	X												8.3.3.2
Central Laboratory Assessments (always taken pre-dose at dosing visits)													
Haematology, WBC w/differential (2 samples) [p]	X			X	X	X	X	X	X	X	X	X	8.3.2
Clinical chemistry	X									X	X		8.3.2
Troponin (T and I)	X			X	X	X	X	X	X	X	X	X	8.3.2
Serum tryptase	X									X		X	8.3.2
Total IgE, FEIA	X									X			8.3.2

Table 1 Schedule of Activities for the DB Treatment Period

Study Procedures	Screening Period			DB Treatment Period									Details in CSP Sections or Appendix
Visit [a]	V1		V2 [b]	V3 (rand. visit) [b]	V4	V5	V6	V7	V8	V9 [c]	Flare visit [d]	IPD visit [e]	
Study Week (calculated from V3) Visit windows: ± 7 days for V4 – V9	Day -3 (Screening Day 1)	Day -2 (Screening Day 2)	Day -1 (Screening Day 3)	0	4	8	12	16	20	24			
Vitamin B12	X												8.3.2
CRP	X									X	X		8.3.2
Lactate dehydrogenase	X									X			8.3.2
ANCA (MPO and PR3)	X												8.3.2
Serum pregnancy test in WOCBP [q]	X												8.3.3.1
FSH [r]	X												8.3.3.1
Serology (Hep B and C, HIV-1 and 2)	X												8.3.3.2
PK [s]	X				X	X		X		X		X	8.5
PK/PD (subset of patients) [t]										X			8.5.1.2
ADA/nAb [u]	X				X	X		X		X		X	8.7
Optional genomics initiative sample [v]				(X)									8.8
Serum biomarkers	X			X		X	X			X	X		8.9
Plasma biomarkers	X			X		X	X			X	X		8.9
Urine biomarkers	X			X		X	X			X	X		8.9
Whole blood for lymphocyte phenotyping	X												8.9
PAXGene RNA [u]	X						X			X	X		8.9
Tissue biopsy (if applicable) [w]	X						X				X		8.9.1
Other Assessments													
Healthcare resource use				X	X	X	X	X	X	X		X	8.11

Table 1 Schedule of Activities for the DB Treatment Period

Study Procedures	Screening Period			DB Treatment Period									Details in CSP Sections or Appendix
Visit [a]	V1		V2 [b]	V3 (rand. visit) [b]	V4	V5	V6	V7	V8	V9 [c]	Flare visit [d]	IPD visit [e]	
Study Week (calculated from V3) Visit windows: ± 7 days for V4 – V9	Day -3 (Screening Day 1)	Day -2 (Screening Day 2)	Day -1 (Screening Day 3)	0	4	8	12	16	20	24			
Mechanistic Sub-study Procedures (if applicable)													
Mechanistic sub-study informed consent	X												Appendix A
Whole blood for PBMC (NIH, NW) and SMART tubes (AZ) [x, y]	X						X			X	X		8.9.2
Whole blood for eosinophil phenotyping (NW) (North America only) [x, y]	X										X		8.9.2
Whole blood for DNA analysis [x, z]	X												8.9.2
Patient Qualitative Interview Sub-study (if applicable)													
Patient qualitative interview sub-study recruitment and consent and sub-study consent confirmation	X			X									Appendix A
Patient qualitative interview [aa]									X			X	8.10.1
OCS and IP Administration													
Dispense sponsor-provided OCS (prednisone/prednisolone) (1 mg/kg/day for 2 days)	X												4.1.1, 6.1.6 Appendix I
Patient takes OCS at home if conditions met		X	X										4.1.1
Administer blinded IP at the site				X	X	X	X	X	X				6.1
Administer open-label benralizumab at the site (first dose of OLE)										X			6.1

[a] An unscheduled visit, for a reason other than HES worsening/flare, may be initiated as needed, and the procedures will be performed as clinically indicated at the discretion of the investigator.

[b] Visit 2 and Visit 3 (randomisation/baseline visit) can be performed the same day, if feasible, given that local laboratory results for corticosteroid responsiveness are obtained and all eligibility criteria confirmed prior to randomisation.

[c] Visit 9 will function as the last visit of the DB period and the first visit of the OLE period. Only patients who enter the OLE will receive IP (first dose of open-label benralizumab) at this visit. All assessments at Visit 9 are to be performed BEFORE administration of open-label benralizumab.

[d] Procedures listed in the table are mandatory for each HES worsening/flare visit. If a flare visit coincides with the regular scheduled visit, procedures should not be duplicated; only additional flare procedures that are not part of the scheduled visit should be performed. Echocardiography may be performed at the discretion of the investigator for patients with known or suspected cardiac involvement. Spirometry only needs to be performed in patients with known or suspected pulmonary involvement. Additional assessments may be performed at these visits, at the discretion of the investigator.

[e] In case of early discontinuation of IP, IPD visit procedures should be performed 4 weeks ± 7 days after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later). Note: The IPD visit replaces the nearest regular visit.

[f] It is recommended that informed consent/assent be obtained prior to Visit 1 to allow the patient to follow medication restrictions for spirometry.

[g] All eligibility criteria must be confirmed prior to randomisation. This includes Visit 1 and Visit 2 local laboratory AEC results that must be available before patient is randomised (Section 5.3).

[h] History of HES to include historical biopsy result(s) (bone marrow, tissue, endoscopy, etc.) related to HES diagnosis/follow-up, if available (within 12 months of Visit 1 and any earlier biopsy reports that were used to diagnose HES).

[i] All PRO assessments will be completed at the site prior to other study procedures. PROMIS fatigue short form 7a, SF-36v2, PGIS, PGIC, and HES symptom questionnaire will be completed by the patient using an eCOA device. Following, the investigator will provide instructions and ask questions from the investigator-led HES symptom interview to the patient and fill in the patient response using an eCOA device.

[j] For flare visits, positive HES signs and symptoms should be reported.

[k] For patients with known or suspected cardiac involvement, heart function should be assessed for clinical significance, either by an historical echocardiogram done within 12 months of Visit 1 or during screening if the historical echocardiogram is not available.

[l] Spirometry will be performed only in patients with pulmonary involvement.

[m] Local clinical chemistry and troponin taken at the investigator's discretion (ie, to follow-up on abnormalities during the screening period or for immediate medical decisions at flare visits).

[n] Local haematology (WBC with differential count) to confirm inclusion and randomisation criteria (see Section 5.1, inclusion criterion 7 and 8). A recent test for an AEC taken within 3 days of Visit 1 may be accepted to support inclusion criterion 7 provided that the testing was performed at the same local laboratory that will be used for further testing during the screening period.

[o] A positive urine pregnancy test result must be confirmed with a serum pregnancy test. If a WOCBP is attending an onsite visit where a urine pregnancy test is not scheduled, she will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.

[p] Two central samples to be collected for haematology and WBC with differential. Sponsor, sites, and patients will be blinded to the differential blood count after Visit 3: AECs, absolute basophil counts, absolute monocyte counts, and differential blood counts (percentage) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) to be redacted; total WBC, absolute neutrophils and absolute lymphocytes will be provided.

[q] Serum pregnancy test to be performed at Visit 1 and subsequently only if the urine pregnancy (dipstick) test is positive.

[r] FSH test done only for female patients to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for ≥ 12 months.

[s] On dosing visits, PK samples will be collected pre-dose. Samples will only be tested for randomised patients.

[t] Additional PK and haematology (AEC only) samples will be collected 24 ± 12 hours after the first dose of open-label benralizumab (Week 24) in a subset of patients (approximately 45 patients entering the OLE). The sample can be waived if not feasible or cannot be tolerated. This sample will only be analysed in patients that received placebo during the DB treatment period.

[u] On dosing visits, ADA samples will be collected pre-dose. ADA/nAb and PAXGene RNA samples will only be tested for randomised patients. Testing for nAb will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

[v] Optional genetic sample: Sample collection is recommended at randomisation but may be drawn at any time after the genetic consent form is signed.

[w] For patients with a skin manifestation of HES, a skin biopsy of the lesion will be collected during screening (Visit 1 or Visit 2). Other biopsy samples from other tissues, if available, collected in the 30 days prior to Visit 1 will also be utilised according to Section 8.9.1. In addition, tissue biopsies to aid the characterisation of HES worsening/flare may be performed at the investigator's discretion but are not mandatory. All biopsy samples will be sent to the central laboratory for central read. Local review of unscheduled biopsies is allowed only after Visit 10/Week 28 unless needed to address an immediate safety concern (Section 8.9.1).

[x] All blood samples related to the mechanistic sub-study apply to all sites, except for whole blood for eosinophil phenotyping, which is applicable to North America only. The other blood samples apply to all study sites and include 2 samples for PBMC analysis, one sample in SMART tubes for immunophenotyping, and one sample for DNA analysis.

[y] The NIH will perform PBMC analysis, Northwestern University will perform additional PBMC analysis and fresh eosinophil phenotyping, and AstraZeneca will perform the analysis of SMART tubes. If the PBMC sample collection is missed at Visit 1, the sample can be taken at Visit 4 or Visit 5 (not Visit 2 or Visit 3).

[z] DNA sample collection preferred at screening, but it can be taken at later time points.

[aa] Each patient will be interviewed once. The interview will take place at least 7 days and up to 21 days after Visit 8 (or after the IPD visit within the DB portion of the study for patients who discontinue treatment prior to Visit 8).

ADA = anti-drug antibodies; AE(s) = adverse event(s); AEC(s) = absolute eosinophilic count(s); ANCA = antineutrophil cytoplasmic antibodies; AZ = AstraZeneca; CRP = C-reactive protein; CSP = clinical study protocol; DB = double-blind; DNA = deoxyribonucleic acid; ECG(s) =electrocardiogram(s); eCOA = electronic clinical outcomes assessments; FEIA = fluorescence enzyme immunoassay; FEV_1 = forced expiratory volume in one second; FSH = follicle-stimulating hormone; FVC = forced vital capacity; Hep = hepatitis; HES = hypereosinophilic syndrome; HIV = human immunodeficiency virus; Ig = immunoglobulin; IP = investigational product; IPD = IP discontinuation; MPO = myeloperoxidase antibodies; nAb = neutralising antibody; NIH = National Institutes of Health; NW = Northwestern; OCS = oral corticosteroid(s); OLE = open-label extension; PBMC(s) = peripheral blood mononuclear cell(s); PD = pharmacodynamics; PGIC = Patient Global Impression of Change: PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PR3 = proteinase 3 antibodies; PRO = Patient-reported Outcomes; PROMIS = Patient-reported Outcomes Measurement Information System; rand = randomisation; RNA = ribonucleic acid; SAEs = serious adverse events; SF-36v2 = 36-Item Short Form Health Survey Version 2; V = visit; WBC = white blood cell; WOCBP = woman/women of childbearing potential.

Table 2 Schedule of Activities for the OLE Treatment Period (Year 1)

Study Procedures	OLE Treatment Period (Year 1)															Details in CSP Sections or Appendix
Visit [a]	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**Flare visit** [c]	**IPD/EOT visit** [d]	
Study Week Visit windows: ± 7 days for V10 – V22	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**			
Visit can be done remotely [b]		**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
General Procedures																
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
HES and PRO [e] **Assessments**																
HES worsening/flare evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1
Brief physical examination [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X [f]	X	8.2.1.1 and Appendix H
Investigator-led HES symptom interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1.2 and Appendix G
PROMIS fatigue short form 7a	X			X			X			X			X		X	8.2.3.1
SF-36v2	X			X			X			X			X		X	8.2.3.2
HES symptom questionnaire	X			X			X			X			X	X	X	8.2.3.5
Vital Signs, AEs, and Instrumental Assessments																
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.2
Echocardiogram														X [c]		8.3.5
Spirometry (pre-bronchodilator FEV_1 and FVC) [g]													X	X		8.10.2
Weight	X						X						X			8.3.1.1
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.4
Local Laboratory Assessments (always taken pre-dose at dosing visits)																
Clinical chemistry														(X) [h]		8.3.2
Troponin														(X) [h]		8.3.2
Urine pregnancy test (dipstick) in WOCBP [i]	X			X			X			X			X			8.3.3.1

Table 2 Schedule of Activities for the OLE Treatment Period (Year 1)

Study Procedures	OLE Treatment Period (Year 1)															Details in CSP Sections or Appendix
Visit [a]	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**Flare visit** [c]	**IPD/EOT visit** [d]	
Study Week Visit windows: ± 7 days for V10 – V22	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**			
Visit can be done remotely [b]		**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**				
Central Laboratory Assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/ differential only (2 samples) [j]	X			X			X			X			X	X	X	8.3.2
Clinical chemistry	X			X			X			X			X	X	X	8.3.2
Troponin (T and I)	X			X			X			X			X	X	X	8.3.2
Serum tryptase				X			X						X		X	8.3.2
CRP							X							X		8.3.2
Lactate dehydrogenase													X			8.3.2
PK [k]				X			X						X		X	8.5
ADA/nAb [l]				X			X						X		X	8.6
Serum biomarkers				X			X						X	X		8.9
Plasma biomarkers				X			X						X	X		8.9
Urine biomarkers				X			X						X	X		8.9
Tissue biopsy (if applicable) [m]														X		8.9.1
Other Assessments																
Healthcare resource use	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.11
IP Administration																
Administer open-label benralizumab [b]	X	X	X	X	X	X	X	X	X	X	X	X	X			6.1

[a] An unscheduled visit, for a reason other than HES worsening/flare, may be initiated as needed and the procedures will be performed as clinically indicated at the discretion of the investigator.

[b] Where permitted, if the patient opts for IP self-administration, these visits can be performed remotely (ie, telephone/telemedicine contact). In such cases, the brief physical examination and vital signs assessments may be skipped.

[c] Procedures listed in the table are mandatory for each HES worsening/flare visit. Echocardiography may be performed at the discretion of the investigator for patients with known or suspected cardiac involvement. Spirometry only needs to be performed in patients with known or suspected pulmonary involvement. Additional assessments may be performed at these visits, at the discretion of the investigator.

[d] In case of early discontinuation from IP, IPD visit procedures should be performed 4 weeks ± 7 days after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later). Note: The IPD visit replaces the nearest regular visit (Section 7.1.1.1). The EOT visit will only be scheduled for ongoing patients following notification of closure of the study, 4 weeks ± 7 days after the last dose of IP (Section 7.1.1.2).

[e] All PRO assessments will be completed at the site prior to other study procedures. PROMIS fatigue short form 7a, SF-36v2, and HES symptom questionnaire will be completed by the patient using an eCOA device. Following, the investigator will provide instructions and ask questions from the investigator-led HES symptom interview to the patient and fill in the patient response using an eCOA device.

[f] For flare visits, positive HES signs and symptoms should be reported.

[g] Spirometry will be performed only in patients with pulmonary involvement.

[h] Local clinical chemistry and troponin taken at the investigator's discretion at any flare visit, as required (ie, for immediate medical decisions).

[i] A positive urine pregnancy test result must be confirmed with a serum pregnancy test. During the telemedicine (remote) visits, a WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.

[j] Two central samples to be collected for haematology and WBC with differential. Sponsor, sites, and patients will be blinded to the differential blood count until Week 28: AECs, absolute basophil counts, absolute monocyte counts, and differential blood counts (percentage) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) to be redacted; absolute neutrophils and absolute lymphocytes will be provided.

[k] On dosing visits, PK samples will be collected pre-dose.

[l] Testing for nAb will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

[m] A tissue biopsy to aid in the characterisation of HES worsening/flare may be performed at the investigator's discretion. All biopsy samples will be sent to the central laboratory for central read. Local review of unscheduled biopsies is allowed only after Visit 10/Week 28 unless needed to address an immediate safety concern (Section 8.9.1).

ADA = anti-drug antibodies; AEs = adverse events; AECs = absolute eosinophil counts; CSP = clinical study protocol; CRP = C-reactive protein; eCOA = electronic clinical outcomes assessments; EOT = end of treatment; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HES = hypereosinophilic syndrome; IP = investigational product; IPD = IP discontinuation; nAb = neutralising antibody; OLE = open-label extension; PK = pharmacokinetic(s); PRO = Patient-reported Outcomes; PROMIS = Patient-Reported Outcomes Measurement Information System; SAEs = serious adverse events; SF-36v2 = 36-Item Short Form Health Survey Version 2; V = visit; WBC(s) = white blood cell(s); WOCBP = woman/women of childbearing potential.

Table 3 Schedule of Activities for the OLE Treatment Period (Year 2)

Study Procedures	OLE Treatment Period (Year 2)															Details in CSP Sections or Appendix
Visit [a]	V23	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	V35	Flare visit [c]	IPD/EOT visit [d]	
Study Week Visit windows: ± 7 days	80	84	88	92	96	100	104	108	112	116	120	124	128			
Visit can be done remotely [b]	X	X		X	X		X	X		X	X		X			
General Procedures																
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
HES Assessments																
HES worsening/flare evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1
Brief physical examination [b]			X			X			X			X		X [e]	X	8.2.1.1 and Appendix H
investigator-led HES symptom interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1.2 and Appendix G
Vital Signs, AEs, and Instrumental Assessments																
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.2
Echocardiogram														X [c]		8.3.5
Weight						X						X				8.3.1.1
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.4
Local Laboratory Assessments (always taken pre-dose at dosing visits)																
Clinical chemistry														(X) [f]		8.3.2
Troponin														(X) [f]		8.3.2
Urine pregnancy test (dipstick) in WOCBP [g]			X			X			X			X				8.3.3.1
Central Laboratory Assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/ differential only			X			X			X			X		X	X	8.3.2
Clinical chemistry			X			X			X			X		X	X	8.3.2
Troponin (T and I)			X			X			X			X		X	X	8.3.2
Serum tryptase			X			X			X			X			X	8.3.2
CRP						X								X		8.3.2

Table 3 Schedule of Activities for the OLE Treatment Period (Year 2)

Study Procedures	OLE Treatment Period (Year 2)															Details in CSP Sections or Appendix
Visit [a]	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**	**V34**	**V35**	**Flare visit** [c]	**IPD/EOT visit** [d]	
Study Week Visit windows: ± 7 days	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**	**124**	**128**			
Visit can be done remotely [b]	**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**		**X**			
PK [h]						X						X			X	8.5
ADA/nAb [i]						X						X			X	8.6
IP Administration																
Administer open-label benralizumab [b]	X	X	X	X	X	X	X	X	X	X	X	X	X			6.1

[a] An unscheduled visit, for a reason other than HES worsening/flare, may be initiated as needed and the procedures will be performed as clinically indicated at the discretion of the investigator.

[b] Where permitted, if the patient opts for IP self-administration, these visits can be performed remotely (ie, telephone/telemedicine contact). In such cases, the vital signs assessments may be skipped.

[c] Procedures listed in the table are mandatory for each HES worsening/flare visit. Echocardiography may be performed at the discretion of the investigator for patients with known or suspected cardiac involvement. Additional assessments may be performed at these visits, at the discretion of the investigator.

[d] In case of early discontinuation from IP, IPD visit procedures should be performed 4 weeks ± 7 days after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later). Note: The IPD visit replaces the nearest regular visit. EOT visit will only be scheduled for ongoing patients following notification of closure of the study, 4 weeks ± 7 days after the last dose of IP.

[e] For flare visits, positive HES signs and symptoms should be reported.

[f] Local clinical chemistry and troponin taken at the investigator's discretion at any flare visit, as required (ie, for immediate medical decisions).

[g] A positive urine pregnancy test result must be confirmed with a serum pregnancy test. During the telemedicine (remote) visits, a WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.

[h] On dosing visits, PK samples will be collected pre-dose.

[i] Testing for nAb will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

ADA = anti-drug antibodies; AEs = adverse events; CRP = C-reactive protein; CSP = clinical study protocol; EOT = end of treatment; HES = hypereosinophilic syndrome; IP = investigational product; IPD = IP discontinuation; nAb = neutralising antibody; OLE = open-label extension; PK = pharmacokinetic(s); SAEs = serious adverse events; V = visit; WBC(s) = white blood cell(s); WOCBP = woman/women of childbearing potential.

Table 4 Schedule of Activities for the OLE Treatment Period (Year 3 and Beyond [a])

Study Procedures	OLE Treatment Period (Year 3)															Details in CSP Sections or Appendix
Visit [b]	V36	V37	V38	V39	V40	V41	V42	V43	V44	V45	V46	V47	V48	Flare visit [d]	IPD/EOT visit [e]	
Study Week Visit windows: ± 7 days	132	136	140	144	148	152	156	160	164	168	172	176	180			
Visit can be done remotely [c]	X		X	X		X	X		X	X		X	X			
General Procedures																
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
HES Assessments																
HES worsening/flare evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1
Brief HES physical examination [c]		X			X			X			X			X [f]	X	8.2.1.1 and Appendix H
Investigator-led HES symptom interview	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1.2 and Appendix G
Vital Signs, AEs, and Instrumental Assessments																
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.2
Echocardiogram														X [d]		8.3.5
Weight					X						X					8.3.1.1
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.4
Local Laboratory Assessments (always taken pre-dose at dosing visits)																
Clinical chemistry														(X) [g]		8.3.2
Troponin														(X) [g]		8.3.2
Urine pregnancy test (dipstick) in WOCBP [h]		X			X			X			X					8.3.3.1
Central Laboratory Assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/ differential only		X			X			X			X			X	X	8.3.2
Clinical chemistry		X			X			X			X			X	X	8.3.2
Troponin (T and I)		X			X			X			X			X	X	8.3.2
Serum tryptase		X			X			X			X				X	8.3.2
CRP					X									X		8.3.2

Table 4 Schedule of Activities for the OLE Treatment Period (Year 3 and Beyond [a])

Study Procedures	OLE Treatment Period (Year 3)															Details in CSP Sections or Appendix
Visit [b]	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**V44**	**V45**	**V46**	**V47**	**V48**	**Flare visit** [d]	**IPD/EOT visit** [e]	
Study Week Visit windows: ± 7 days	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**	**164**	**168**	**172**	**176**	**180**			
Visit can be done remotely [c]	**X**		**X**	**X**		**X**	**X**		**X**	**X**		**X**	**X**			
PK [i]					X						X				X	8.5
ADA/nAb [j]					X						X				X	8.6
IP Administration																
Administer open-label benralizumab [c]	X	X	X	X	X	X	X	X	X	X	X	X	X			6.1

[a] After Year 3, assessments should be performed with a similar schedule and frequency as for Year 3; eg, the assessments at the first visit of Year 3 (Visit 37/Week 136) should be performed at the first visit of Year 4 (Visit 49/Week 184).

[b] An unscheduled visit, for a reason other than HES worsening/flare, may be initiated as needed and the procedures will be performed as clinically indicated at the discretion of the investigator.

[c] Where permitted, if the patient opts for IP self-administration, these visits can be performed remotely (ie, telephone/telemedicine contact). In such cases, the vital signs assessments may be skipped.

[d] Procedures listed in the table are mandatory for each HES worsening/flare visit Echocardiography may be performed at the discretion of the investigator for patients with known or suspected cardiac involvement. Additional assessments may be performed at these visits, at the discretion of the investigator.

[e] In case of early discontinuation from IP, IPD visit procedures should be performed 4 weeks ± 7 days after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later). Note: The IPD visit replaces the nearest regular visit. EOT visit will only be scheduled for ongoing patients following notification of closure of the study, 4 weeks ± 7 days after the last dose of IP.

[f] For flare visits, positive HES signs and symptoms should be reported.

[g] Local clinical chemistry and troponin taken at the investigator's discretion at any flare visit, as required (ie, for immediate medical decisions).

[h] A positive urine pregnancy test result must be confirmed with a serum pregnancy test. During the telemedicine (remote) visits, a WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.

[i] On dosing visits, PK samples will be collected pre-dose.

[j] Testing for nAb will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

ADA = anti-drug antibodies; AEs = adverse events; CRP = C-reactive protein; CSP = clinical study protocol; EOT = end of treatment; HES = hypereosinophilic syndrome; IP = investigational product; IPD = IP discontinuation; nAb = neutralising antibody; OLE = open-label extension; PK = pharmacokinetic(s); SAEs = serious adverse events; V = visit; WBC = white blood cell; WOCBP = woman/women of childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

The central role of eosinophilia in the pathophysiology of HES suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of HES. Benralizumab (30 mg SC Q4W) was shown in a Phase II study to significantly reduce AEC over 12 weeks of treatment compared with placebo in patients with symptomatic HES. Benralizumab was well-tolerated in patients who remained on open-label treatment through Week 48. The purpose of this Phase III study is to build on the Phase II findings and confirm the use of benralizumab as an effective and well-tolerated option for *FIP1L1-PDGFRA* fusion tyrosine kinase translocation-negative HES.

2.2 Background

HES is a group of rare diseases with persistent blood eosinophilia, defined as AEC > 1500 cells/μL, and evidence of eosinophil-mediated end-organ damage or dysfunction. Other potential causes for the organ damage or dysfunction must be excluded in order for HES to be diagnosed. Although any organ system can be involved, HES commonly involves the skin, heart, lungs, gastrointestinal tract, or central nervous system.

Based on clinical, laboratory, and molecular features, HES has been divided into multiple subtypes (eg, lymphocytic, myeloproliferative, idiopathic) (Roufosse et al 2017, Curtis and Ogbogu 2016). Patients with myeloproliferative HES have clinical features consistent with a myeloid disorder or have a specific gene mutation (eg, *FIP1L1-PDGFRA* fusion). Approximately 10% of all HES patients have the *FIP1L1-PDGFRA* mutation resulting from gene fusion of *FIP1L1* and *PDGFRA* resulting in a constitutively active tyrosine kinase. Some of the other much less common mutations in patients with myeloproliferative HES include fusion of *PDGFRA* with other partner genes, fusions involving *PDGFRB,* or point mutations in *PDGFRA* (Roufosse et al 2017, Curtis and Ogbogu 2016).

The goals of treatment include reduction of blood and tissue eosinophilia, reductions in signs and symptoms, and prevention of disease progression (Klion 2015). Current management of patients who have active symptomatic HES is based on long-term systemic corticosteroids (Ogbogu et al 2009), the exception being for the myeloproliferative variant of HES associated with the *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation for which imatinib mesylate is considered first-line therapy (Dispenza and Bochner 2018, Curtis and Ogbogu 2016, Khoury et al 2016). Although most patients have an initial response to corticosteroids (Khoury et al 2018, Ogbogu et al 2009), chronic use leads to considerable morbidity, and attempts are made to reduce doses due to steroid toxicity. Steroid-sparing agents such as hydroxyurea, IFN-α, methotrexate, or IPs (Dispenza and Bochner 2018) are then often

introduced. However, many of these agents also have side effects that can be intolerable or impact the patient's quality of life.

Eosinophilic diseases are in large part driven by IL-5, a cytokine produced by type-2 T helper cells, innate lymphocyte type-2 cells, and mast cells and a key mediator in eosinophil activation. Benralizumab is a mAb that binds to the alpha chain of the IL-5Rα that is expressed not only by mature eosinophils, but also by eosinophil progenitor cells and basophils. Benralizumab is a humanised, recombinant IgG, subclass 1, κ isotype mAb. It has been engineered to be afucosylated (without a fucose sugar residue) which enhances the interaction of benralizumab with FcγRIIIa that are expressed on immune effector cells on natural killer cells and macrophages. This results in enhanced ADCC. Benralizumab targets eosinophils and other cells expressing IL-5Rα in the circulation and residing in tissues for ADCC which results in depletion of eosinophils in the circulation, bone marrow, and tissues (Busse et al 2013, Kolbeck et al 2010). Benralizumab also targets the IL-5Rα receptor on eosinophil precursors in the bone marrow leading to their depletion via ADCC. The direct eosinophil-depleting ability of benralizumab is effective in eosinophilic asthma (Bleecker et al 2016, Fitzgerald et al 2016) and in steroid-dependent asthma (Nair et al 2017).

The safety and efficacy of benralizumab for the treatment of HES was evaluated in a Phase II randomised, DB, placebo-controlled study of benralizumab (30 mg administered SC Q4W for 3 doses) in 20 symptomatic patients with a diagnosis of *FIP1L1-PDGFRA* fusion tyrosine kinase translocation-negative HES and an AEC ≥ 1000 cells/μL on stable HES therapy (Kuang et al 2019, NCT02130882). This was followed by an open-label period during which background HES therapy could be tapered as tolerated. The primary endpoint was a ≥ 50% reduction in AEC at Week 12.

Patients who received benralizumab during the placebo-controlled period of the study were more likely to achieve the primary endpoint (a reduction of at least 50% in the AEC at Week 12) than those who received placebo (9 of 10 patients vs 3 of 10 patients, $p < 0.02$). Clinical and haematologic response was observed in 17 of 19 patients (89%) in the open-label period and was sustained to Week 48 in 14 of 19 patients (74%), many of whom were able to taper background HES therapies. Bone marrow and tissue eosinophilia were also suppressed with benralizumab therapy. Adverse events were similar in the benralizumab-treated group compared to the placebo-treated group, and drug-related AEs were few and transient in nature. Of the many potential predictors of response examined, only clinical HES subtype appeared to be associated with initial response or relapse. In this Phase II study, benralizumab was effective and well-tolerated in reducing eosinophilia in patients with symptomatic HES.

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab is provided in the IB.

2.3 Benefit/Risk Assessment

Safety and tolerability data from the Phase II study of benralizumab in patients with HES (Kuang et al 2019) showed that benralizumab was well tolerated, with similar rates of AEs observed between active and placebo groups. Total AEs, Grade 3 AEs, and the number of patients reporting an AE were similar between the benralizumab and placebo groups. No new safety signals for benralizumab were identified in this study of patients with HES.

Given the initial study results for benralizumab in HES, potential benefits of this similarly designed Phase III study include reduction in the incidence of HES worsening/flare, reduction in haematological relapse, and improvement in patient symptoms while exhibiting a safety profile similar to placebo.

Previous studies (Bleecker et al 2016, Fitzgerald et al 2016) have shown that the overall safety profile of benralizumab in severe asthma patients is similar to placebo up to approximately 1 year. The most commonly reported AEs included nasopharyngitis, asthma, and upper respiratory tract infections. The majority of AEs were mild to moderate in nature. Numerically fewer patients in the benralizumab group reported SAEs compared with placebo. Longer-term safety studies have been conducted in patients who completed one of the predecessor studies for up to an additional 1 year (adults) and 2 years (adolescents). In general, the safety results (Busse et al 2019) were reflective of the patient population and consistent with the predecessor studies (Bleecker et al 2016, Fitzgerald et al 2016).

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

Development of 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.

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. Helminthic parasitic infections and malignancy will continue to be monitored as part of routine pharmacovigilance practices.

Given the extensive safety data already available at the dosing regimen to be studied, the benefit/risk profile in patients with HES is expected to continue to be favourable, commensurate with that observed in the benralizumab asthma pivotal trials and the HES Phase II study. Risk minimisation measures include exclusion of patients with life-threatening

HES and/or HES complication(s), patients with a history of thrombotic complications, stroke, or significant cardiac damage related to HES, untreated parasitic infection, a history of anaphylaxis to any biologic therapy, active or recent malignancy with certain exceptions, and exclusion of pregnant women (Section 5.2). Risk minimisation measures will be maintained during the conduct of this study, in conjunction with the performance of AstraZeneca's routine pharmacovigilance activities.

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

See Section 9.6 and Appendix A for information regarding the DSMB.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the DB treatment period and the OLE treatment period of the study are presented in Table 5 and Table 6, respectively.

Table 5 Study Objectives - DB Treatment Period

Objectives	Endpoints
Primary:	
To evaluate the effect of benralizumab on the time to first HES worsening/flare	Time to first HES worsening/flare [a] • Population [b]: Full analysis set • Intercurrent event strategy [b]: Included in analysis regardless of treatment discontinuation (treatment policy) • Population-level summary: Hazard ratio
Secondary:	
To evaluate the effect of benralizumab on the proportion of patients who experience an HES worsening/flare	Key: Proportion of patients who experience an HES worsening/flare during the DB treatment period [a, c]
To evaluate the effect of benralizumab on the number of HES worsenings/flares	Key: Number of HES worsenings/flares (annualised rate/year) during the DB period [a, c]
To evaluate the effect of benralizumab on the time to first haematological relapse	Key: Time to first haematologic relapse (AEC ≥ 1000 cells/µL) during the DB period [c, d]
To evaluate the effect of benralizumab on patient-reported measure of fatigue	Key: Fatigue severity (PROMIS fatigue short form 7a) at Week 24 [c]
To evaluate the effect of benralizumab on the proportion of patients with haematologic relapse	Proportion of patients who have haematologic relapse during the DB treatment period [d]
To evaluate the effect of benralizumab on the number of patients who maintain AEC < 500 cells/µL for 24 weeks	Proportion of patients who have AEC < 500 cells/µL for 24 weeks

Table 5 Study Objectives - DB Treatment Period

Objectives	Endpoints
To evaluate the effect of benralizumab on corticosteroid use	Proportion of patients who require an increase in corticosteroid dose from baseline at any point in the DB treatment period
To evaluate the effect of benralizumab on health status/HRQoL measures	HRQoL ([SF-36v2]), PGIS, and PGIC
To evaluate the PK and immunogenicity of benralizumab in patients with HES	Serum benralizumab concentrations Anti-benralizumab antibodies and nAbs
Safety:	
To evaluate the safety and tolerability of benralizumab in patients with HES	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory assessments. Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
Exploratory:	
To evaluate the effect of benralizumab on healthcare resource utilisation due to HES	Number of HES-related hospitalisations; length of hospital stay; Intensive care unit days; number of HES-related ER visits; number of HES-related outpatient visits (by type); number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on HES-related hospitalisation	Proportion of HES worsening/flare resulting in hospitalisation
To evaluate the effect of benralizumab on patient-reported measure of HES symptom severity	HES symptom questionnaire
To characterise the patient-reported experience and treatment benefits of benralizumab through patient interviews	Patient qualitative interview to characterise patient-reported experience and treatment benefits (sub-study)
To evaluate the effect of benralizumab on CRP	CRP levels
To evaluate the effect of benralizumab on biomarkers related to the mechanism of action of benralizumab, eosinophilic inflammation, and HES disease pathogenesis, as well as HES clinical subtypes and baseline predictors of response to benralizumab	Exploratory biomarkers in: • Serum • Plasma • Urine • Whole blood (including mechanistic sub-study) • Tissue biopsies
To assess effect of lymphocyte phenotype on responsiveness to benralizumab	Whole blood lymphocyte phenotyping

[a] For HES worsening/flare, see Section 8.2.1.
[b] The population and intercurrent event strategy also apply to the secondary endpoints.
[c] Key secondary endpoint (multiplicity protected)
[d] Haematologic relapse post-baseline: AEC ≥ 1000 cells/μL; baseline is the randomisation AEC

AE(s) = adverse event(s); AEC = absolute eosinophil count; CRP = C-reactive protein; DB = double-blind; ER = emergency room; HES = hypereosinophilic syndrome; HRQoL = health-related quality of life; IP = investigational product; nAb = neutralising antibody; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics; PROMIS = Patient-reported Outcomes Measurement Information System; SF-36v2 = 36-Item Short Form Health Survey version 2.

Table 6 Study Objectives – OLE Treatment Period

Objectives	Endpoints
To evaluate the effect of benralizumab on the proportion of patients who experience an HES worsening/flare [a]	Proportion of patients who experience an HES worsening/flare [b]
To evaluate the effect of benralizumab on the number of HES worsenings/flares [a]	Annualised rate of HES worsening/flare [b]
To evaluate the effect of benralizumab on patient-reported measure of fatigue [c]	Fatigue (PROMIS fatigue short form 7a)
To evaluate the effect of benralizumab on HRQoL [c]	HRQoL (SF-36v2)
To evaluate the safety and tolerability of benralizumab in patients with HES [a]	Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory assessments. Assessments related to AEs include: • Occurrence/frequency • Relationship to IP as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To evaluate the PK and immunogenicity of benralizumab in patients with HES [a]	Serum benralizumab concentrations Anti-benralizumab antibodies and nAbs
To evaluate the effect of benralizumab on healthcare resource utilisation due to HES [c]	Number of HES-related hospitalisations; length of the hospital stay; intensive care unit days; number of HES-related ER visits; number of HES-related outpatient visits (by type); number of HES-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab on patient-reported measure of HES symptom severity [c]	HES symptom questionnaire
To evaluate the effect of benralizumab on CRP [a]	CRP levels

Table 6 Study Objectives – OLE Treatment Period

Objectives	Endpoints
To evaluate the effect of benralizumab on biomarkers related to the mechanism of action of benralizumab, eosinophilic inflammation, and HES disease pathogenesis [c]	Exploratory biomarkers in: • Serum • Plasma • Urine • Tissue biopsies
To better characterise the early onset of eosinophil depletion to support extrapolation to build a relationship between adults, adolescents, and younger patients	PK: Benralizumab concentrations PD: Eosinophil counts

[a] Applicable to full duration of the OLE
[b] For HES worsening/flare, see Section 8.2.1.
[c] Applicable to 1st year of OLE only
AEs = adverse events; CRP = C-reactive protein; ER = emergency room; HES = hypereosinophilic syndrome; HRQoL= health-related quality of life; IP = investigational product; nAbs = neutralising antibodies; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; PROMIS = Patient-reported Outcomes Measurement Information System; SF-36v2 = 36-Item Short Form Health Survey version 2.

4 STUDY DESIGN

4.1 Overall Design

This is a multicentre, randomised, DB, parallel-group, placebo-controlled, 24-week Phase III study to compare the efficacy and safety of benralizumab 30 mg versus placebo administered by SC injection Q4W in patients with HES. This study will be conducted at approximately 45 sites in 13 countries.

The target patient population is male and female patients 12 years of age and older with symptomatic active HES. Eligible patients must be negative for the *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation.

Potentially eligible patients will enter a 3-day screening period and will be required to have documented stable HES therapy for at least 4 weeks prior to Visit 1 and AEC ≥ 1000 cells/µL at local laboratory testing to proceed to the second day of the screening period. Patients will be assessed for corticosteroid responsiveness (defined as an AEC < 1000 cells/µL after 2 days of OCS [prednisone/prednisolone] 1 mg/kg/day given on top of the patient's background therapy for HES) prior to randomisation; other OCSs in equivalent doses are permitted (Appendix I). Patients who are not corticosteroid responsive or fail any other eligibility criteria will be screen failed.

It is expected that approximately 120 patients will be randomised at a 1:1 ratio at the randomisation/baseline visit (Visit 3) to receive either benralizumab or matching placebo

Q4W for a 24-week DB treatment period. Recruitment may continue beyond 120 patients if required to achieve the target number of HES worsening/flares. Recruitment of adolescent patients is targeted to be broadly in line with expected prevalence rates of adolescents in the overall population. Approximately 4 to 6 adolescent patients (aged 12 to 17) are targeted to be randomised. Randomisation will be stratified as defined in Section 6.3.1. Approximately 40 patients will participate in a noninterventional interview to collect data on HRQoL and the patients' experience during the DB portion of the study (Section 8.10.1).

All patients will remain on stable dose(s) and regimen of background HES therapy (Section 6.5.1) during the screening period and throughout 36 weeks of treatment (until Visit 12/Week 36 when the therapy can be adjusted). During this time, background HES therapy may only be modified if a patient has an HES clinical worsening/flare or an AE thought to be due to background therapy.

AstraZeneca, sites, and patients will be blinded to the absolute eosinophil, basophil, and monocyte counts, differential blood counts (percentages) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes), and biopsy cell counts (if applicable) after randomisation/baseline (Visit 3/Week 0), during the entire DB treatment period, and for the first 4 weeks of the OLE treatment period (until Visit 10/Week 28) after which no blinding to WBC counts or biopsy cell counts is required (Section 6.3.2). After the primary DBL, AstraZeneca will become unblinded to all patients' blood and biopsy cell counts obtained during DB treatment period.

The final dose of the DB treatment period will be given at Week 20, and the DB treatment period will complete at Week 24.

All patients who complete the DB treatment period on IP may be eligible to continue into an OLE treatment period on benralizumab (30 mg SC Q4W). The OLE is intended to allow treatment with open-label benralizumab for at least 1 year for adults and at least 2 years for adolescents after completion of the DB treatment period of the study (earlier enrolled patients may therefore be in the OLE for longer than 1 year). AstraZeneca may choose to extend the study depending on the overall development program. Moreover, AstraZeneca reserves the right of terminating the OLE early (eg, if development of the asset is terminated or marketing authorisation is obtained).

The primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period. Treatment allocation will remain blinded until the primary DBL. A patient must complete the 24-week DB treatment period on IP to be eligible to enter the OLE treatment period. The final DBL will occur after the last patient completes the OLE. Data from the OLE treatment period of the

study will be presented in an addendum to the primary analysis CSR and/or a separate OLE treatment period CSR.

The general study design is summarised in Figure 1. For details on the study population and inclusion and exclusion criteria, see Section 5. For details on the efficacy and safety endpoints, see Section 3.

4.1.1 Screening (Enrolment up to Randomisation)

Potentially eligible patients will enter a 3-day screening period to assess eligibility.

Enrolment

Each potential patient will provide written informed consent/assent prior to any study-specific procedures. It is recommended that informed consent/assent be obtained prior to Visit 1 to allow the patient to follow medication restrictions for spirometry; refer to Section 8.10.2 for details. The patient's enrolment should be registered in an IWRS/IVRS on the day the ICF/assent is signed.

Patients included in this study will be provided with a patient participation card.

Following the registration of a patient and assignment of an enrolment code, the screening procedures will be initiated to assess the study eligibility criteria (Table 1).

Screening Day 1 (Visit 1)

Visit 1 is primarily focused on screening assessments (eg, confirmation of the HES diagnosis, history of treatment for HES, review of available medical documentation, and performing assessments necessary to evaluate the patient's eligibility). A complete HES physical examination (Appendix H) will be conducted, an investigator-led HES symptom interview (Appendix G) will be administered, and laboratories will be assessed (Table 1) to evaluate signs and/or symptoms of HES worsening/flare. The complete list of Visit 1 procedures is provided in Table 1.

For patients with known or suspected cardiac involvement, heart function should be assessed. Documented echocardiography results obtained within 12 months of Visit 1 will be collected if available and assessed for clinical significance by the investigator. If no historical echocardiography results are available, an echocardiogram will be performed during screening.

History of HES to include historical biopsy result(s) (bone marrow, tissue, endoscopy, etc.) related to HES diagnosis/follow-up, if available (within 12 months of Visit 1, and any earlier biopsy reports that were used to diagnose HES). Information about historical blood eosinophil values, including the highest absolute value of eosinophils in the year prior to enrolment (if

available), will be obtained and recorded in the electronic eCRF. Historical eosinophil values must be supported by respective source documentation.

Documented historical negative testing for *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation must be obtained and recorded in the eCRF as part of study eligibility.

An initial measurement of blood eosinophil levels will be performed at Visit 1 and analysed by the local laboratory to determine if the AEC is ≥ 1000 cells/µL as per inclusion criterion 7. A recent test for an AEC taken within 3 days of Visit 1 may be accepted to support inclusion criterion 7 provided that the testing was performed at the same local laboratory that will be used for further testing during the screening period.

Assessment for Corticosteroid Responsiveness

At the end of Visit 1, the patients who are deemed to be potentially eligible, pending confirmation of inclusion criterion 7 and 8, will be provided a bottle containing a 2-day supply of OCS (prednisone/prednisolone) at a dose of 1 mg/kg/day; other OCSs in equivalent doses are permitted (Appendix I). Patients will be asked to wait for further instruction from the site regarding whether the OCS should be taken.

The site staff will contact patients as soon as the result for the screening AEC is obtained from the local laboratory (same day):

- If the local laboratory Visit 1 AEC result is ≥ 1000 cells/µL, patients will be instructed to take the dispensed OCS for 2 days starting the next morning (screening Day 2) with the second dose taken the morning of screening Day 3 (Visit 2). This dose will be taken on top of the patient's regular background medications (including OCS).
- If the AEC is < 1000 cells/µL, the patient will be screen failed as not meeting inclusion criterion 7 and will be instructed to return or discard the dispensed OCS.

NOTE: OCS (prednisone/prednisolone) dose variations within ± 5 mg are acceptable if needed to allow dosing with locally available OCS formulation. If calculated OCS dose for steroid responsiveness assessment exceeds maximum locally approved daily dose, or in the investigator's opinion exceeds maximum tolerable dose for the patient, it can be reduced to maximum locally approved/tolerable dose at the discretion of the investigator; the decision and justification should be documented.

Screening Day 3 (Visit 2)

Patients will return to the site on the second day of taking dispensed OCS. A local laboratory eosinophil test to assess corticosteroid responsiveness should be taken 4 to 8 hours after the second OCS (prednisone/prednisolone) dose. If the AEC is < 1000 cells/µL at screening Day 3 (Visit 2), the patient will be deemed corticosteroid responsive and meeting inclusion criterion 8. If the AEC remains ≥ 1000 cells/µL, the patient will be screen failed.

Corticosteroid responsive patients who meet all other eligibility criteria may proceed to randomisation (Visit 3) on the same day if feasible, or the next day at the latest.

4.1.2 DB Treatment Period (Randomisation to Week 24)

Randomisation (Visit 3) may occur the same day as Visit 2, or the next day at the latest. The patient's eligibility must be verified and confirmed prior to the randomisation transaction in IWRS/IVRS.

Patients confirmed to be eligible will be randomised at a 1:1 ratio to receive benralizumab 30 mg or matching placebo Q4W for a 24-week DB treatment period. The first dose of the IP will be administered at Week 0 after the patient's randomisation. The final dose of the DB treatment period will be given at Week 20, and the DB treatment period will complete at Week 24.

Patients will attend scheduled clinic visits at 4-week intervals throughout the DB treatment period. When clinically indicated, a flare visit is used to assess the patient for potential HES worsening/flare. Mandatory procedures for flare visits are described in Table 1. Additional assessments may be performed at these visits, at the discretion of the investigator. Patients not able to get to the site due to the HES worsening/flare are strongly recommended to visit their local physician and should provide the physician with their patient participation card containing study site contact information for health providers (Section 8.2.1). Unscheduled visits, for a reason other than HES worsening/flare, may be initiated as needed, and assessments may be performed as clinically indicated at the discretion of the investigator.

Patients will be maintained on a stable dose of background HES medication throughout the DB treatment period, unless modification is required for an HES clinical worsening/flare or an AE thought to be due to background therapy (Section 6.5.1). Background medications can be changed after a patient has their first HES worsening/flare.

Patients who prematurely discontinue IP will return to the study site within the recommended window of 4 weeks (± 7 days) after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on IPD was made later), and complete the IPD visit procedures (Section 7.1.1), and then continue in the study until the end of the DB treatment period (Week 24).

4.1.3 OLE Treatment Period (Week 24 to End of Treatment)

Patients who complete the DB treatment period on IP may be eligible to continue into the OLE treatment period on benralizumab. The first dose of the open-label benralizumab (30 mg SC Q4W) will be administered at Week 24 after completion of the Visit 9 assessments. The OLE treatment period is intended to allow patients treatment with open-label benralizumab for

at least 1 year for adults and at least 2 years for adolescents. AstraZeneca may choose to extend the study beyond 1 year and reserves the right of terminating the OLE early.

Patients will attend scheduled clinic visits at 4-week intervals throughout the OLE treatment period; however, to reduce patient burden and allow flexibility, patients will have the option to self-administer IP or have IP administered by their caregiver at home or at a remote location using an APFS after Visit 10/Week 28 (Section 6.1.5). For these patients, some visits do not include extensive onsite assessments and can optionally be performed as remote visits through telephone/telemedicine contact as indicated in the SoA (Table 2, Table 3, and Table 4).

When clinically indicated, a flare visit is used to assess the patient for potential HES worsening/flare. Mandatory procedures for flare visits are described in Table 2, Table 3, and Table 4. Additional assessments may be performed at these visits, at the discretion of the investigator. Patients not able to get to the site due to the HES worsening/flare are strongly recommended to visit their local physician and should provide the physician with their patient participation card containing study site contact information for health providers (Section 8.2.1). Unscheduled visits, for a reason other than HES worsening/flare, may be initiated as needed, and assessments may be performed as clinically indicated at the discretion of the investigator.

Patients will be maintained on a stable dose of HES medication for the first 12 weeks of the OLE treatment period (until Week 36/Visit 12). Background therapy for HES may be adjusted after this time (Section 6.5.1), unless a modification is required for an HES clinical worsening/flare or an AE thought to be due to background therapy.

Patients who prematurely discontinue IP will return to the study site within the recommended window of 4 weeks (± 7 days) after the last dose of IP, or as soon as feasible if this interval is missed (eg, if decision on IPD was made later), and complete the IPD visit procedures (Section 7.1.1), after which they will exit the study.

4.1.4 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 AstraZeneca 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 GCP, and minimize risks to study integrity.

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

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the patient's visit 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 patients. The investigator should confirm this with the designated study physician.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home 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.

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

4.2 Scientific Rationale for Study Design

The DB portion of the study is designed to compare the efficacy and safety of benralizumab to placebo while the OLE will provide an opportunity to assess long-term safety and tolerability of benralizumab in this patient population. The primary objective of this study is to assess the efficacy of benralizumab on the time to first HES worsening/flare in patients with symptomatic active HES on stable background HES therapy.

The study population is based on the findings from the previous investigator-initiated Phase II study (Kuang et al 2019). The primary endpoint, time to first HES worsening/flare, measures an endpoint of clinical relevance to patients and providers (the length of time the IP prevents worsening/flare of HES symptoms that require additional HES therapy and/or hospitalisation). Additionally, the proposed study design has the potential to minimise patients' exposure to ineffective treatment, as patients who discontinue IP at any time will be allowed to modify their HES background therapy and still be followed at study visits. It is expected that the majority of patients who discontinue IP and switch to other therapies would do so after an HES worsening/flare, and so the time to first HES worsening/flare is considered to be a meaningful endpoint that is least impacted by this potential switch.

The duration of the DB treatment period is planned as 24 weeks for each patient, which is expected to be sufficient time to capture enough HES worsening/flare events to detect a

statistically significant difference between benralizumab and placebo while simultaneously monitoring patients' safety. This expectation is based on the results of a randomised, DB, placebo-controlled, Phase II study evaluating the safety and efficacy of an anti-IL-5 mAb, mepolizumab, which was conducted in patients with HES who were negative for *FIP1L1-PDGFRA* fusion gene and required daily prednisone to maintain a stable clinical status and a blood eosinophil count of < 1000 cells/μL (Rothenberg et al 2008).

4.3 Justification for Dose

The approved dosing regimen of benralizumab in severe asthma is 30 mg Q4W for the first 3 doses, and then Q8W thereafter by SC injection. In the severe asthma studies (SIROCCO [Bleecker et al 2016] and CALIMA [Fitzgerald et al 2016]), near complete depletion of blood eosinophils was observed in patients receiving benralizumab 30 mg at both the approved Q8W regimen and the Q4W regimen, with both regimens demonstrating acceptable safety profiles. However, patients with HES generally have a greater blood and tissue eosinophil burden than patients with severe asthma. As detailed in Section 2.2, in an investigator-initiated Phase II study of patients with HES (Kuang et al 2019), benralizumab 30 mg Q4W was the regimen studied. The more frequent Q4W dose with higher serum concentration at steady state was effective in reducing blood and tissue eosinophilia in patients with varied clinical subtypes of HES, with an acceptable safety profile.

Given that depletion of eosinophils in the circulation as well as in the tissues of patients is considered important for control of HES, the proposed dosing regimen for benralizumab in this study is 30 mg SC Q4W. The PK/PD relationship of adolescents with asthma has been shown to be consistent with those of adults (SIROCCO [Bleecker et al 2016] and CALIMA [Fitzgerald et al 2016]), and given that PK/PD relationships are consistent across disease populations, the same benralizumab 30 mg SC Q4W will be given to adolescents with HES.

4.4 End-of-Study Definition

For the purpose of clinical trial transparency, 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 patient for any protocol-related activity.

Food and Drug Administration requirements define 2 completion dates:

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

In this study, a patient is considered to have completed the study when he/she has completed his/her last scheduled visit/telephone contact.

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

As patients will be offered the opportunity to participate in an OLE of at least 1 year for adults and at least 2 years for adolescents after completing the DB treatment period of the study on IP, the end of study is planned to be when the last randomised adult patient completes 1 year in the OLE on IP and the last randomised adolescent patient completes 2 years in the OLE on IP.

However, as AstraZeneca may choose to extend the OLE treatment period (Section 4.1), this decision will determine when the end of the study is declared. Notification of closure of the study will be communicated to sites at least 3 months in advance of the end of study, unless faster termination is warranted (eg, emergence of a safety concern).

Managed discontinuation of IP for ongoing patients at the end of the study is described in Section 7.

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

5 STUDY POPULATION

Prospective approval of protocol deviations to inclusion or exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study in order to be randomised to IP. 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 patients who have signed (or whose legally acceptable representative have signed) informed consent/assent. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients, see Section 7.1.2.

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

5.1 Inclusion Criteria

Informed Consent/Age/Gender

1 Provision of the signed and dated written informed consent of the patient or the patient's legally authorised representative, and informed assent from the patient (per local regulations) prior to any mandatory study-specific procedures, sampling, and analyses.

Note: The informed consent process is described in Appendix A 3.

2 Males and females 12 years of age and older at the time of signing the ICF.

Type of Patients and Disease Characteristics

3 Documented diagnosis of HES (history of persistent eosinophilia > 1500 cells/µL without secondary cause on 2 examinations [interval ≥ 1 month; Valent et al 2012] and evidence of end organ manifestations attributable to the eosinophilia).

4 Documented negative testing for the *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation.

5 Stable HES treatment dose(s) and regimen for ≥ 4 weeks at the time of Visit 1 (see Section 6.5.1).

6 Signs or symptoms of HES worsening/flare and/or laboratory abnormalities indicative of HES worsening/flare (other than isolated eosinophilia) at Visit 1

OR

A documented history of 2 or more HES worsening/flares within 12 months prior to Visit 1 requiring an escalation in therapy.

- At least one flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare.

7 AEC ≥ 1000 cells/µL at Visit 1 (assessed by local laboratory).

8 Corticosteroid responsiveness defined as an AEC < 1000 cells/µL after a 2-day course of OCS (prednisone/prednisolone) 1 mg/kg/day at Visit 2 (assessed by local laboratory). Other OCSs in equivalent doses are permitted (Appendix I).

Reproduction

9 WOCBP must agree to use a highly effective method of birth control (confirmed by the investigator) from enrolment, throughout the study duration, and within 12 weeks after last dose of IP and have a negative urine dipstick pregnancy test result on Visit 1.

Highly effective methods of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

(a) Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal,

(b) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable,

(c) Intrauterine device,

(d) Intrauterine hormone-releasing system,

(e) Bilateral tubal occlusion,

(f) Sexual abstinence, ie, 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),

(g) Vasectomised sexual partner (provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomised partner has received medical assessment of the surgical success).

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

(a) Women < 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels are in the postmenopausal range. Until FSH is documented to be within menopausal range, the patient should be treated as a WOCBP.

(b) Women ≥ 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

Other

11 French patients: In France, a patient will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

5.2 Exclusion Criteria

Medical Conditions

1 Life-threatening HES and/or HES complication(s) as judged by the investigator:

(a) Medical intervention for HES-related life-threatening event(s) within 12 weeks prior to randomisation.

(b) History of thrombotic complications, stroke, or significant cardiac damage related to HES, if the respective events were life threatening and currently represent a risk of life-threatening disease complications. Events that occurred in the past but considered resolved or stable, can be accepted if, as per investigator's judgment, participation in the study will not put the patient at risk.

(c) Disease severity that in the opinion of the investigator makes the patient inappropriate for inclusion in the study.

2 Presence of *FIP1L1-PDGFRA* fusion tyrosine kinase gene translocation or other known imatinib-sensitive mutation.

3 Definitive diagnosis of eosinophilic granulomatosis with polyangiitis.

4 Known, preexisting, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological, respiratory, or any other system abnormalities that are not associated with HES and are uncontrolled with standard treatment 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 patient's ability to complete the entire duration of the study.

5 Hypereosinophilia of unknown significance.

6 Cardiovascular: Documented history of any clinically significant cardiac damage, clinically significant echocardiography (if available) or ECG findings within 12 months prior to Visit 1 or clinically significant ECG findings at screening that in the opinion of the investigator may put the patients at risk.

7 Known currently active liver disease.

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

(b) ALT or AST level $\geq 3 \times$ ULN during the screening period (AST or ALT $> 5 \times$ ULN if documented HES with liver manifestations). Transient increase of AST/ALT level that resolves by the time of randomisation is acceptable if, in the investigator's opinion, the patient does not have an active liver disease and meets other eligibility criteria.

8 Current or history of malignancy within 5 years before the screening visit with the following exceptions:

(a) Patients treated for in situ carcinoma of the cervix who have completed curative therapy and are in remission for at least 12 months prior to signing the informed consent and

(b) Patients with basal cell or superficial squamous skin cancer.

(c) 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 the date informed consent was obtained.

9 Diagnosis of systemic mastocytosis.

10 Chronic or ongoing active infections requiring systemic treatment, as well as clinically significant viral, bacterial, or fungal infection within 4 weeks prior to Visit 1.

11 A helminth parasitic infection diagnosed within 24 weeks prior to Visit 1 that has not been treated or has failed to respond to standard of care therapy. A confirmation of a complete resolution of any helminth parasitic infection prior to Visit 1 should be available.

12 A history of known immunodeficiency disorder other than that explained by the use of OCS or other therapy taken for HES. Positive HIV test.

13 Any clinically significant abnormal findings in HES physical examination, vital signs, haematology, or clinical chemistry, during the screening 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 patient's ability to complete the entire duration of the study.

Prior/concomitant Therapy

14 Evidence of prior benralizumab treatment failure.

15 Treatment with injectable (SC, IV, or IM) corticosteroids in the 4-week period prior to randomisation.

16 Receipt of any IP within the past 30 days or 5 half-lives, whichever is longer, prior to Visit 1, or current participation in any other interventional clinical study (with the exception of "registry"/"cohort" trials that may include periodic biological sampling and/or patient questionnaires but in which no other unlicensed IP is administered).

17 Receipt of any marketed or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer. Patients on stable therapy for at least 3 months before randomisation who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study.

18 Receipt of live attenuated vaccines 30 days prior to Visit 1.

Other Exclusions

19 History of hypersensitivity (including anaphylaxis) to any biologic therapy (including benralizumab) or any steroid or steroid-containing product. Known history of allergy or reaction to any component of the IP formulation.

20 Receipt of Ig or blood products within 30 days prior to Visit 1.

21 Patients with a known or suspected history of alcohol or substance abuse at Visit 1, which in the opinion of the investigator, could interfere with the patient's proper completion of the protocol requirements.

22 For women only: Currently pregnant, breastfeeding, or lactating women

(a) Both urine and serum pregnancy tests will be done for WOCBP at Visit 1. If serum test is positive, the patient should be excluded.

5.3 Criteria to be Confirmed/Reconfirmed Prior to Randomisation (Visit 3)

All inclusion/exclusion criteria must be verified prior to randomisation. The following assessments must be performed during the screening period and results must be in place by Visit 3.

- **Local laboratory:**
  - AEC ≥ 1000 cells/µL at Visit 1 (inclusion criterion 7).
  - Corticosteroid responsiveness: AEC < 1000 cells/µL at Visit 2 (inclusion criterion 8).
  - Laboratory abnormality: No evidence of clinically significant abnormality in the haematological or clinical chemistry screen at Visit 1, as judged by the investigator (exclusion criterion 13).
  - Negative local express HIV test result.
  - Liver function tests: Obtained at Visit 1 and on repeat testing prior to Visit 3 if needed (exclusion criterion 7):
    - ALT ≥ 3 × ULN (ALT > 5 × ULN if documented HES with liver manifestations).
    - AST ≥ 3× ULN (AST > 5 × ULN if documented HES with liver manifestations).
- **ECG:** No evidence of clinically significant abnormality from the ECG performed at Visit 3 (exclusion criterion 6).

5.4 Lifestyle Considerations

Restrictions on strenuous exertion and dietary considerations are required prior to spirometry measurements, as described in Section 8.10.2.

Women of childbearing potential must use highly effective contraceptive methods from enrolment throughout the study and at least for 12 weeks after last administration of the IP, as stated in inclusion criterion 9, Section 5.1.

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent/assent and for 12 weeks after last dose of IP.

5.5 Screen Failures

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

These patients should have the reason for study withdrawal recorded as 'screen failure' (ie, patient does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures and not randomised patients.

5.5.1 Rescreening

Rescreening is allowed only once for a patient not meeting corticosteroid responsiveness criteria after discussions and approval from the AstraZeneca study physician/designee.

For all other patients, if the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits, transient events during the screening period that contraindicate IP administration, AEC < 1000 cells/µl at Visit 1), patients may be rescreened more than once. These cases should be discussed with AstraZeneca study physician/designee prior to rescreening and appropriately documented.

To be considered for rescreening, the patient must meet all eligibility criteria, including being on a stable dose and regimen of background HES treatment for ≥ 4 weeks at the time of Visit 1 (Section 6.5.1). For this reason, patients who fail to demonstrate steroid responsiveness cannot be rescreened for at least 4 weeks after the date of the first screen failure.

A documented approval for rescreening should be filed in the investigator study file.

Rescreened patients should be assigned the same patient number as for the initial screening, meaning that the patient should keep the same E-code as was originally assigned.

Rescreened patients should sign a new ICF/assent. All procedures from the screening period should be repeated.

6 STUDY INTERVENTION

Study intervention is defined as any IP(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study patient according to the CSP. Study intervention, or IP, in this study refers to benralizumab or placebo.

The IP will be administered Q4W from randomisation/baseline (Visit 3) until Week 20/Visit 8 in a DB fashion. Those patients who complete the DB treatment period on IP, may be eligible to receive OLE benralizumab administered Q4W from Week 24/Visit 9 until the end of the study.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Descriptions of the study interventions (ie, IPs) are provided in Table 7. Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution.

Table 7 Study Interventions

	Benralizumab	Placebo
Intervention name	Benralizumab	Matching placebo
Dosage formulation	Benralizumab 30 mg/mL solution for injection in an APFS, 1-mL fill volume	Matching placebo solution for injection in an APFS, 1-mL fill volume
Route of administration	SC injection	SC injection
Dosing instructions	Benralizumab active solution will be administered to patients by HCPs, patients, or their caregivers using an APFS. Refer to Section 6.2.	Placebo solution will be administered to patients by HCPs using an APFS. Refer to Section 6.2.
Packaging and labelling	Study treatment will be provided in an APFS and will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The label will be translated into local languages where applicable and required by local regulations. The label will include the following information: • Study code • IP/study treatment dosage form, route of administration, and quantity of dosage units • Kit ID assigned by IWRS; each kit contains one syringe • Packing lot ID	Study treatment will be provided in an APFS and will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The label will be translated into local languages where applicable and required by local regulations. The label will include the following information: • Study code • IP/study treatment dosage form, route of administration, and quantity of dosage units • Kit ID assigned by IWRS; each kit contains one syringe • Packing lot ID

Table 7 Study Interventions

	Benralizumab	Placebo
	• Expiry date • Investigator name (to be written on the label) • Enrolment number (to be written on the label); patient is identified with this unique E-code • Sponsor name and contact details • Directions for use • Storage condition • Standard statements required	• Expiry date • Investigator name (to be written on the label) • Enrolment number (to be written on the label); patient is identified with this unique E-code • Sponsor name and contact details • Directions for use • Storage condition • Standard statements required

APFS = accessorised prefilled syringe; GMP = good manufacturing practice; HCPs = health care professionals; ID = identification; IP = investigational product; IWRS = interactive web response system; SC = subcutaneous(ly)

6.1.2 Medical Devices Including Combination Products with a Device Constituent

The AstraZeneca manufactured combination product with a device constituent provided for use in this study is:

- Benralizumab APFS (status: investigational)

Other medical devices (not manufactured by or for AstraZeneca) provided for use in this study are:

- Spirometer
- ECG

Both spirometer and ECG machine are provided by a central vendor and have regulatory approval for their intended use(s) within this study.

Instructions for medical device use are provided in the Instructions for Use for the AstraZeneca manufactured combination product with a device constituent and the device manuals provided by the vendor for third-party devices. The benralizumab APFS instructions for use are located in the pharmacy manual, and the ECG and spirometer instructions are located in the study manual.

All medical device deficiencies and device constituent deficiencies (including malfunction, use error, and inadequate labelling), hereafter referred to as medical device deficiencies, shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.11) and appropriately managed by AstraZeneca.

6.1.3 Investigational Product Administration

Before IP Administration

All applicable visit procedures, including sample collection, should be completed prior to IP administration. If the patient cannot tolerate a particular procedure during the visit (eg, spirometry), IP can be administered, and the procedure should be rescheduled for a different date, preferably within the visit window. No procedures should be performed after the dosing on the day of IP administration. The PK and ADA samples must always be collected before IP administration.

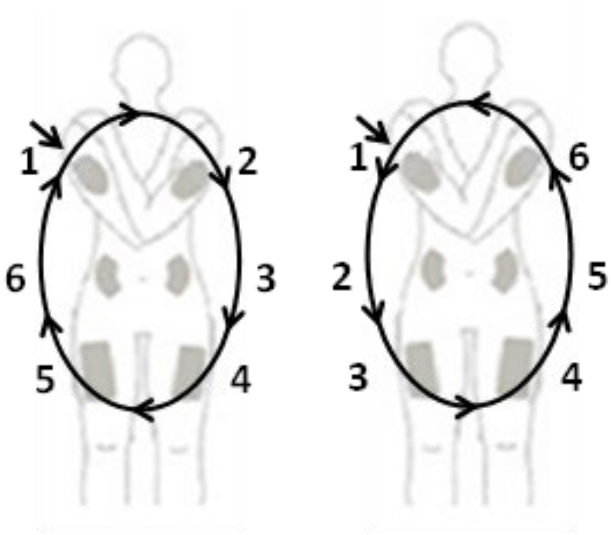
Prior to each IP administration:

- The investigator or designee will evaluate the patient's condition for potential contraindications for IP administration (Section 6.5.3).
- The investigator or designee will assess the injection site as per standards of medical care.

IP Administration

The IP will be administered SC as a single injection via the APFS by the investigator, or designee. It is advised that the site of IP injection be rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (Figure 2). The injection site must be documented in the source at each treatment visit and recorded in the eCRF. The date and time of all IP administrations, as well as any missed doses, should be recorded in the appropriate section of the eCRF.

Figure 2 Injection Sites and Examples of Rotation Schema



If rotation of the injection site is not possible, the reason for this must be documented in the source.

The specific details for IP administration are provided in the IP handling instruction. The IP administration must be carried out in line with these instructions.

After IP Administration

After IP administration at the study site, the patient should be observed for potential acute drug reactions in line with clinical practice. When patients or their caregivers administer IP at home or at a remote location, the investigator or qualified designee is encouraged to contact the patient after the dose administration for the possibility of acute reactions in line with clinical practice.

6.1.4 Investigational Product Administration Rescheduling

Every effort should be taken to keep IP administration within the scheduled window.

If a patient presents with a condition that contraindicates IP administration, IP will be withheld and administered as soon as possible after the contraindicating condition resolves.

The IP should not be administered, and the dosing is to be rescheduled in the presence of the following conditions:

- An intercurrent illness that in the opinion of the investigator may compromise the safety of the patient.
- Signs of a clinically significant infection. Benralizumab should not be administered to a patient with a clinically significant active infection treated with oral or IV antimicrobials, antivirals, or antifungals until it is confirmed by the investigator that the infection has resolved.
- Any event or laboratory abnormality that in the opinion of the investigator or AstraZeneca contraindicates IP dosing or could result in complications.

It is recommended that AstraZeneca study physician or designee be contacted in case of any questions.

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.

Rescheduled IP dose can then be administered at an unscheduled visit. Physical examination and vital signs assessments are the minimum procedures to be performed at this visit. 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 (eg, the patient is unable to attend the study site), then the entire visit will be rescheduled along with IP dose.

If a dose is significantly delayed, it is recommended to keep at least a 2-week 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 always be calculated from randomisation visit date.

If a patient misses more than one dose of IP during the DB treatment period, or more than 2 doses of IP (consecutively or non-consecutively) at any time within a calendar year during the OLE treatment period, it is recommended that a conversation between the investigator and sponsor study physician/designee takes place to review the patient's adherence to treatment and decide on the patient's further disposition.

6.1.5 Optional Self-Administration of Investigational Product

To reduce patient burden and to allow flexibility, patients will have the option to self-administer IP or have IP administered by their caregiver at home or at a remote location using the APFS after Visit 10, where allowable by local health authorities and ethics committees. The investigator/designee must evaluate the patient and/or their caregiver to ensure they are capable of performing the IP self-administration and provide them with appropriate training. All necessary supplies and instructions for administration will be provided.

After Visit 10, some visits do not include extensive onsite assessments and can optionally be performed as remote visits through telephone/telemedicine contact (Table 2, Table 3, and Table 4) for patients who opted for IP self-administration. IP kits for the remote visits may be dispensed starting from Visit 10/Week 28) as described in 'Study Instructions for Self-Administration of Investigational Product by the Patient and/or Caregiver'. After Visit 10, mandatory onsite visits will occur quarterly, and patients may be dispensed IP kits to perform self-administration in between. Urine pregnancy tests will be performed onsite per the SoA.

If the IP is administered by the patient or their caregiver, IP should be administered on the day of a scheduled visit after all remote visit assessments are completed.

The investigator or designee will conduct a telemedicine contact prior to IP self-administration to confirm that the patient does not have any contraindications for IP dosing. A WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.

It is strongly recommended that the patient is contacted by the investigator or qualified designee after the dose is administered to evaluate for any potential acute reactions in line with clinical practice. Any AEs reported by the patient should be recorded in source documents and entered in the eCRF.

Refer to the 'Study Instructions for Self-Administration of Investigational Product by the Patient and/or Caregiver' for step-by-step guidance including investigator assessment/training of patient and/or caregiver and drug accountability.

The option of self-administration of IP will only be available in countries where allowed according to local regulations.

The site can at any time invite the patient for an onsite visit instead of an at-home visit or for an onsite unscheduled or flare visit, as necessary, and perform additional unscheduled assessments in case of medical need.

6.1.6 Sponsor-provided Oral Corticosteroids for Assessment of Corticosteroid Responsiveness

All patients who meet eligibility criteria will receive a 2-day course of OCS (prednisone/prednisolone) at a dose of 1 mg/kg/day to assess corticosteroid responsiveness (as described in Section 4.1.1). Other OCSs in equivalent doses are permitted (Appendix I). This OCS is not regarded as IP but can be reimbursed/provided by AstraZeneca on request according to local regulations. This dose will be given on top of the patient's regular background HES therapy.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation and Handling of Investigational Product

Up to and including Visit 10, the IP will be administered at the study site on treatment visits and within the visit windows as specified in the SoA (Table 1 and Table 2). After Visit 10, IP may be administered within the treatment window as described in Table 2, Table 3, and Table 4 either onsite by an HCP or optionally administered 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 6.1.5).

The IP will be supplied to the site in a kit with an APFS of either benralizumab or placebo. Each kit will have a unique identification that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Only patients enrolled in the study may receive IP and only authorised site staff or trained patients/caregivers may dispense and administer IP.

6.2.2 Shipping and Storage

All shipments of IP include a data logger, which will allow the investigator or designee to confirm that appropriate temperature conditions have been maintained during transit for all IP received. Any discrepancies must be reported and resolved before use of the IP.

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

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

Damaged IP should be documented using an IWRS/IVRS (please refer to IWRS/IVRS manual for further details).

All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container. The IP must be kept under conditions specified on the label (between 2°C to 8°C [36°F to 46°F] and protected from light), with access limited to the investigator and authorised site staff. The temperature should be monitored daily and documented in the temperature monitoring log.

6.2.3 Accountability

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

A Sponsor site monitor will account for all IP received at the site, for unused IP, and for appropriate destruction of unused study treatments. Any unused kits will be destroyed locally (for further details, refer to the pharmacy manual). Documentation of IP delivery and destruction should be maintained according to applicable Sponsor and institution procedures.

Further guidance and information for the final disposition of unused study treatment are provided in the pharmacy manual (provided to the sites). In the case of a malfunctioning IP APFS/device, the site should contact the study monitor to initiate a product complaint process according to applicable guidelines.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Methods for Assigning Treatment Groups

Randomisation will occur at Visit 3. All eligible patients will be centrally randomly assigned in a 1:1 ratio to receive either benralizumab or placebo. Randomisation will be done using an IWRS/IVRS. The telephone number and call-in directions for the IVRS and/or the login information and directions for the IWRS will be provided to each site prior to the study initiation.

The investigator(s) will:

At Visit 1:

1 Obtain signed informed consent/assent from the potential patient before any study-specific procedures are performed.

2 Assign the potential patient a unique enrolment number (which begins with an 'E' [referred to as E-code]) via the IWRS.

3 Confirm whether the patient consented to participate in the optional genomics initiative research.

4 Confirm whether the patient consented to participate in the mechanistic sub-study (whole blood for eosinophil phenotyping will be selected sites only, whilst all other blood samples, including whole blood for DNA analysis, will be from all sites).

5 **At Visit 3:**

1 Determine patient eligibility for randomisation at Visit 3.

2 Confirm corticosteroid responsiveness: AEC < 1000 cells/μL at Visit 2.

3 Confirm whether the patient consented to participate in the Patient Qualitative Interview Sub-study (applicable only for sites participating in the Patient Qualitative Interview).

4 Randomise the eligible patient at Visit 3 via the IWRS/IVRS, which will assign the patient with a unique randomisation code.

Patients will be allocated to treatment groups at a 1:1 ratio. The randomisation will be stratified by geographic region (North America, Europe, Asia, and Rest of the World) and HES flare status at screening.

Randomisation codes will be assigned strictly sequentially in each stratum as patients become eligible for randomisation. The randomisation code will be assigned from a randomisation list prepared by a computerised system provided on behalf of AstraZeneca.

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

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

6.3.2 Methods for Ensuring Blinding – DB Treatment Period

The first 24 weeks of this study are a DB treatment period. During this portion of the study, benralizumab and placebo will not be visually distinct from each other. All packaging and labelling of the IP will be done in such a way as to ensure blinding for all sponsor and investigational site staff. Neither the patient nor any of the investigators or sponsor staff who are involved in the treatment, clinical evaluation, and monitoring of the patients will be aware

of the treatment received. Since benralizumab and placebo are not visually distinct, IP will be handled by an appropriately qualified member of the study team (eg, pharmacist, investigator, or designee) at the site.

A site monitor will perform IP accountability. In the event that the treatment allocation for a patient becomes known to the investigator or other study staff involved in the management of study patients or needs to be known to treat an individual patient for an AE, AstraZeneca must be notified promptly by the investigator and before unblinding (if possible).

The following personnel will have access to the randomisation list during the study, prior to the primary DBL:

- Those generating the randomisation list
- Personnel at the IXRS company
- The AstraZeneca supply chain department
- Drug safety services representatives (data entry site case handlers)
- Bioanalytical laboratory performing the PK sample analysis
- The independent statistical data analysis centre, which prepares data for the DSMB presentations
- Unblinded programmer
- Unblinded medical monitor

The information in the randomisation list will be kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at AstraZeneca, or any CRO handling data, will have access to the randomisation scheme during the conduct of the study.

6.3.2.1 Maintaining the Blind to the Patient's Eosinophil Counts

While not entirely specific, patients on active benralizumab treatment are expected to have lower eosinophil and basophil counts than patients on placebo. The following procedures to mitigate unblinding on this basis will be in place for each patient from randomisation/baseline (Visit 3/Week 0), during the entire DB treatment period, and for the first 4 weeks of the OLE treatment period (until Visit 10/Week 28 after which no blinding to WBC counts or biopsy cell counts is required):

- Haematology will be run by the central laboratory. Eosinophil and basophil absolute counts will be redacted from the full haematology reports sent back to the investigative sites. Because complete knowledge of the differential (percentage) for WBCs could permit estimation of the 'eosinophil + basophil' compartment, the, absolute monocyte count, and differential (percentage) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) will also be redacted from the full haematology reports

sent back to the investigative sites. Only the total WBC and absolute count for neutrophils and lymphocytes will be visible to investigators in the central laboratory haematology reports.

- If the investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if haemoglobin is desired, the investigator should avoid ordering a complete blood cell count with a differential count. Investigators are encouraged to order any unscheduled haematology tests from the central laboratory to avoid accidental exposure to WBC differential results as described above.
- In cases of medical emergency (eg, life-threatening condition), when the knowledge of an eosinophil and basophil absolute counts, absolute monocyte count, or differential (percentages) for WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) is absolutely necessary for managing of immediate safety issues, the investigator may order these tests as per regular site practice. AstraZeneca should be notified of all such cases.
- Site staff who are directly involved in the patient's management should remain blinded to any eosinophil and basophil absolute counts, absolute monocyte count, and differential (percentages) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management to receive and blind eosinophil and basophil absolute counts, absolute monocyte count, and differential (percentages) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) results prior to the report being handed over to the site staff involved in the patient's management and prior to filing the laboratory report as a source document. Similarly, eosinophil and basophil absolute counts, absolute monocyte count, and differential (percentages) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) results must be redacted from all communications with AstraZeneca.
- Tissue biopsies: Site staff who are directly involved in the patient's management should remain blinded to cell counts from any tissue biopsy (Section 8.9.1). To ensure the blind, all information pertaining to cell counts will be redacted from central biopsy reports sent to the study sites. Local review of unscheduled biopsies is allowed only after Visit 10/Week 28 unless needed to address an immediate safety concern. In rare instances where local review of biopsy is required before Visit 10, prior permission from AstraZeneca is required. All necessary precautions including redaction of the report (see above bullet points) to maintain the blinding should be exercised.

After the primary DBL, AstraZeneca will become unblinded to all patients' blood and biopsy cell counts obtained during the DB treatment period. The site and patients will remain blinded after the primary DBL (ie, study conduct at the site and patient level remains the same throughout the DB period).

6.3.3 Methods for Unblinding – DB Treatment Period

The IWRS/IVRS will provide to the investigator(s) or pharmacists the kit ID number to be allocated to the patient at the dispensing visit.

Routines for this will be described in the IWRS/IVRS user manual that will be provided to each 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 will document and report the action to AstraZeneca, without revealing the patient's treatment randomisation to AstraZeneca staff.

Emergency unblinding should also be available to a third-party physician/medical professional who is not participating in the study (eg, staff in a hospital's ER). As soon as possible, the investigator should first contact the study physician to discuss the medical emergency and the reason for revealing the actual treatment received by that patient; however, this may not be mandatory and should not cause any delay in unblinding in case of emergencies. The treatment assignment will be unblinded by the investigator through IWRS.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to IP and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.3.4 OLE Period – Benralizumab Administration Only

Patients will keep the same patient number in the OLE as assigned in the DB treatment period of the study. Open-label IP administration will begin at Week 24/Visit 9. The IWRS/IVRS will continue to allocate IP kit number for each dosing visit of the OLE.

6.4 Study Intervention Compliance

The administration of all study treatments (both in the DB and OLE treatment periods of the study) 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 CSP.

The IP will be administered at the study site on treatment visits and within visit windows as specified in the SoA (Table 1, Table 2, Table 3, and Table 4). Any change from the dosing schedule, dose interruptions, or dose discontinuations must be recorded in the eCRF; dose modifications are prohibited. Sites should call patients 1 to 2 days before each visit to remind the patient of the visit.

If a patient misses more than one dose of IP during the DB treatment period, or more than 2 doses of IP (consecutively or non-consecutively) at any time within a calendar year during the OLE treatment period, it is recommended that a conversation between the investigator and

Sponsor study physician/designee takes place to review the patient's adherence to treatment and decide on the patient's further disposition.

6.5 Concomitant Therapy

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

Investigator, or designee, will collect and record information about concomitant medications as follows:

- All background HES therapy (eg, methotrexate, OCS, treatments to control HES symptoms, etc.) and treatment for HES worsening/flares in the 12 months prior to Visit 1
- All other medications taken for any reason in the 3 months prior to Visit 1
- Concomitant treatments given during the study (at each study visit)

6.5.1 HES Background Therapy

The aim of this study is to establish the treatment effect of benralizumab as an add-on to HES background therapy.

Background therapies for HES may include OCS, immunosuppressive/cytotoxic agents, IFN-α, and other agents used to control HES, and/or manage HES symptoms (eg, topical or nasal steroids, inhaled medications, etc.). Background therapies for HES that patients receive as standard of care before and during the study are not regarded as IP and will not be provided or reimbursed by AstraZeneca.

All patients are required to be treated with background therapy for HES on a stable dose and regimen for ≥ 4 weeks prior to Visit 1.

In the rare instance that a patient is on no HES background treatment for ≥ 4 weeks prior to Visit 1 (eg, due to failed treatment in the past, tolerability issues, lack of efficacy, etc.) the investigator should clearly document the justification for not receiving background therapy despite the need and capture failed treatment details including the dates and reasons for failure in the patient's notes.

Background HES therapy should remain stable from Visit 1, throughout the screening period and the DB treatment period, and for the first 12 weeks of the OLE treatment period (until Visit 12/Week 36), unless a modification is required for a HES clinical worsening/flare or an AE thought to be due to background therapy. Background medications can be changed after a

patient has their first HES worsening/flare. For patients who enter the OLE, background therapy may be adjusted after Visit 12/Week 36. Minor changes between the formulations and devices are allowed provided that the patient remains on a stable (or equivalent) dose and regimen.

In a rare instance that a patient is on no background treatment as described above, they should remain on the same regimen (eg, no treatment) from Visit 1 and throughout the study until they reach Visit 12/Week 36), unless they experience an HES worsening/flare at which time treatment can be initiated as medically necessary.

A decrease in background therapy before Visit 12/Week 36) below baseline dose(s) at Visit 1 is discouraged unless there is a concern the medication is causing an AE.

For patients who have discontinued IP and continue in the study off IP (Section 7.1.1), changes to a patient's background therapy may be allowed if judged medically necessary by the investigator and the prohibited and restricted medications requirements in this section no longer apply.

See Table 8 for medication restrictions.

6.5.2 Other Concomitant Medication

Medication other than that described in Section 6.5.1 (HES therapy), which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.5.3 Restrictions

The medication restrictions that apply during the study are summarised in Table 8. If a patient needs treatment with any restricted or prohibited medication, or requires changes in background HES therapy, the investigator should contact the AstraZeneca study physician/designee to discuss justification.

Unless specifically indicated, all conditions apply from enrolment (Visit 1) throughout the study duration (the end of the OLE).

The medication restrictions in Table 8 may be waived for patients who have discontinued IP if the treatment is considered medically necessary by the investigator.

Table 8 Allowed, Restricted, and Prohibited Medications

Medication/class of drug	Usage (including limits for duration permitted and special situations in which it is allowed)
Immunosuppressive therapy	Stable background OCS therapy and other immunosuppressive medications for HES maintenance are allowed (Section 6.5.1). Additional immunosuppressive medications or changes in dose of current immunosuppressive therapy is not allowed except to treat HES worsening/flare or AEs where no alternative treatment is available (see Section 6.5.1 for treatment change limitations until Visit 12/Week 36).
Injectable (SC, IV, or IM) corticosteroids	Not allowed in the 4-week period prior to randomisation or during the study except to treat HES worsening/flare.
Dermal topical steroids, nasal steroids, topical ophthalmic and otic corticosteroids; other topical immunosuppressive medications	Allowed at the discretion of the investigator (see Section 6.5.1 for treatment change limitations until Visit 12/Week 36).
Live attenuated vaccines	Not allowed within 30 days prior to Visit 1, during the treatment period, and for 12 weeks after the last dose of the IP.
Inactive/killed vaccinations (eg, inactive influenza)	Not recommended within the 7 days before or within 7 days after any IP dosing study visit.
Any IP	Not allowed within 30 days or 5 half-lives (whichever is longer) prior to Visit 1, during the treatment period, and is not recommended within 12 weeks after the last dose of the IP.
Any biologic product (monoclonal or polyclonal antibody)	Not allowed within 4 months or 5 half-lives (whichever is longer) prior to Visit 1, during the treatment period, including treatment for HES worsening/flare, and is not recommended within 12 weeks after the last dose of the IP. Patients on stable therapy for at least 3 months before randomisation who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study (AstraZeneca should be informed when COVID-19 prevention or treatment is utilised).
Allergen immunotherapy	Allowed if on stable maintenance regimen during the treatment period. Should not be given on the same day as IP administration.

AEs = adverse events; COVID-19 = coronavirus disease 2019; HES = hypereosinophilic syndrome; IM = intramuscular; IP = investigational product; IV = intravenous; OCS = oral corticosteroids; SC = subcutaneous(ly)

6.6 Dose Modification

Modification of the dose (benralizumab or placebo) is not permitted. Management of missed doses is covered in Section 6.1.4.

6.7 Intervention After the End of the Study

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

6.8 Treatment of Overdose

No clinical data regarding overdose are available. Doses of up to 200 mg of benralizumab were administered SC in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities.

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

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

In the event of an overdose, the investigator should:

- Evaluate the patient to determine, in consultation with the study clinical lead, if possible, whether IP should be interrupted.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities as medically appropriate. Refer to Section 8.4.10 for details of AE/SAE reporting related to overdose.

7 DISCONTINUATION OF STUDY INTERVENTION AND PATIENT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Before a decision to discontinue a patient from IP (study intervention) is instituted, the AstraZeneca study physician/designee should be consulted regardless of the reason for discontinuation. In case of safety concerns, it is recommended that IP administration be withheld until the final decision is made.

If any of the following criteria are met, IP should be withheld, and a conversation between the investigator and Sponsor study physician/ designee is to take place to determine 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.

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment. The patient should always be asked about the reason(s) and presence of any AEs.
- AE that in the opinion of the investigator contraindicates further dosing.

- Severe non-compliance with the CSP.
- Risk to patient as judged by the investigator or AstraZeneca.
- IP unblinding.
- Development of any of the following study-specific criteria for discontinuation:
  - Anaphylactic reaction requiring administration of epinephrine.
  - Development of helminth parasitic infestation requiring hospitalisation.
  - A respiratory-related event requiring more than 3 days of invasive mechanical ventilation.
  - Patient experiences severe organ damage due to HES or life-threatening HES worsening/flare as judged by the investigator.

The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF. Conditions that require administration of IP to be temporarily withheld are described in Section 6.1.4.

Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study. Patients discontinuing from IP are strongly encouraged to continue in the study (without IP administration) up to the study completion as described in Section 7.1.1.

7.1.1 Procedures for Early Discontinuation of Study Intervention and at End of Study

A patient who decides to discontinue IP should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Patients permanently discontinuing IP administration should be given locally available standard-of-care therapy, at the discretion of the investigator. Patients who discontinue IP at any time will be allowed to modify their HES background therapy and still be followed at study visits. Discontinuation of IP will be registered in IWRS/IVRS.

See the SoA (Table 1, Table 2, Table 3, and Table 4) for data to be collected at the IPD or EOT visit and for any further evaluations that need to be completed. The EOT visit is only used for ongoing patients following the last dose of IP when AstraZeneca declares the end of the study (Section 4.4). The IPD visit is used in all other cases when a patient discontinues IP.

7.1.1.1 Early Discontinuation of Study Treatment

All patients who prematurely discontinue IP (during either the DB or OLE treatment periods) should return to the study site for an IPD visit 4 weeks (± 7 days) after the last dose of IP for procedures, or as soon as feasible if this interval is missed (eg, if decision on IPD was made later), as described in Table 1, Table 2, Table 3, and Table 4. Reasons for patients not electing to go into the OLE will be collected.

IPD During DB Treatment Period

Patients who prematurely discontinue IP during the DB treatment period will attend an IPD visit 4 weeks (± 7 days) after the last IP dose or as soon as feasible if this interval is missed (eg, if decision on IPD was made later); procedures are described in Table 1.

At the IPD visit, the patient will be offered the following options for further follow-up:

- Patients are encouraged to return to all scheduled site visits and perform all procedures/blood draws, but without IP administration, until the end of the DB treatment period (Week 24/Visit 9), at which point the patient will exit the study.
- If the patient is unwilling or unable to attend the scheduled site visits until the end of the DB treatment period, he/she will be offered a follow-up option that includes monthly telephone contact instead. During follow-up telephone contact, the investigator will collect information about concomitant medications, including OCS use, information on HES worsening/flare, and AE/SAE(s) (Section 8.4). Patients will continue to have telephone contact until the end of the DB treatment period (Week 24/Visit 9), at which point the patient will exit the study.
- Patients who discontinue IP during the DB treatment period and are unwilling to attend scheduled visits or have telephone contact will exit the study after completion of the IPD visit.
- Patients who completed the DB period on treatment but are ineligible or unwilling to enter the OLE will have an IPD visit, after which they will exit the study.

IPD During OLE Treatment Period

Patients who discontinue IP during the OLE treatment period will attend the IPD visit 4 weeks (± 7 days) after the last IP dose, or as soon as feasible if this interval is missed (eg, if decision on IPD was made later), after which they will exit the study; procedures are described in Table 2, Table 3, and Table 4.

7.1.1.2 End of Treatment Upon Notification of Closure of Study

The EOT visit (4 weeks [± 7 days] after the last dose of IP) should be performed (Table 2, Table 3, or Table 4) for all ongoing patients within 3 months of notification from AstraZeneca of closure of the study (Section 4.4). The IPD visit is used in all other cases when a patient discontinues IP during the OLE period.

7.1.2 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 IP. 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 and must be withdrawn (screen failed) from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on IP, the investigator should inform AstraZeneca study physician/designee immediately, and a discussion should occur between AstraZeneca study physician/designee and the investigator regarding whether to continue or discontinue the patient from IP.

If the agreed decision is to discontinue IP, patients should be encouraged to remain in the study and continue to be followed-up until the end of the DB treatment period (Section 7.1.1).

The decision to discontinue/continue IP must be appropriately documented, including rationale, particularly if the agreed decision is to continue IP treatment.

7.2 Withdrawal from the Study

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

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. It is the investigator's responsibility to fully evaluate the patient upon discontinuation or withdrawal to ensure that the patient receives appropriate treatment according to his/her clinical status/condition. An IPD visit is essential to collect study data and monitor for patient's safety as described in the SoA (Table 1, Table 2, Table 3, and Table 4). The withdrawal visit (IPD assessments) should take place as soon as the patient notifies the investigator, or designee, of intent to withdraw consent, without the need to wait until 4 weeks after the last dose. In this instance, no further follow-up is expected as the patient has withdrawn from the study prematurely.

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

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

If the patient only withdraws consent for use of exploratory samples, or the retention of biological samples for future exploratory use, the patient will not be withdrawn from the study.

Withdrawal of consent from the study must be ascertained and documented by the investigator and recorded in the eCRF as well as in the ICF.

7.2.1 Discontinuation or Suspension of the Whole Study Program

If AstraZeneca decides to prematurely terminate or suspend the study, the investigator and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The investigator will immediately notify the decision to the

patients and, if relevant, give appropriate medical treatment, take necessary measures, and document these in the source notes.

7.3 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 patient being lost to follow-up, it is recommended that the study sites maintain up-to-date contact details for patients, including next of kin or other emergency contacts (if allowed by national regulation).

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 site for required study visits:

- 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. At this time, ascertain whether the patient should or wishes to or continue in the study.
- Before a patient is deemed lost to follow-up, repeated attempts must be made to regain contact with the patient or next of kin/emergency contact by repeat telephone calls, emails, and/or certified letter to the patient's last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.

Efforts to reach the patient should continue until the end of the study.

The patient will be classified as lost to follow-up 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 above listed efforts. For the primary analysis purposes, a patient will be classified as lost to follow-up if he/she has failed to return for the required study visits and his/her vital status remains unknown at the time of primary DBL.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1, Table 2, Table 3, and Table 4).

The investigator will ensure that data are recorded on the eCRFs. A web-based data capture system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, 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 eCRFs. A copy of the completed eCRFs will be archived at the study site.

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

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential 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.

Procedures conducted as part of the patient's routine clinical management (eg, blood test, echocardiography, biopsy, etc.) and obtained before signing of the ICF/assent may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for patient visits, assessments, medication distribution, and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements (Section 4.1.4 and Appendix J).

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel starting from randomisation/baseline (Visit 3/Week 0) until Visit 10/Week 28 (Section 6.3.2).

8.1 Administrative and General/Baseline Procedures – Not Applicable

8.2 Efficacy Assessments

8.2.1 HES Worsening/Flare

Patients entering this study should have HES worsening/flare characterised at Visit 1 by the findings in the HES physical examination (Section 8.2.1.1), investigator-led HES symptom interview (Section 8.2.1.2), and/or laboratory assessments in addition to isolated eosinophilia

(Section 8.2.1.3). Visit 1 HES worsening/flare characterisation is important because these same assessments will be used to capture subsequent HES worsening/flares, especially since the investigator and study team will be blinded to part of the patient's WBC differential (including blood eosinophils) starting from randomisation/baseline (Week 0/Visit 3) until Week 28/Visit 10 (Section 6.3.2).

For patients entering the study without an active HES worsening/flare at Visit 1, these assessments will also be performed at Visit 1 (HES physical examination, investigator-led HES symptom interview, and laboratory assessments). All patients, whether or not entering the study with an HES worsening/flare, will undergo these assessments for HES worsening/flare identification throughout the study.

An HES worsening or flare during the study is defined as HES clinical manifestations or lab abnormalities that result in an increase/burst of OCS (prednisone/prednisolone) ≥ 10 mg/day for at least 2 days (other OCSs in equivalent doses permitted [Appendix I]), **OR** an increase or addition of new cytotoxic and/or immunosuppressive therapy, **OR** hospitalisation.

- The start date of HES worsening/flare is defined as the first day of increased dose/burst of OCS, first day of any increase or addition of new cytotoxic and/or immunosuppressive therapy, or date of hospital admission, whichever occurs first.
- The stop date of HES worsening/flare is defined as the last day of an increased dose/burst of OCS, last day of increased cytotoxic and/or immunosuppressive therapy, or hospital discharge date, whichever occurs later. In case when a stop date cannot be determined using the above criteria (eg, if the patient's background therapy is adjusted and they remain on increased doses of OCS/cytotoxic/immunosuppressive therapy after the event has resolved), the stop date will be defined by a clinical stabilisation or improvement/ resolution of symptoms after the start of a new therapy as judged by the investigator.
- To be considered as a separate HES worsening/flare, the start date of an HES worsening/flare must be at least 14 days apart from the stop date of the preceding HES worsening/flare.

The HES worsening/flare will be assessed by the investigator through conduct of a brief physical examination (Appendix H and Section 8.2.1.1), an investigator-led HES symptom interview (Appendix G and Section 8.2.1.2), laboratory assessments (Sections 8.2.1.3 and 8.3.2), and other routine safety assessments (eg, spirometry) at scheduled or flare visits as outlined in the SoA (Table 1, Table 2, Table 3, and Table 4). The investigator may also request additional laboratory or other safety assessments including tissue biopsy as warranted; see Section 6.3.2 for maintaining the blind to patient's cell counts.

The patient will be advised to contact the study site every time they think their symptoms are getting worse and come to the site for HES worsening/flare visit assessments as applicable.

If the patient cannot get to the site for examination due to the HES worsening/flare, the patient is strongly recommended to visit their local physician/emergency care or another healthcare facility as necessary and show their patient participation card containing study site contact information for health providers. The local physician will be strongly encouraged to contact the site staff to discuss necessary assessments and the management of patient's condition given the patient's participation in the clinical study. The patient will be instructed to collect copies of medical records and assessment results pertaining to that visit (with the exception of haematology laboratory results that should be redacted (Section 6.3.2) in a closed envelope and bring to the study site at their next visit. In such cases, the investigator-led HES symptom interview with the patient is strongly recommended to be conducted by the site staff via telephone.

If the investigator is unavailable, an 24/7 emergency medical coverage number provided on the patient participation card may be used by the health provider.

8.2.1.1 HES Physical Examinations

A complete HES or brief physical examination will be performed at the visits indicated in the SoA (Table 1, Table 2, Table 3, and Table 4). A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems (see Appendix H for details). A brief physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, and abdomen. For flare visits, positive HES signs and symptoms should be reported.

The investigator will use the HES physical examination (Appendix H) to help identify specific organ involvement and to help identify subsequent HES worsening/flare (Section 8.2.1) during the study.

Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs, see Section 8.4.4 for details.

8.2.1.2 Investigator-led HES Symptom Interview

The investigator-led HES symptom interview will be completed by the investigator at visits indicated in the SoA (Table 1, Table 2, Table 3, and Table 4). The investigator will provide instructions and ask questions from the investigator-led HES symptom interview to the patient and fill in the patient response using an eCOA device.

The investigator will use the investigator-led HES symptom interview (Appendix G) to determine baseline HES symptoms and to help identify subsequent HES worsening/flare (Section 8.2.1) during the study. The investigator will ask the patient if she/he is currently experiencing a specific symptom. If the patient answers 'yes', she/he will be asked to rate the

intensity of the symptom (mild, moderate, or severe). The symptoms are grouped into the following 7 categories: general, skin, digestive, chest and breathing, nasal and vision, muscle and joint, and neurological. At Visit 1, the investigator will also ask the patient to choose and rank the top 3 most bothersome current symptoms (1 = most bothersome; 3 = least bothersome) as well as rate the intensity of the symptom (no symptom, mild, moderate, or severe) when he/she is not experiencing an HES worsening/flare.

8.2.1.3 Laboratory Assessments

Reviewing laboratory abnormalities and other routine safety assessments (eg, spirometry), excluding laboratory assessments that must remain blinded until Week 28/Visit 10 (Section 6.3.2), will aid in identifying HES worsening/flare. See Section 8.3.2 for details on clinical laboratory assessments performed during the study.

8.2.2 Haematologic Relapse

At randomisation (Visit 3), patients must have an AEC < 1000 cells/µL, based on local laboratory assessment (following a 2-day course of OCS) – this is the baseline AEC. Post-randomisation haematologic relapse will be defined as an AEC of ≥ 1000 cells/µL at any post-randomisation visit, based on central laboratory assessment.

In order to maintain the blind (Section 6.3.2), eosinophil counts will be redacted from the laboratory reports sent back to the study sites, and data to support endpoints of time to first haematologic relapse and the proportion of patients who experience a first haematologic relapse over the DB treatment period will be derived from central laboratory dataset by AstraZeneca after DBL (Section 9.4.2.1).

8.2.3 Patient-reported Outcomes

All PRO assessments will be performed during site visits in accordance with the SoA (Table 1 and Table 2).

The following PROs will be used in this study: PROMIS fatigue short form 7a, SF-36v2, PGIS, PGIC, and HES symptom questionnaire (Sections 8.2.3.1 to 8.2.3.5). These PRO assessments will be completed prior to the investigator-led HES symptom interview (Section 8.2.1.2).

Patients will complete all PRO assessments using a site-based handheld eCOA device. Patients and sites will be trained on the use of the eCOA device. Sites should be aware of the guidelines for PRO administration as provided to the sites in a separate manual. The investigator will also ensure that patients are properly trained on the importance of completing assessments as scheduled.

Sites and investigators should be aware that the eCOA device is the only acceptable source of PRO data; paper questionnaires are not acceptable.

8.2.3.1 PROMIS Fatigue

The PROMIS, led by the National Institutes of Health and now facilitated by Northwestern University, is a set of person-centred measures that evaluates and monitors physical, mental, and social health (Cella et al 2010). The PROMIS fatigue short form 7a consists of 7 questions assessing the severity of the patient's fatigue-related symptoms and the impact of these symptoms on HRQoL. The questions have a 7-day recall period, and the response options are on a 5-point Likert scale ranging from 1 (never) to 5 (always).

The standardised T-score (range 0 to 100) is obtained by rescaling the raw total score using the score conversion table (see SAP for more details). The mean T-score for the reference population of US adults is 50; the standard deviation of the reference population is 10. Higher T-scores represent greater fatigue.

Patients will complete the PROMIS fatigue short form 7a at the site using the eCOA device prior to other study procedures.

8.2.3.2 Short Form-36 Version 2 (Acute Recall)

The SF-36v2 (acute recall) is a 36-item, self-report survey of functional health and well-being, with a 1-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 one week ago and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Psychometrically-based PCS and MCS scores are computed from subscale scores to give a broader metric of physical and mental HRQoL.

Patients will complete the SF-36v2 at the site using the eCOA device prior to other study procedures.

8.2.3.3 Patient Global Impression of Severity

The PGIS is a single item designed to capture the patient's perception of overall symptom severity over the past week using a 6-point categorical response scale (0 = 'no symptoms' to 5 = 'very severe symptoms').

Patients will complete the PGIS at the site using the eCOA device prior to other study procedures.

8.2.3.4 Patient Global Impression of Change

The PGIC instrument captures the patient's overall evaluation of response to treatment. The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point scale (1 = 'much better' to 7 = 'much worse').

Patients will complete the PGIC at the site using the eCOA device prior to other study procedures.

8.2.3.5 HES Symptom Questionnaire

The HES symptom questionnaire asks patients to assess their symptoms at their worst over the past 7 days. The 34-item questionnaire covers general, skin, digestive, chest and breathing, nasal and vision, muscle and joint, and neurological symptoms. Responses range from 0 = 'did not experience symptom' to 10 = 'worst imaginable'.

The patient will complete the HES symptom questionnaire at the site using the eCOA device.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1, Table 2, Table 3, and Table 4).

8.3.1 Physical Examination

Complete HES or brief physical examinations will be performed at the visits indicated in the SoA (Table 1, Table 2, Table 3, and Table 4).

The physical examinations are described in Section 8.2.1.1.

8.3.1.1 Height and Weight

The patient's height will be measured at Visit 1 only. Weight will be measured in accordance with the SoA (Table 1, Table 2, Table 3, and Table 4). The patient's weight will be recorded in kilograms, and height will be recorded in centimetres.

8.3.2 Vital Signs

Pre-dose vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) will be assessed in accordance with the SoA (Table 1, Table 2, Table 3, and Table 4).

It is recommended that vital signs are assessed before any interventional study procedures (blood test collection, spirometry, IP administration).

Body temperature will be measured in Celsius in accordance with local standards.

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

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

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

8.3.3 Clinical Safety Laboratory Assessments

See Table 9 for the list of clinical safety laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments, as defined in Table 9, must be conducted in accordance with the laboratory manual and the SoA (Table 1, Table 2, Table 3, and Table 4).

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.4.4.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator; see Section 6.3.2 for maintaining the blind to patient's cell counts. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed at the central laboratory and at both local and central laboratories at Visit 1.

It is understood that central laboratory results may become available after randomisation; therefore, local laboratory tests will be performed at Visit 1 and Visit 2 to inform the eligibility criteria assessment.

Local laboratory testing at the site will be done for the following:

- Local haematology (including WBC with differential) will be assessed at Visit 1 to confirm AEC per inclusion criterion 7 and at Visit 2 to support inclusion criterion 8.
- Local clinical chemistry (AST, ALT, total bilirubin, uric acid, and creatinine) and troponin will be assessed at Visit 1 to inform safety aspects of patients' eligibility. Additional local laboratory parameters may be included at discretion of the investigator.

Optional blood sample(s) for local clinical chemistry can be taken at the discretion of the investigator at Visit 2 (eg, to follow-up on any abnormalities found during the screening period), at a flare visit, or at an unscheduled visit (eg, for immediate medical decisions).

Table 9 Central Laboratory Safety Variables

Haematology/Haemostasis (whole blood) [a]	**Clinical chemistry (serum or plasma)**
Haemoglobin	Creatinine
Haematocrit	Glucose
Total leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Bilirubin, direct
Platelet count	Bilirubin, indirect
Neutrophils (absolute and differential [%])	Alkaline phosphatase
Lymphocytes (absolute and differential [%])	AST
Monocytes (absolute and differential [%])	ALT
Eosinophils (absolute and differential [%])	Uric acid
Basophils (absolute and differential [%])	Gamma glutamyl transaminase
	Albumin
Other laboratory parameters	Chloride
Hepatitis B surface antigen	Bicarbonate
Hepatitis C antibody	Blood urea nitrogen
ANCA (MPO and PR3)	Potassium
Total IgE, FEIA	Calcium, total
CRP	Sodium
Troponin T and I	Creatine kinase
Tryptase	Inorganic phosphate
Vitamin B12	Magnesium
HIV-1 and HIV-2	
FSH	
Serum pregnancy test (WOCBP)	
Lactate dehydrogenase	

[a] Eosinophil, basophil, absolute monocyte count, and differential (percentages) for all WBCs (eosinophils, basophils, monocytes, neutrophils, and lymphocytes) will be redacted from central laboratory reports from Visit 3/Week 0 until Visit 10/Week 28.

ALT = alanine aminotransferase; ANCA = antineutrophil cytoplasmic antibodies; AST = aspartate aminotransferase; CRP = C-reactive protein; FEIA = fluorescence enzyme immunoassay; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; Ig = immunoglobulin; MPO = myeloperoxidase antibodies; PR3 = proteinase 3 antibodies; WBC = white blood cells; WOCBP = woman/women of childbearing potential.

8.3.3.1 Pregnancy Tests

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in the SoA (Table 1, Table 2, Table 3, and Table 4).

- Serum beta-HCG: To be performed at Visit 1 and subsequently only if the urine pregnancy (dipstick) test is positive. This test applies to all females, except for those who are NOT of childbearing potential as defined in inclusion criterion 9. This test is to be sent to and analysed at the central laboratory.
- FSH: To be performed at Visit 1 only for female patients < 50 years who have been amenorrhoeic for ≥ 12 months prior to the planned date of randomisation to confirm postmenopausal status. This test is to be sent to and analysed at the central laboratory; all women should be treated as premenopausal until results are received from the central laboratory.
- Urine HCG (dipstick): Dipstick test will be performed locally at the study site at Visit 1 to confirm eligibility and at other time points as indicated in the SoA (Table 1, Table 2, Table 3, and Table 4). This test applies to all female patients except for those who are NOT of childbearing potential as defined in inclusion criterion 9. A positive urine test result must be confirmed with a serum beta-HCG.

Note: A WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed if they are attending an optional remote visit with IP self-administration and at any onsite visit where a urine pregnancy test is not scheduled. Testing can be used to confirm pregnancy status.

If a WOCBP becomes pregnant, see Section 8.4.8 for additional information, including reporting requirements in case of a pregnancy during the study.

8.3.3.2 Serology

Hepatitis B surface antigen and hepatitis C antibody tests will be assessed in accordance with the SoA (Table 1); tests to be performed at the central laboratory.

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

Local HIV express test will be performed at Visit 1 to inform eligibility. The sample from Visit 1 will also be sent to the central laboratory for HIV-1 and HIV-2 antibodies (along with p24 antigen) assessment. If, after randomisation, the result of the central laboratory HIV test is positive, the patient will be discontinued from treatment (Section 7.1.2).

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

8.3.4 Electrocardiograms

A single 12-lead ECG will be obtained at baseline (Visit 3) as outlined in the SoA (Table 1) using an ECG machine provided by a central vendor. Only this equipment should be used for assessment throughout the patient's participation in the study. An individual ECG tracing will be obtained.

The ECG will be taken in the supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry and IP administration).

The ECG will be reviewed locally by a specialist to identify potential cardiac problems and monitoring for acute events and will also be transmitted to a central reader. The investigator, or designee, will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printout will be signed and dated by the investigator and stored at the study site. Any findings from local and/or central read will be recorded in the eCRF. Procedures for collecting and reading ECGs will be documented in an ECG charter.

8.3.5 Echocardiogram

For patients with known or suspected cardiac involvement, heart function should be assessed for clinical significance, either by a historical echocardiogram done within 12 months of Visit 1 or during screening if a historical echocardiogram is not available.

For patients with known or suspected cardiac involvement, heart function may be further assessed locally by an echocardiogram at flare visits during the DB and OLE treatment periods at the discretion of the investigator, as outlined in the SoA (Table 1, Table 2, Table 3, and Table 4). Echocardiogram will be read locally by a specialist and any findings will be recorded in the eCRF.

8.4 AEs, SAEs, and Other Safety Reporting

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.

The definitions of medical device-related safety events can be found in Appendix E. Medical device deficiencies are covered in Section 8.4.11.

Patients (or, when appropriate, a caregiver, surrogate, or the patient's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE, it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. 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. For information on how to follow-up AEs, see Section 8.4.2.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to the IP
- 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 SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to (see definition of SAE in Appendix B 2)
- 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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected starting from Visit 1, throughout the treatment periods, and including the follow-up period's last contact with the patient.

Serious AEs will be recorded from the time the patient signs the ICF/assent, throughout the duration of the study.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 8.4.7. 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 AEs or SAEs in former study patients. However, if the investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a treated patient, the investigator shall, without undue delay, report the SAE to AstraZeneca.

The method of recording, evaluating, and assessing causality of AE and SAE are provided in Appendix B.

8.4.2 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 will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

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

8.4.3 Causality Collection

The investigator will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the IP?’

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP. For medical devices, a guide to the interpretation of the causality question can be found in Appendix E.

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they meet any of the following:

- They fulfil any of the SAE criteria or
- They are the reason for discontinuation of the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms or known clinical diagnosis, the diagnosis (preferably) or the clinical sign/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 should use the clinical term rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

Any new or aggravated clinically relevant abnormal medical finding at an HES physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the DUS (Section 8.4.6).

The results from the protocol mandated laboratory tests and vital signs will be summarised in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF.

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

8.4.6 Disease Under Study

Symptoms of DUS are those which might be expected to occur as a direct result of HES worsening/flare (eg, skin rash in a patient with HES who has a skin rash as a manifestation of their HES worsening/flare). Events which are unequivocally due to the DUS (see investigator-led HES symptom interview [Appendix G]) should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.4.7 Reporting of SAEs

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

If any SAE occurs during the study, then investigators or other site personnel inform the appropriate Sponsor representatives within **one calendar day** (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

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

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

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate sponsor representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed.

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

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

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

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.4.8 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 IP
- Pregnancies in the partner of male patients

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

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

8.4.8.1 Maternal Exposure

If a patient becomes pregnant during the study, IP should be temporarily withheld, and a conversation between the investigator and a study physician must take place to determine whether continuation on IP or discontinuation of IP is in the best interest of the patient.

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

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate Sponsor representatives immediately but **no later than 24 hours** after 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 pregnancies associated with SAEs (Section 8.4.7) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

When the eCRF module is used include the following: The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.9 Medication Error, Drug Abuse, and Drug Misuse

8.4.9.1 Timelines

If an event of a 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 medication error, drug abuse, or misuse (Section 8.4.7) and **within 30 days** for all other events.

8.4.9.2 Medication Error

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

The full definition and examples of a medication error can be found in Appendix B 4.

8.4.9.3 Drug Abuse

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

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study patient) of IP or AstraZeneca non-IP for medicinal purposes outside of the authorised product information, or for unauthorised IPs or AstraZeneca non-IPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.10 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

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

If an overdose on an IP or AstraZeneca non-IP 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 (Section 8.4.7) and **within 30 days** for all other overdoses.

8.4.11 Medical Device Deficiencies

Combination products with a device constituent are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definition of a medical device deficiency that occur during the study with the device constituent of the benralizumab combination product.

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

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

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

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

The AstraZeneca clinical study medical device/device constituent report form and/or product complaint intake form will be used to collect the deficiency. For third-party medical devices, the deficiency will be reported to the manufacturer, who will be responsible for fulfilling their regulatory obligations.

8.4.11.1 Time Period for Detecting Medical Device Deficiencies

Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.

If the investigator learns of any medical device deficiency at any time after a patient has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify AstraZeneca.

The method of documenting a medical device deficiency is provided in Appendix E.

8.4.11.2 Follow-up of Medical Device Deficiencies

Follow-up applies to all patients, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the original form used to report the deficiency, with all changes signed and dated by the investigator.

8.4.11.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

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

The AstraZeneca clinical study medical device/device constituent report form and/or product complaint intake form will be sent to AstraZeneca by email. If email is unavailable, then fax should be utilised.

Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.4.7.

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

8.4.11.4 Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for AstraZeneca to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.

For further guidance on the definition of an SAE, see Appendix E of the CSP.

8.4.12 Management of Investigational Product-related Drug Reactions

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions should be available when IP is administered, and study site personnel must be trained to recognise and treat anaphylaxis (

Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F.

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

5 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both and at least one of the following:

   (a) respiratory compromise; or

(b) reduced blood pressure or symptoms of end-organ dysfunction; or

6 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms; or

7 Reduced blood pressure after exposure.

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix F.

Patients will have had a pre-assessment (ie, vital signs and lung function) prior to IP administration. Patients should be observed (or contacted when participating in the self-administration programme) after each 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 laboratory at the discretion of the investigator.

8.5 Pharmacokinetics

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

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

Instructions for sample collection, processing, storage, and shipment can be found in the separate laboratory manual provided to the study sites.

All PK samples will be collected pre-dose according to the SoA (Table 1, Table 2, Table 3, and Table 4).

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

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

For storage, reuse, and destruction of samples for PK see Appendix C.

Pharmacokinetics samples will be disposed of after the bioanalytical report finalisation or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless consented for future analyses.

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

8.5.1.1 Determination of Drug Concentration (PK Samples)

Blood samples for determination of benralizumab concentration in serum will be analysed by a third-party bioanalytical laboratory on behalf of AstraZeneca, using a validated bioanalytical method.

The bioanalytical laboratory will have access to the randomisation list (Section 6.3.2). The following samples will be analysed:

DB treatment period:

- All PK samples from patients assigned to the benralizumab treatment group.

OLE treatment period:

- PK samples from patients assigned to the placebo treatment group in the DB treatment period of the study that are collected 24 hours (± 12 hours) after the first dose of benralizumab in the OLE (Week 24/Visit 9) (Section 8.5.1.2).
- PK samples from all patients at all other time points in the OLE regardless of treatment assignment in the DB treatment period.

8.5.1.2 Pharmacokinetics/Pharmacodynamics (Subset of Patients)

A serum and whole blood sample (AEC only) will be collected 24 hours (± 12 hours) after the first dose of benralizumab in the OLE (Week 24/Visit 9) according to the SoA (Table 1).

All patients will be informed of the need for this sample to be collected as part of the consenting process, but samples are only required from 45 patients to support the objective of a more in-depth characterisation of the decline phase of eosinophilia and extrapolation to build a relationship between adults, adolescents, and younger patients. Therefore, after samples have been collected from approximately 45 patients, further patients reaching this time point in the study will not need to provide these samples.

This sample will only be analysed in patients that received placebo during the DB treatment period.

8.6 Pharmacodynamics

Pharmacodynamic parameters will be evaluated using biomarkers (Section 8.9).

8.7 Immunogenicity Assessments

Antibodies to benralizumab will be evaluated in serum samples collected pre-dose from all patients according to the SoA (Table 1, Table 2, Table 3, and Table 4). These samples will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples will be analysed from all patients at all time points indicated in the SoA (Section 1.3).

Serum samples will be screened for ADA and the titre of confirmed positive samples will be reported. Other analyses may be performed to further characterise the immunogenicity of benralizumab.

In vitro nAb testing will occur for all samples that are ADA positive using a validated immunoassay. Samples that are ADA negative will not be tested for nAb.

Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

For storage, reuse, and destruction of ADA samples see Appendix C.

Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years post-CSR finalisation. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.8 Optional Genomics Initiative

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

A blood sample for DNA isolation will be collected from adult patients who have consented to participate in the genetic analysis component of the study according to the SoA (Table 1). Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study. Samples can be collected at any time after the genetic ICF is signed but is recommended at randomisation/baseline (Visit 3).

See Appendix D for information regarding the optional genomics initiative sample. Details on processes for collection, shipment, and destruction of these samples can be found in the appendices of this protocol or in the separate laboratory manual provided to the sites.

For storage and destruction of genetic samples see Appendix D.

8.9 Biomarkers

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

Blood (serum, plasma, and whole blood PAXgene RNA) and urine samples for biomarker research are required and will be collected according to the SoA (Table 1 and Table 2) in order to evaluate the effect of benralizumab on biomarkers of eosinophil recruitment and activation, inflammation, and immunological mechanisms related to HES.

All samples should be collected pre-dose and will be analysed centrally at contracted third-party labs.

Biomarkers that may be analysed include but are not limited to WBCs, whole blood gene expression, serum/plasma/urine proteins including but not limited to eosinophil granule proteins, cytokines, chemokines, and inflammatory mediators associated with HES, eosinophil activation, immunological function, and/or the pharmacology of benralizumab. The intended purpose is to evaluate the association of these biomarkers with observed clinical responses over the entire treatment duration of the clinical study and to enhance knowledge of HES pathogenesis.

Whole blood for lymphocyte phenotyping will be collected at baseline (Visit 1). The results of lymphocyte phenotyping analyses may provide information that can be used to predict which patients are likely to be more or less responsive to benralizumab treatment.

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

The results from these exploratory biomarker analyses will not be reported in the CSR but in separate reports and in scientific publications as appropriate. The results of the biomarker research may be pooled with biomarker data from other studies with the IP to generate hypotheses to be tested in future research.

8.9.1 Biopsy

Tissue biopsies will be collected as applicable (see below) according to the SoA (Table 1 and Table 2).

Any available historical biopsy reports obtained within the past year and any earlier biopsy reports that were used to diagnose HES will be collected and captured in the eCRF at Visit 1 to characterise HES history and support the exploratory biomarker endpoint analysis.

In addition, tissue biopsies will be collected, wherever possible (as described below), to support the exploratory biomarker endpoint during the study. A baseline biopsy sample may be captured in one of 2 ways:

- Any medically-indicated biopsy (skin, bone marrow, endoscopic, etc.) that was taken within 30 days of screening Visit 1. Histological report also to be collected if available.
- For adult patients with a skin manifestation of HES, a skin biopsy of the lesion will be collected during screening unless taking the biopsy is contraindicated as judged by the investigator, refused by the patient, or already performed within 30 days of Visit 1.

For adult patients, a repeat biopsy will be collected at Visit 6/Week 12 unless taking the biopsy is contraindicated as judged by the investigator, or refused by the patient, or the patient already had a repeated on-treatment biopsy prior to Visit 6/Week 12 (eg, due to a HES worsening/flare). Repeat skin or endoscopic biopsies at or prior to Week 12 should be taken from a location as close to the baseline biopsy as possible.

In addition, tissue biopsies to aid the characterisation of HES worsening/flare may be performed at the investigator's discretion but are not mandatory. All biopsy samples will be sent to the central laboratory for central read. Local review of unscheduled biopsies is allowed only after Visit 10/Week 28 unless needed to address an immediate safety concern. In rare instances where local review of biopsy is required before Visit 10, prior permission from AstraZeneca is required. All necessary precautions including redaction of the report (Section 6.3.2) to maintain the blinding should be exercised.

The biopsy samples collected during screening and at Visit 6 will be collected and processed according to the separate laboratory manual and sent to the central laboratory for final processing. In the case of any available biopsies taken within 30 days of Visit 1 or any other medically-indicated biopsies during the DB or OLE periods, fixed paraffin-embedded blocks (preferred), slides or smears, as available, should be sent to the central laboratory. Analyses of the tissue samples will be performed at a central laboratory and will include but not be limited to staining for markers specific for eosinophils and other immune cells.

Study personnel should remain blinded to the cell counts in biopsy reports obtained from randomisation/baseline (Visit 3), during the DB treatment period, and for the first 4 weeks of the OLE period (until Visit 10/Week 28).

To ensure the blind, all information pertaining to cell counts will be redacted from the biopsy reports sent to the study sites (Section 6.3.2).

All unredacted biopsy results will be available upon request to the site personnel after Visit 10/Week 28.

No protocol mandated, prospective collection of biopsies will be performed on adolescents, but samples from medically indicated biopsies are encouraged to be collected and sent to the central laboratory.

8.9.2 Mechanistic Sub-study

To assist in identifying HES clinical subtypes, as well as predictors and mechanisms of response to benralizumab, additional exploratory analyses will be performed in adults. Additional whole blood samples will be collected according to the SoA (Table 1).

All blood samples related to the mechanistic sub-study apply to all sites, except for whole blood for eosinophil phenotyping, which is applicable to North America only due to the downstream assay requiring a fresh sample to be received within 24 hours after the sample is collected. The other blood samples apply to all study sites and include 2 samples for PBMC analysis, one sample in SMART tubes for immunophenotyping, and one sample for DNA analysis to determine clinical subtype of HES by targeted PCR. This sample for DNA analysis is distinct from the optional exploratory genetic sample described in Section 8.8.

For storage, reuse, and destruction of biomarker samples see Appendix C.

8.10 Other Assessments

8.10.1 Patient Qualitative Interview Sub-study

Up to 40 adult patients will be invited to participate in a concept elicitation interview to characterise their experience during the DB treatment period of the study. The interview will be noninterventional and will collect data on HRQoL and patients' experiences with the study treatment. The interview will be performed by an AstraZeneca vendor via telephone contact on a one-to-one basis. Interview duration will be approximately 90 minutes. Please refer to a separate patient qualitative interview sub-study manual describing the interview process in greater detail.

Patients will be introduced to the sub-study during the informed consent process described in Appendix A 3 using patient communication materials and the sub-study patient handout attached to the patient qualitative interview sub-study manual. Interested patients will indicate their willingness to participate via the master ICF and will provide consent to participate in the sub-study via a sub-study ICF addendum. Patients will be contacted, and interviews scheduled by research staff using communication materials attached to the patient qualitative interview sub-study manual.

Each participating patient will be interviewed once. The interview will last approximately 90 minutes and will take place at least 7 days and up to 21 days after Visit 8 (or after the IPD visit within the DB treatment period of the study as indicated in Table 1). The interview will

be audio recorded with the patient's permission (ascertained via the consent addendum and confirmed verbally prior to the start of the interview).

During the interview, patients will be asked a set of open-ended questions with probes to explore their experiences with study treatment. They will be asked about their experience of the condition, how their experience may have changed over time, and current signs, symptoms, and impacts of the condition and study treatment. The interview discussion guide is provided as an appendix to the patient qualitative interview sub-study manual.

Interview transcripts will be completed for each interview in the language in which they are conducted and translated into English (if necessary). Translated transcripts will be coded using qualitative data analysis software.

All sub-study data (including audio recordings, interview transcripts and translations, ATLAS.ti codebooks, and other analyses) will be de-identified and stored in the vendor's secure server in a password-protected file. Aggregated results and summary analyses will be prepared in English.

Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (not in the CSR) and the data (transcriptions) will not be entered into the study database. No identifiable data will be reported.

In the event that any sub-study patient reports or is noted to have experienced an AE involving study treatment, information about the AE will be reported to AstraZeneca's pharmacovigilance organisation. AstraZeneca will follow standard procedures for handling AEs reporting involving these patients.

8.10.2 Spirometry

General Requirements

Only patients with pulmonary involvement will undergo spirometry at screening (Visit 1), other scheduled visits, and flare visits according to the SoA (Table 1 and Table 2).

Lung function (FEV1 and FVC) will be measured pre-bronchodilator at the study site by spirometry using equipment provided by a central vendor. The central spirometry vendor will ensure that the spirometer meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly certified.

Spirometry will be performed by the investigator, or designee, according to ATS/ERS guidelines (Miller et al 2005).

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

- Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to all lung function assessments at the study site.
- Patients should avoid eating a large meal for at least 2 hours prior to all lung function assessments at the study site.
- Patients should withhold their usual background inhaled therapies on the day(s) when lung function testing is being performed as below:
  - Short-active β agonists and short-acting muscarinic antagonist should be withheld at least 6 hours prior to scheduled spirometry at the study site.
  - Twice daily long-acting β2 agonist- or long-acting muscarinic antagonist-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at the study site.
  - Once daily long-acting β2 agonist- or long-acting muscarinic antagonist-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at the study site.
  - Twice daily theophylline should be withheld for at least 12 hours prior to scheduled spirometry at the study site.
  - Once daily theophylline for at least 24 hours prior to scheduled spirometry at the study site.

NOTE: If medications cannot be withheld prior to spirometry for Visit 1 and/or any HES worsening/flare visit, the spirometry assessment may be performed with a respective comment entered by the site in the MasterScope.

Time of Day for Scheduled Site Visit Spirometry

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

Spirometry Technique

Forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. The patient should use mouthpieces of the same dimension and shape from enrolment throughout the study.

The forced expiratory manoeuvre (FEV_1 and FVC) should start with a maximal inspiration followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak, or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3, but no more than 8) will be performed for each site spirometry session. Spirometry grading will conform to ATS/ERS acceptability and reproducibility criteria as detailed in the spirometry manual. The highest FEV_1 and FVC will be based on the best efforts meeting acceptability criteria. The highest recorded FEV_1 and FVC do not need to be from the same effort and can be derived from separate efforts. The absolute measurement (for FEV_1 and FVC) and the percentage of PN value (Quanjer et al 2012) will be recorded. Further details on spirometry are provided in the spirometry manual.

The patient's usual morning background respiratory therapy (if applicable) must not be given until after the pre-bronchodilator spirograms are complete for the reasons discussed above. Dosing of IP should be after spirometry is complete. If the patient cannot tolerate a spirometry assessment during the visit, it can be rescheduled for a different date, preferably within the visit window. There is no need to withhold IP in this case; it can be administered during the visit as scheduled.

Record Keeping

A signed and dated copy of the spirometry printout must be kept at the study site for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, and visit number.

Spirometry References

The Global Lung Function Initiative equations will be used to determine the patients' PN values and are pre-programmed into the spirometer (Quanjer et al 2012).

The FEV_1 is expressed as percent of the PN value will be calculated as follows:

$$FEV_1\% \text{ of PN} = FEV_1 \text{ measured}/FEV_1\text{PN} \times 100$$

8.10.3 Patient Testing Due to Public Health Crisis

If patient testing is performed due to the public health crisis, the results may be documented for this study.

8.11 Healthcare Resource Utilisation

Broad-based HES-related healthcare resource utilisation information will be collected by the investigator, or designee, in accordance with the SoA (Table 1 and Table 2) and recorded in

the appropriate eCRF module. Protocol-mandated procedures, tests, and encounters are excluded.

At randomisation, HES-related healthcare resource utilisation information will be collected with a 1-year recall period. All the subsequent visits will collect HES-related healthcare resource utilisation information with a recall period of 'since last scheduled visit'.

Note: Cases of hospitalisation must be reported as an SAE (Section 8.4).

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

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

8.12 Study Participant Feedback Questionnaire – Not Applicable

This study will NOT include an option for patients to complete a study participant feedback questionnaire.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised prior to the primary DBL, and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The primary endpoint is the time to first HES worsening/flare. The primary analysis is to compare the time to first HES worsening/flare in patients on benralizumab versus placebo. The null hypothesis is that the time to first HES worsening/flare is not different between benralizumab and placebo. The alternative hypothesis is that time to first HES worsening/flare is different between benralizumab and placebo. The primary endpoint will be tested at the CCI significance level using a stratified log-rank test adjusting for region and HES flare status at screening.

A treatment policy estimand will be applied to the primary analysis of the primary endpoint. The analysis of time to first HES worsening/flare will use all observed HES worsening/flare events during the DB treatment period regardless of adherence to the allocated treatment at the

time of the HES worsening/flare event. Patients will be censored at the time of DB study completion or withdrawal from the study during the DB treatment period.

A multiple testing procedure will be applied to the primary and key secondary endpoints; details are provided in Section 9.4.5.

9.2 Sample Size Determination

Approximately 120 patients are expected to be randomised at a 1:1 ratio to receive benralizumab or matching placebo; however, recruitment may continue beyond 120 patients to achieve the target number of events.

The primary analysis will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period. Approximately 38 first HES worsening/flare events during the DB period are required to detect a statistically significant difference between treatment groups at the CCI significance level with approximately CCI power if the true treatment effect is a hazard ratio of CCI (equivalent to CCI of patients on benralizumab experiencing an event by the end of the DB period compared to CCI of patients on placebo).

9.3 Populations for Analyses

The study populations are defined in Table 10.

Table 10 Populations for Analysis

Population/analysis set	Description
Enrolled analysis set	The enrolled analysis set will include all patients who sign the ICF/assent.
Randomly-assigned to study treatment analysis set	The randomly assigned to study treatment analysis set will include all patients who sign the ICF/assent and are randomised to an IP regardless of whether they receive a dose of an IP or exit prior to receiving the first dose.
Full analysis set	The full analysis set will include all patients who are randomised and receive at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be analysed using the full analysis set.
Safety analysis set	The safety analysis set will include all patients who receive at least one dose of IP. Erroneously treated patients (eg, those randomised to benralizumab but actually given placebo) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received active IP is classified as active

Table 10 Populations for Analysis

Population/analysis set	Description
PK analysis set	The PK analysis set will include all patients who receive at least one dose of IP and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set.
OLE analysis set	The OLE analysis set will include all patients who enter the OLE part of the study and who receive at least one dose of IP during the OLE treatment period.

ICF = informed consent form; IP = investigational product; OLE = open-label extension; PK = pharmacokinetics

9.4 Statistical Analyses

9.4.1 General Considerations

All personnel involved in the analysis of the study will remain blinded until the primary DBL and protocol deviations are identified.

Analyses will be performed by AstraZeneca representatives. A comprehensive SAP will be developed and finalised before the primary DBL and will describe the patient populations to be included in the analyses, and the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Categorical variables will be summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population unless otherwise stated.

Continuous variables will be summarised with descriptive statistics of number of available observations, mean, standard deviation, median, minimum, maximum, and quartiles where more appropriate.

All point estimates will be presented together with 95% CIs as measures of precision.

9.4.2 Efficacy Analyses

Efficacy analyses will be performed using the full analysis set. All analyses described below apply to the primary analysis through to the end of the DB treatment period (Week 24) unless otherwise stated. The primary DBL will occur when approximately 38 patients have had their first HES worsening/flare event during the DB treatment period and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period. Unblinding and primary data analysis will occur after primary DBL.

A treatment policy estimand will be applied to the primary analysis of the primary endpoint and secondary endpoints whereby all data are included regardless of adherence to the allocated treatment.

9.4.2.1 Calculation or Derivation of Variable for Efficacy Analyses

Time to First HES Worsening/Flare (Primary Endpoint)

First HES worsening/flare is declared by the investigator and defined as a HES clinical manifestation or laboratory abnormality that results in an increase/burst of OCS (prednisone/prednisolone) ≥ 10 mg/day for at least 2 days (other OCSs in equivalent doses permitted [Appendix I]), **OR** in increase or addition of new cytotoxic and/or immunosuppressive therapy, **OR** hospitalisation.

The time to first HES worsening/flare is calculated as:

Start date of first HES worsening/flare event - date of randomisation + 1

Patients who have not experienced an event of HES worsening/flare during the DB treatment period will be right censored at the time of DB study completion or withdrawal from the study during the DB treatment period.

Proportion of patients with a HES Worsening/Flare Event (Key Secondary Endpoint)

The proportion of patients who experience an HES worsening/flare over the DB treatment period will be a key secondary endpoint (Section 9.4.2.3). For this endpoint, any patients who withdraw from the study without having flared will be considered as if they had a flare event, so the analysis will represent the proportion of patients with a HES worsening/flare or who withdrew from the study during the DB period.

Number of HES Worsening/Flare Events (Key Secondary Endpoint)

The number of individual flare events a patient has over the DB period will be analysed as a key secondary endpoint using the same flare definition as the primary endpoint. To estimate an annualised flare rate, the logarithm of the patient's follow-up time will be used as an offset in the analysis to adjust for patients having different exposure times at the time the events occur. Maximum follow-up time for a patient is approximately 24 weeks (defined as the time from randomisation to the date of the Week 24 visit). For a patient lost to follow-up, the maximum follow-up time will be defined as the time from randomisation to the time point after which a flare could not be assessed.

Time to First Haematologic Relapse (Key Secondary Endpoint)

First haematologic relapse is declared when AEC ≥ 1000 cells/µL.

The time to first haematologic relapse is calculated as:

Start date of first haematologic relapse - date of randomisation + 1

Patients who have not experienced an event of haematologic relapse during the DB treatment period will be right censored at the time of DB study completion or withdrawal from the study during the DB treatment period.

Proportion of patients who experience haematologic relapse over the DB treatment period will be used as a supportive endpoint of time to first haematologic relapse and calculated with the population of interest.

Change from Baseline in PROMIS Fatigue Short Form 7a (Key Secondary Endpoint)

Change from baseline in the PROMIS fatigue short form 7a standardised total score will be calculated at each visit over the DB treatment period. The change from baseline to Week 24 will be a key secondary endpoint.

Proportion of Patients Who Have AEC < 500 cells/µL for 24 Weeks

Patients who have AEC < 500 cells/µL for 24 weeks of the DB treatment period will be considered as maintaining remission throughout the DB treatment period. Proportion of patients who maintain remission will be calculated using the population of interest.

Proportion of Patients Who Require an Increase in Corticosteroid Dose from Baseline at Any Point During the DB Treatment Period

A patient who requires an increase from their baseline corticosteroid dose at any point during the DB treatment period will be assigned a value of 1 for corticosteroid use and 0 if no increase has occurred at any point. Proportion of patients who require an increase in corticosteroid dose from baseline at any point in the DB treatment period will be calculated using the population of interest.

Change from Baseline in SF-36v2

Eight domain profiles will be derived according to the SF-36v2 (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) with physical and mental health components summary scores. Change from baseline will be calculated at each visit over the DB treatment period for these domains and components scores.

A responder rate will be calculated for patients reaching the threshold defined in Table 11 at each visit of the DB treatment period. The SF-36v2 threshold is suitable for interpreting

change at the individual level and is referred to as the responder threshold or responder definition (QualityMetric 2011).

Table 11 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 = emotional problems; RP = role limitations due to physical health; SF = social functioning; SF-36v2 = 36-Item Short Form Health Survey Version 2; VT = vitality

PGIS

The PGIS is a 6-point categorical response scale that is designed to capture the patient's perception of overall symptom severity over the past week of the assessment. The PGIS responses will be summarised by treatment group and visit over the DB treatment period.

PGIC

The PGIC instrument is a 7-point scale that captures the patient's overall evaluation of response to treatment. The PGIC responses will be summarised by treatment group and visit over the DB treatment period.

Patients will also be categorised according to the following improvement categories post-baseline:

- A little better, moderately better, much better → 'A little better'
- Moderately better, much better → 'Moderately better'
- Much better → 'Much better'

The number and percentage of patients defined as PGIC responders will also be presented by treatment group and visit over the DB treatment period.

9.4.2.2 Primary Endpoint Analysis Method

The primary endpoint of the time to first HES worsening/flare (full definition in Section 8.2.1) will be analysed using a stratified log-rank test. The stratified log-rank test will be used to compare the time to first HES worsening/flare between the benralizumab and placebo groups, while adjusting for region and HES flare status at screening. The Cox-proportional hazards model with treatment group, region, and HES flare status at screening as covariates will be used to estimate the hazard ratio and its 95% CI.

9.4.2.3 Secondary Endpoints Analysis Methods

The proportion of patients with a HES worsening/flare or who withdrew from the study in the DB period (a key secondary endpoint) will be compared between the benralizumab and the placebo groups using a CMH test controlling for region and HES flare status at screening. A logistic regression model with treatment group, region, and HES flare status at screening as covariates will be used to obtain the odds ratio.

The number of flare events during the DB period (a key secondary endpoint) will be compared between the benralizumab and placebo groups using a negative binomial model. The response variable in the model will be the number of HES worsening/flare events over the 24-week DB treatment period. The logarithm of the follow-up time will be used as an offset variable in the model. The model will include covariates of treatment group, region, and HES flare status at screening to obtain estimates of the flare rates in each treatment group and the rate ratio for benralizumab versus placebo.

The first haematologic relapse will be calculated as AEC ≥ 1000 cells/μL. The stratified log-rank test will be used to compare the time to first haematologic relapse (a key secondary endpoint) between the benralizumab and placebo groups, while adjusting for region and HES flare status at screening. The hazard ratio and its 95% CI will be obtained from the Cox-proportional hazards model with treatment group, region, and HES flare status at screening as covariates. The proportion of patients with haematologic relapse in the benralizumab group will be compared with the proportion in the placebo group using a CMH test controlling for region and HES flare status at screening. The logistic regression model will be used to analyse first haematologic relapse, with treatment group, region, and HES flare status at screening as covariates to obtain the odds ratio.

The proportion of patients with AEC < 500 cells/μL for 24 weeks in the benralizumab group will be compared with proportion in the placebo group using a CMH test controlling for region and HES flare status at screening. A logistic regression model with treatment group, region, and HES flare status at screening as covariates will be used to analyse the proportion of patients with AEC < 500 cells/μL for 24 weeks to obtain the odds ratio.

The proportion of patients with an increase in corticosteroid dose from baseline at any point in the DB treatment period in the benralizumab group will be compared with the proportion in the placebo group using a CMH test controlling for region and HES flare status at screening. A logistic regression model with treatment group, region, and HES flare status at screening as covariates will be used to analyse an increase in corticosteroid dose from baseline at any point in the DB treatment period to obtain the odds ratio.

Treatment group, region, and HES flare status at screening will be included as covariates in all the mentioned models. Results from the Cox-proportional hazards model will be presented in

terms of an adjusted hazard ratio with its 95% CI. Results for the logistic regression will be presented in terms of an odds ratio with its 95% CI.

The SF-36v2 (PCS, MCS, and each domain) and the PROMIS fatigue short form 7a (a key secondary endpoint) will be assessed as change from baseline over the DB treatment period. The change from baseline in these secondary endpoints will be analysed using a MMRM analysis with treatment group, region, HES flare status at screening, visit, endpoint's baseline, and treatment by visit interaction as covariates. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge, then the Toeplitz variance-covariance matrix will be used instead. The primary analysis will fit a MMRM model using the data collected up to and including the Week 24 time point. The estimate of the treatment effect at Week 24 will be based on a contrast from this MMRM model.

The SF-36v2 will also be analysed with the responder rate of patients reaching a threshold at Week 24 of the DB treatment period. The SF-36v2 responders will be analysed using a CMH test adjusting for region and HES flare status at screening. It will be also analysed using logistic regression with treatment group, region, and HES flare status at screening as covariates.

Descriptive statistics will be provided for PGIC and PGIS. The proportions of patients for each category per visit will be reported. The proportion of PGIC responders will also be summarised at every visit.

9.4.3 Safety Analyses

Safety analyses will be performed using the safety analysis set. Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities that will have been released for execution by AstraZeneca/designee.

Safety data will be presented using descriptive statistics unless otherwise specified. The AEs will be presented for each treatment group by system organ class and/or preferred term covering number and percentage of patients reporting at least one event and number of events where appropriate. An overview of AEs for each treatment group will present the number and percentage of patients with any AE, AEs with outcome of death, SAEs, 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 the most common AEs. In accordance with the requirements of the Food and Drug Administration, a separate table will present non-serious AEs occurring in more than 5% of patients in any treatment group.

Key patient information will be presented for patients with AEs with outcome of death, SAEs, 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:

- AEs with an onset date on or after the first dose of IP
- Worsening of preexisting events on or after the first dose of IP.

Laboratory data will be summarised by presenting shift tables (if applicable) using normal ranges and by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable laboratory abnormalities will be summarised.

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

For patients with post-baseline ECG data collected, the ECG intervals will be summarised by presenting summary statistics of observed values and change from baseline values. Increases in QTc intervals will be summarised for the Bazett's and Fredericia's corrections using the categories from ICH-E14. The incidence of clinically notable ECG abnormalities will be summarised.

The IP exposure time (days on-treatment calculated as: last dose date – first dose date + 1) will be described.

9.4.4 Other Analyses

The PK, PD, and biomarker exploratory analyses will be described in the SAP finalised before the primary DBL. The population PK analysis will be performed using the PK population and be presented separately from the main CSR.

9.4.5 Methods for Multiplicity Control

At the primary analysis, to account for multiplicity for the primary endpoint (time to first HES worsening/flare) and the key secondary endpoints listed below, a hierarchical fixed-sequence testing strategy will be used to strongly control the overall type-I error rate at the CCI level. The primary endpoint will be tested at a CCI significance level.

- If the null hypothesis that there is no difference in time to first HES worsening/flare between treatment groups can be rejected with a p-value CCI, and time to first HES worsening/flare is longer in the benralizumab arm compared to the placebo arm,

hierarchical fixed sequence testing will continue for the key secondary endpoints at the CCI level in the following order:

  - Proportion of patients who experience an HES worsening/flare during the DB period
  - Number of HES worsenings/flares during the DB period
  - Time to first haematologic relapse during the DB period
  - Change from baseline in PROMIS fatigue short form 7a score at Week 24
- If at any time the null hypothesis cannot be rejected at the CCI level, or if the treatment difference favours the placebo arm, further testing for the key secondary endpoints will stop, and no subsequent null hypothesis in the testing hierarchy will be rejected.

The analyses of the OLE period will not be multiplicity protected.

9.4.6 OLE Period Analyses

Data collected during the OLE period will be analysed using the OLE analysis set. All summaries will be descriptive, with details included in the SAP.

9.4.7 Sensitivity Analyses and Missing Data Handling

Sensitivity analyses may be conducted based on 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, utilising multiple imputation approaches. For the time-to-event analyses such as the primary efficacy variable, a sensitivity analysis may be performed to assess possible evaluation-time bias that may be introduced when evaluations cannot be performed at the scheduled time point. Full details of the sensitivity analyses will be prespecified in the SAP.

9.4.8 Subgroup Analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses will be provided for, but may not be limited to, the following factors: age, geographic region, HES flare status at screening, gender, HES subtype, and race. These analyses are to be considered as exploratory and will be performed on the full analysis set. Full details will be specified in the SAP.

9.5 Interim Analyses

No formal interim analysis is planned for the study. AstraZeneca's internal personnel or its designees will monitor the overall rate of HES worsening/flare (blinded to treatment assignment) to ensure that the final sample size will be adequate to provide the approximately 38 events needed for the primary analysis.

Adjustments to the sample size may be necessary to maintain the power of the study. The blinded data review will be performed by AstraZeneca internal personnel or its designees, and the full details of the review will be specified in a blinded data review plan.

9.6 Data Safety Monitoring Board

A DSMB will be utilised for this study. Appendix A 5 provides more details on the rationale for and the remit of the committee.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the CSP 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.

AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of an IP under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IP under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and AstraZeneca policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a patient 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-CTR 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) 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 AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. 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 and that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent, and assent when applicable, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent/assent was obtained before the patient was enrolled in the study and the date and time the written consent/assent was obtained. The authorised person obtaining the informed consent/assent 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 participation in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient, and he/she will not be excluded from other aspects of the study.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator, or designee, will explain to each patient the objectives of 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 exploratory research. Patients who decline to participate in this optional

research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, the AstraZeneca will not be obliged to destroy the results of this research.

The ICF will contain a separate sub-study addendum that addresses "Mechanistic Sub-study" and procedures. The investigator, or designee, will explain to each patient the objectives of the "Mechanistic Sub-study". 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 additional specimens to be used for the "Mechanistic Sub-study". 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.

The ICF will contain a separate sub-study addendum that addresses "Qualitative Patient Interview Sub-study" and procedures. The investigator, or designee, will explain the objectives of the "Qualitative Patient Interview Sub-study" to each patient. 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 sub-study.

A 4 Data Protection

Patients will be assigned a unique identifier by AstraZeneca. Any patient records or datasets transferred to AstraZeneca will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred.

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

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

A 5 Committees Structure

Data Safety Monitoring Board

An independent DSMB consisting of 2 clinicians (including at least one HES expert) and a statistician will be used for this study to monitor overall patient safety. The DSMB will receive patient profiles including safety data and unblinded patient laboratory results on a regular basis and will meet to discuss the data as needed. Based on their review, the DSMB

may recommend changes to the study design or conduct or that individual patients be discontinued from the study for safety reasons.

A separate statistical data analysis centre, independent of the CRO and AstraZeneca, will be appointed to generate datasets and analyses for the DSMB.

The statistical data analysis centre and DSMB will have access to the individual treatment codes and will be able to merge these with the collected study data while the study is ongoing as needed. The personnel involved in the clinical study at AstraZeneca and the CRO will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

The DSMB will communicate decisions/recommendations to an internal (AstraZeneca) Executive Committee that will consist of representatives from regulatory affairs, clinical development, biostatistics, and patient safety and will remain blinded to data. The committee will decide on the implementation of the DSMBs requests and will communicate back their actions and justification for them to the DSMB.

Further details, composition, and operation of the DSMB are described in the separate DSMB charter.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety.

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

A 7 Data Quality Assurance

All patient data relating to the study will be recorded in the eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.

AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study, which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the monitoring plan.

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

AstraZeneca assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).

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

A 8 Source Documents

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

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to

request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the monitoring plan.

A 9 Study and Site Start and Closure

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

The AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca 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, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further IP development

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

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.

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

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

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

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, 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 preexisting medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no IP has been administered.

B 2 Definition of Serious Adverse Events

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

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

Adverse events for **malignant tumours** reported during a study should generally be assessed as **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 (eg, Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy).

Life-threatening

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

Examples of such events are:

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

Intensity Rating Scale

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 an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the 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 recognised feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed 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 DUS has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

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

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 patient.

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IWRS/IVRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

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

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

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 patient or if the drug abuse involves a person not enrolled in the study (such as a relative of the study patient).

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 patient 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 patient) 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 patient or if the drug misuse regards a person not enrolled in the study (such as a relative of the study patient).

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 patient feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

All appropriately consented samples will be retained for maximum 15 years from last patient last visit.

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 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/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

Labelling and Shipment of Biohazard Samples

The International Air Transport Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies biohazardous agents into 3 categories: Category A, Category B or Exempt.

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

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

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

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

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

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

Appendix D Optional Genomics Initiative Sample

D 1 Use/analysis of DNA

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.

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 healthcare, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

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.

This optional genetic research may consist of the analysis of the structure of the patient's DNA, ie, the entire genome.

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

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

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

Study Selection Record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines participation, 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 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
- Healthy volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

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 7.2 of the main CSP.

Collection of Samples for Genetic Research

The blood sample for this genetic research will be obtained from the patients at Visit 3 or at any other visit if not collected at randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

Coding and Storage of DNA Samples

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

An additional second code will be assigned to the blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at 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 A.

Informed Consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study, the patient must sign and date both the consent form for the main study and the optional genetic research information ICF. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study site. The principal investigator(s) is(are) 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 or genotype results to patients, any insurance company, any employer, their family members, or 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. 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 organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this 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 Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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

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

The detection and documentation procedures described in this protocol apply to all sponsor combination products provided for use in the study. See Section 6.1.2 for the list of sponsors combination products.

E 1 Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition

- A medical device AE is any untoward medical occurrence in a clinical study patient, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medical device. This definition includes events related to the medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to medical devices.
- An ADE is defined as an AE related to the use of a medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device as well as any event resulting from use error or from intentional misuse of the medical device.

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

Medical Device SAE Definition

A medical device SAE is any AE that:

- Led to death.
- Led to serious deterioration in the health of the patient, that either resulted in:
  - A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

  - A permanent impairment of a body structure or a body function.
  - Inpatient or prolonged hospitalisation. Planned hospitalisation for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Chronic disease (European Medical Device Regulation 2017/745).
- Led to foetal distress, foetal death, or a congenital anomaly or birth defect.

A Medical Device SADE is:

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

Unanticipated SADE (USADE) Definition

- An USADE (also identified as UADE in United States Regulations 21 CFR 812.3), is defined as a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (Section 2.3).

E 3 Definition of Medical Device Deficiency

Medical Device Deficiency Definition

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

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

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the patient's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to AstraZeneca in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by AstraZeneca. In this case, all patient identifiers, except for the patient number, will be redacted on the copies of the medical records before submission to AstraZeneca.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the causal relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB or US Product Information/European Union Summary of Product Characteristics in his/her assessment.
- For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to AstraZeneca. However, it is very important

that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to AstraZeneca.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Medical Device Coordination Group 2020 Guidance

For the purpose of harmonising reports, each SAE will be classified according to five different levels of causality. AstraZeneca and the investigators will use the following definitions to assess the relationship of the SAE to the investigational[1] device or procedures.

1 Not related: Relationship to the device or procedures can be excluded when:

- The event has no temporal relationship with the use of the investigational device or the procedures;
- The serious event does not follow a known response pattern to the investigational device (if the response pattern is previously known) and is biologically implausible;
- The discontinuation of investigational device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact the serious event;
- The event involves a body-site or an organ not expected to be affected by the device or procedure;
- The serious event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors)
- The event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2 Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3 Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or

[1] Investigational device: any device object of the clinical investigation, including the comparators

concurrent illness/ clinical condition or/and an effect of another medical device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4 Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5 Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- The event is a known side effect of the product category the investigational device belongs to or of similar devices and procedures;
- The event has a temporal relationship with investigational device use/application or procedures;
- The event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures influence;
- The serious event follows a known response pattern to the investigational device (if the response pattern is previously known);
- The discontinuation of investigational device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- Other possible causes (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- Harm to the patient is due to error in use;
- The event depends on a false result given by the investigational device used for diagnosis, when applicable.

To establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by AstraZeneca to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other HCPs.
- If a patient dies during participation in the study or during a recognised follow-up period, the investigator will provide AstraZeneca with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the original form used to report the deficiency.
- The investigator will submit any updated SAE data to AstraZeneca **within 24 hours** of receipt of the information.

E 5 Reporting of Medical Device SAEs and SADEs

- All medical device SAEs will be reported in accordance with Section 8.4.7.

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

- Any medical device deficiency that is associated with an SAE must be reported to AstraZeneca **within 24 hours** after the investigator determines that the event meets the definition of a medical device deficiency.
- In addition to the reporting process described in Section 8.4.7, the AstraZeneca clinical study medical device/device constituent report form will be used to capture details of the device and related deficiency (Section 8.4.11.3).
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca clinical study medical device/device constituent report form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the site file.

Appendix F Anaphylaxis: Definition, Signs, Symptoms, and Management

F 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organisation has categorised anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg, IgG and immune complex-mediated]) and nonimmunologic (Johansson et al 2004). The clinical criteria for defining anaphylaxis for this study are listed in Appendix F 2. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Appendix F 3. Appropriate drugs (ie, epinephrine, antihistamines, corticosteroids, etc.) and medical equipment to treat anaphylactic reactions should be available at study sites, and study personnel should be trained to recognise and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected at 90 minutes ±30 minutes after the event; analysis for serum tryptase will be performed at a local or central laboratory. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local laboratory at the discretion of the investigator.

F 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

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 (eg, generalised hives, pruritus or flushing, swollen lips-tongue-uvula)

2 AND AT LEAST 1 OF THE FOLLOWING:

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

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

3 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 (eg, generalised hives, itch-flush, swollen lips-tongue-uvula).

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

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

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

4 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that patient's baseline.

Immune Complex Disease

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

F 3 Signs and symptoms and management of acute anaphylaxis

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

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

Other earlier or concomitant signs and symptoms can include:

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

F 4 Management of Acute Anaphylaxis

F 4.1 Immediate Intervention

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

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

F 4.2 Possibly Appropriate, Subsequent Measures Depending on Response to Epinephrine

1 Place patient in recumbent position and elevate lower extremities.

2 Establish and maintain airway.

3 Administer oxygen.

4 Establish venous access.

5 Normal saline IV for fluid replacement.

F 4.3 Specific Measures to Consider after Epinephrine Injections, Where Appropriate

1 Consider epinephrine infusion.

2 Consider H1 and H2 antihistamines.

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

4 Consider systemic corticosteroids.

5 Consider vasopressor (eg, dopamine).

6 Consider glucagon for patient taking β-blocker.

7 Consider atropine for symptomatic bradycardia.

8 Consider transportation to an ER or an intensive care unit facility.

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

Adapted from Kemp et al 2008.

Appendix G Investigator-led HES Symptom Interview

The following assessments were adapted from signs and symptoms reported in Curtis and Ogbogu 2016, Kovacs et al 2016, Ogbogu et al 2009, and Weller and Bubley 1994. The assessments should be based on the symptoms the patient is currently experiencing (see Section 8.2.1.2 for details).

Visit 1 only

The investigator asks the patient whether she/he has had these symptoms from HES:

The investigator asks the patient if she/he is currently experiencing one of the symptoms listed.

Yes or no?

For all Yes responses:

Ask the patient to rate the severity of the symptom now: mild/moderate/severe

- Mild – the symptom results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (for example, insomnia, mild headache).
- Moderate – the symptom is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (for example, fever requiring antipyretic medication).
- Severe – symptom results in significant symptoms that prevent normal daily activities; may require hospitalisation or invasive intervention.

Ask the patient to rate the severity of the symptom when not experiencing a worsening/flare: no symptom/mild/moderate/severe

The investigator asks the patient to list the top 3 most bothersome symptoms and rank them from 1 (most bothersome) to 3 (least bothersome).

Visit 1 only

General symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when <u>not</u> experiencing a flare?
Fatigue	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Fever	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Chills / sweats	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Malaise – general feeling of discomfort, illness, or lack of well-being	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Hair loss	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate

			☐Severe
General weakness	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Skin Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when not experiencing a flare?
Skin rash	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Skin hives (urticaria)	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Skin itching	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Skin swelling (angioedema)	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild

		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Digestive Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when <u>not</u> experiencing a flare?
Nausea / vomiting	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Difficulty swallowing	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Upper abdomen discomfort (bloating, tightness, fullness)	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Abdominal pain	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Diarrhoea	☐Yes	☐Mild	☐No symptom

	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Constipation	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Chest and Breathing Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when not experiencing a flare?
Shortness of breath	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Cough	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Wheeze	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Chest pain	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Heart palpitations	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Nasal and Vision Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when <u>not</u> experiencing a flare?
Sinus congestion (pain, pressure)	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Runny nose	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Ear pain / drainage	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate

			☐Severe
Eye redness / irritation	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Blurry vision	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Muscle and Joint Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when not experiencing a flare?
Muscle pain	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe
Joint pain	☐Yes	☐Mild	☐No symptom
	☐No	☐Moderate	☐Mild
		☐Severe	☐Moderate
			☐Severe

Visit 1 only

Neurological Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?	**If yes,** what is the severity when not experiencing a flare?
Headache	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Dizziness / light-headedness	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Trouble with balance / coordination	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Memory / cognitive difficulties	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe
Tingling / burning / numbness	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate

			☐Severe
Weakness in 1 or more extremities	☐Yes ☐No	☐Mild ☐Moderate ☐Severe	☐No symptom ☐Mild ☐Moderate ☐Severe

Rank the top 3 most bothersome symptoms from 1 = most bothersome to 3 = least bothersome.

Most bothersome symptom – rank 1: <spinner: list only symptoms with "Yes" responses>

Most bothersome symptom – rank 2: <spinner: list only symptoms with "Yes" responses, removing rank 1 symptom>

Most bothersome symptom – rank 3: <spinner: list only symptoms with "Yes" responses, removing rank 1 and rank 2 symptoms>

<Confirmation screen showing top 3 most bothersome symptoms and ranks>

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

The investigator asks the patient whether she/he has had these symptoms from HES:

The investigator asks the patient if she/he is currently experiencing 1 of the symptoms listed.

Yes or no?

For all Yes responses

Ask the patient to rate the severity of the symptom now: mild/moderate/severe

- Mild – the symptom results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (for example, insomnia, mild headache).

- Moderate – the symptom is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (for example, fever requiring antipyretic medication).
- Severe – symptom results in significant symptoms that prevent normal daily activities; may require hospitalisation or invasive intervention.

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

General symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Fatigue	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Fever	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Chills / sweats	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Malaise – general feeling of discomfort, illness, or lack of well-being	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Hair loss	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
General weakness	☐Yes ☐No	☐Mild ☐Moderate

		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Skin Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Skin rash	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Skin hives (urticaria)	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Skin itching	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Skin swelling (angioedema)	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Digestive Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Nausea / vomiting	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Difficulty swallowing	☐Yes	☐Mild

	☐No	☐Moderate
		☐Severe
Upper abdomen discomfort (bloating, tightness, fullness)	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Abdominal pain	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Diarrhoea	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Constipation	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Chest and Breathing Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Shortness of breath	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Cough	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

Wheeze	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Chest pain	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Heart palpitations	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Nasal and Vision Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Sinus congestion (pain, pressure)	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Runny nose	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Ear pain / drainage	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Eye redness / irritation	☐Yes	☐Mild
	☐No	☐Moderate

		☐Severe
Blurry vision	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Muscle and Joint Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Muscle pain	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Joint pain	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe

After Visit 1 (subsequent regularly scheduled visits and worsening/flare visits):

Neurological Symptoms	**Is the patient currently experiencing this symptom?**	**If yes,** what is the severity now?
Headache	☐Yes	☐Mild
	☐No	☐Moderate
		☐Severe
Dizziness /	☐Yes	☐Mild
light-headedness	☐No	☐Moderate
		☐Severe

Trouble with balance / coordination	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Memory / cognitive difficulties	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Tingling / burning / numbness	☐Yes ☐No	☐Mild ☐Moderate ☐Severe
Weakness in 1 or more extremities	☐Yes ☐No	☐Mild ☐Moderate ☐Severe

Appendix H HES Physical Examination

The following assessments were adapted from Bates 1991.

Category	Item	Response	If yes/abnormal…
General	Physical appearance	Free text	
	Speech	Normal/abnormal	Specify
Skin	Rash	Yes/no	Location, description
	Lesions	Yes/no	Location, description
	Cyanosis, pallor	Yes/no	Specify
	Ulcers	Yes/no	Specify
Head	Head motion	Normal/abnormal	Specify
	Face expression, asymmetry	Normal/abnormal	Specify
Eyes	PERRLA	Normal/abnormal	Specify
	Eye movements	Normal/abnormal	Specify
	Sclera jaundice	Yes/no	Specify
	Red eyes	Yes/no	Specify
Nose	Discharge	Yes/no	Specify
	Congestion of turbinates	Yes/no	Specify
	Polyps	Yes/no	Specify
	Sinus tenderness	Yes/no	Specify
Mouth/throat	Ulcerations	Yes/no	Location, description
	Pharynx congestion	Yes/no	Specify
	Exudates	Yes/no	Specify
	Gum swelling	Yes/no	Specify
	Palate/tongue asymmetry	Yes/no	Specify
Neck	Inspect	Normal/abnormal	Specify
	Lymph nodes	Normal/abnormal	Specify
	Masses	Yes/no	Specify
	Thyromegaly	Yes/no	Specify
Chest/lungs	Inspect	Normal/abnormal	Specify
	Palpate	Normal/abnormal	Specify
	Auscultation	Normal/abnormal	Rales, rhonchi, or wheeze
Heart	Inspect	Normal/abnormal	Specify
	Palpate	Normal/abnormal	Specify
	Auscultation/abnormal heart sounds	Normal/abnormal	Abnormal rate/rhythm? Murmur? Distant/faint?

Category	Item	Response	If yes/abnormal…
	Arrhythmia	Yes/no	Specify
Abdomen	Inspection	Normal/abnormal	Scar? Hernia? Ascites?
	Auscultation	Normal/abnormal	Specify
	Palpation	Normal/abnormal	Tenderness? Masses? Liver/spleen enlargement?
Upper extremities	Nails	Normal/abnormal	Clubbing Splinter haemorrhage
	Mobility (range of motion)	Normal/abnormal	Specify
	Muscle tenderness?	Yes/no	Specify
	Signs of joint inflammation	Yes/no	Specify
	Strength	Normal/abnormal	Specify
	Deep tendon reflexes	Normal/abnormal	Specify
Lower extremities	Mobility (range of motion)	Normal/abnormal	Specify
	Muscle tenderness?	Yes/no	Specify
	Signs of joint inflammation	Yes/no	Specify
	Swelling	Yes/no	Specify
	Strength	Normal/abnormal	Specify
	Deep tendon reflexes	Normal/abnormal	Specify
	Oedema	Yes/no	Specify
Neurological	Gait	Normal/abnormal	Specify
	Romberg, finger-nose-finger	Normal/abnormal	Specify
	Test for vibration	Normal/abnormal	Specify
	Test for light touch	Normal/abnormal	Specify
	Cranial nerves (not examined already + summary)	Normal/abnormal	Specify

A brief physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, and abdomen.

For flare visits, positive HES signs and symptoms should be reported.

BMI = body mass index; HES = hypereosinophilic syndrome; PERRLA = pupils equal, round, and reactive to light and accommodation.

Appendix I Oral Corticosteroid Dose Equivalences

Systemic corticosteroid	Approximate equivalence dose (mg)
Prednisone	10
Prednisolone	10
Cortisone	50
Hydrocortisone	40
Methylprednisolone	8
Triamcinolone	8
Betamethasone	1.2
Budesonide	4.2
Dexamethasone	1.5
Deflazacort	12

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

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study 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 agreement from AstraZeneca 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 assessment and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions, and other measures implemented to ensure patient's safety. In case of doubts please contact the AstraZeneca Study Physician. If patient testing is performed as a result of the public health crisis, results may be documented for this study.

J 1 Consent /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, eg, remote visits. Consent/Reconsent should be obtained for the alternative means of carrying out visits and assessments prior to performing the procedures described in Sections J 2to J 6. Local and regional regulations and/or guidelines regarding consenting/reconsenting of study patients should be checked and followed. Consent/reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal consent/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.

J 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. 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 5.5.1, the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a patient in addition to that detailed in Section 5.5.1. The procedures detailed in Section 5.5.1 must be undertaken to confirm eligibility using the same randomisation number as for the patient].

J 3 Home or Remote Visit to Replace Onsite Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the patients at home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP. If applicable, assessments will be performed according to the revised SoA.

J 4 Telemedicine Visit to Replace Onsite 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, onsite visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow the study team to report and document information about AEs, concomitant medication, and other assessments that may be collected at the discretion of the investigator. If applicable, safety procedures will be performed according to the revised SoA in the study instructions for 'Mitigation Due to Civil Crisis, Natural Disaster, or Public Health Crisis'.

J 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, eg, site closures due to natural disaster.

J 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.

J 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.

J 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 will be reported by the patient themselves.

Appendix K Protocol Amendment History

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

K 1 Amendment 7 (12 June 2023)

CSP version 8 (12 June 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Amendment

The primary reason for this amendment is to modify the number of patients required to have a flare for the primary analysis from 47 to approximately 38 flares and to ensure that enough patients are enrolled in order to observe this number of flares. Clinical trial patients are challenging to identify and recruit from rare disease patient populations, which is further exacerbated in hypereosinophilic syndrome by the availability of mepolizumab as a treatment option. This reduced flare target will still allow high power CCI for statistical significance to be demonstrated under the assumptions outlined in the sample size justification.

In addition, the primary analysis will now be implemented when the flare target is achieved, rather than when all randomised patients are followed-up for 24 weeks. A follow-up analysis will be completed once all randomised patients complete the 24 weeks of the double-blind period. This updated primary analysis target is appropriate for an event-driven primary endpoint given that the appropriate power for the primary analysis is achieved when the target number of flare events are available.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
All applicable sections	The number of patients required to have a flare for the primary analysis was changed from 47 to approximately 38 flares.	This revision was made due to the challenges in identifying and recruiting HES patients as well as the availability of mepolizumab as a treatment option. This change in the number of flares still provides robust data to adequately assess the clinical objectives.
1.1 Synopsis 1.2 Schema 1.3 SoA 4.1Overall Design 9.4.2 Efficacy Analysis	The following revision was made: Originally, the primary DBL was set to occur when at least 47 patients have had their first HES worsening/flare event during the DB period and all randomised patients had the opportunity to complete the 24-week DB period.	This updated primary analysis target is appropriate for an event-driven primary endpoint given that the appropriate power for the primary analysis is achieved when the target number of flare events are available.

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
	In CSP v8.0, the data cut-off for the primary DBL will now occur when approximately 38 patients have had their first HES worsening/flare during the DB period.	
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The following endpoints in the DB period are now "key secondary endpoints": • Proportion of patients who experience an HES worsening/flare during the DB period. • Number of HES worsenings/flares (annualised rate/year) during the DB period. • Time to first haematologic relapse (AEC ≥ 1000 cells/μL) during the DB period. • Fatigue severity (PROMIS fatigue short form 7a) at Week 24.	Adjustment of endpoint prioritisation including promotion of endpoints to key secondary endpoints to ensure that clinically meaningful endpoints are multiplicity protected.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	The exploratory objective in the DB period (in CSP v7.0) "To evaluate the effect of benralizumab on the number of HES worsenings/flares" and its corresponding endpoint "Number of HES worsenings/ flares (annualised rate/year) during the DB period" are now (in CSP v8.0) a key secondary objective and endpoint.	Revision was made to align with health authority precedent for this endpoint for label inclusion.
1.1 Synopsis 4.1 Overall Design 9.2 Sample Size Determination	Text added to indicate that approximately 120 eligible patients will be randomised, but recruitment may continue until the target number of HES worsening/flares is achieved.	To clarify that more than 120 patients may be recruited if the target number of HES worsenings/flares (n = 38) has not been reached at 120 randomised patients. This will ensure that the target number of flares to allow high power CCI for statistical significance is achieved.
1.1 Synopsis 9.2 Sample Size Determination	The following revision was made: <u>Previous CSP v7.0 text:</u> Assuming at least 120 patients are randomised, with CCI of patients on benralizumab experiencing an event by the end of the DB treatment period compared to CCI of patients on placebo (equivalent to a hazard ratio of CCI), 47 first HES worsening/flare events during the DB treatment period are required to detect a difference between treatment groups at the CCI CCI significance level with CCI power. <u>New CSP v8.0 text:</u> Approximately 38 first HES worsening/flare events during the DB period are required to detect a statistically significant difference between treatment groups at the CCI significance level with approximately CCI power if the true treatment effect is a hazard ratio of CCI (equivalent to CCI of patients on benralizumab experiencing an event by the end of the DB period compared to CCI of patients on placebo).	This revision was made due to the challenges in identifying and recruiting HES patients as well as the availability of mepolizumab as a treatment option. This change in the number of flares still provides robust data to adequately assess the clinical objectives.
1.1 Synopsis	The following revision was made: <u>Previous CSP v7.0 text:</u> To account for multiplicity testing for the primary endpoint (time to first HES worsening/flare) and the key secondary endpoint (time to first haematologic relapse), a hierarchical fixed-	To describe the plan to multiplicity-protect the primary and updated key secondary endpoints at the primary analysis. This revision is in line with key secondary endpoint reprioritisation to ensure that

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
	sequence testing strategy will be used to control the overall type I error rate at the [redacted] level. New CSP v8.0 text: To account for multiple testing for the primary endpoint (time to first HES worsening/flare during the DB period) and the key secondary endpoints (proportion of patients who experience an HES worsening/flare during the DB period, number of HES worsenings/flares during the DB period, time to first haematologic relapse during the DB period, change from baseline in PROMIS fatigue score at Week 24), a hierarchical fixed-sequence testing strategy (testing endpoints in the order outlined above at the primary analysis) will be used to control the overall type I error rate at the [redacted] level.	clinically meaningful endpoints are multiplicity protected.
9.4.5 Methods for Multiplicity Control	The following revisions were made: • Hierarchical fixed sequence testing will now occur for the primary endpoint and the 4 key secondary endpoints (testing endpoints in the order outlined above) instead of for the primary endpoint and "time to first haematologic relapse." • If at any time the null hypothesis cannot be rejected, or if the treatment difference favours the placebo arm, no further testing of the key secondary endpoints will occur. • Only the primary analysis will be multiplicity protected; the updated analysis of the DB treatment period and the analyses of the OLE period will not be multiplicity protected.	In line with the reprioritisation of key secondary endpoints, the multiplicity procedure has been updated to control for multiple testing across the primary and key secondary endpoints at the primary analysis.

AEC(s) = absolute eosinophil count(s); DB = double blind; CSP = clinical study protocol; DBL = database lock; HES = hypereosinophilic syndrome; n = number of patients in the respective category; OLE = open-label extension; PROMIS = Patient-reported Outcomes Measurement Information System; SoA = schedule of activities; v7.0 or v8.0 = version 7.0 or version 8.0.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Cover page	Added row for EudraCT/EU CT number	This row was added per AstraZeneca CSP template requirements for studies conducted in EU/EEA.
All applicable sections	Total WBC count will not be blinded to site staff and investigators.	Total WBC will not unblind the treatment arm.
All applicable sections	Minor updates to footnotes were added as needed.	Revisions were made to correct typos, add new definitions, and correct format as needed.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
All applicable headings and sections	Minor updates were made to several heading and subheading titles. Several sections were rearranged throughout the protocol.	Revisions were made to align headings/sections with the current AstraZeneca CSP template.
All applicable sections	The following revision was made: The option for at-home self-administration of IP and remote visits was changed from "after Visit 16" to "after Visit 10."	To reduce patient and site burden, optional remote visits with IP administration will start earlier.
List of Abbreviations	The abbreviations list was updated as needed.	List updated per AstraZeneca CSP template requirements
1.1 Synopsis	A new section "Brief Summary" was added. This summary provides a short description of the clinical study, including the clinical study's hypothesis. The summary includes the condition/disease, study duration, treatment duration, health measurement/observation, and visit frequency.	New section added per AstraZeneca CSP template requirements. The summary should make clear what the study is about and can be used for informed consents and ethics committee submissions as well as the summary in clinicaltrials.gov.
1.1 Synopsis	A new section "Disclosure Statement" was added: This is a randomised, DB, parallel-group, interventional study with 2 treatment arms (benralizumab and placebo) that are blinded to patients, site-staff, and investigators.	New section added per AstraZeneca CSP template requirements.
1.1 Synopsis	Text was revised in the synopsis (text deleted is strikethrough and text added is underlined): Patients who ~~fail~~ are not corticosteroid responsive or fail any other eligibility criteria will be screen failed.	To clarify that corticosteroid responsiveness is necessary for eligibility; text revised to ensure consistency with Section 4.1.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	Text was added to secondary endpoints (text added is underlined): • Time to first haematologic relapse (AEC ≥ 1000 cells/μL) during the DB period. • Proportion of patients who have haematologic relapse during the DB period.	Text added to ensure consistency with the other secondary endpoints.
1.1 Synopsis 3 OBJECTIVES AND ENDPOINTS	ECG removed as a safety endpoint/variable for the DB and OLE periods.	Revisions align with PSSR and labelling; Electrocardiographic safety has been well characterised from multiple studies conducted for product development. Routine cardiac monitoring is not required. ECG can be done if clinically indicated.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3 SoA (all tables) 3 OBJECTIVES AND ENDPOINTS 8.9.1 Biopsy	The following revisions were made: • Tissues biopsies will only be performed during the DB (Table 1) and first year of the OLE (Table 2) as per the SoA; biopsies were removed from Year 2 (Table 3) of the OLE until the end of the study (Table 4). • Evaluation of exploratory biomarkers in tissue biopsies is now applicable only to the DB period and Year 1 of the OLE.	Additional biopsies removed to reduce site and patient burden.
1.1 Synopsis 4.1 Overall Design	Text was added: Treatment allocation will remain blinded until the primary DBL. After the study is unblinded for the primary analysis, patients and investigators will remain blinded to patients' individual treatment allocations until after the final patient completes the DB treatment period.	Text added for clarification.
1.1 Synopsis 4.1 Overall Design 9.4.1 General Considerations	Text was added to indicate that a follow-up analysis will be completed once all randomised patients complete the 24 weeks of the DB period.	This revision ensures that safety and efficacy data are collected for the full DB period.
1.3 SoA (all tables)	The following revisions were made: • Urinalysis (local [dipstick] and central lab assessments) were removed from all SoA tables.	Reduce patient and site burden as urinalysis results have been well characterised from multiple studies for product development.
	• Footnotes revised or added to all SoA tables to clarify that 2 central samples will be collected for haematology and WBC with differential. Current Table 1 footnote "p" and Table 2 footnote "j" were revised; current Table 3 footnote "h" and Table 4 footnote "i" were added.	Text added to clarify study procedures.
	• New footnote was added to the brief physical examination at a flare visit (all tables): For flare visits, positive HES signs and symptoms should be reported.	
	• Urine pregnancy testing schedule updated from before each IP administration to quarterly tests.	Alignment with Clinical Trials Facilitation and Coordination Group guidance on pregnancy testing in clinical trials.
1.3 SoA (Table 2, Table 3, and Table 4)	The following revisions were made: • Table 2: Spirometry removed from V12 and V19 and changed to end of OLE Year 1 (V22). Assessment retained for flare visits. • Table 3 and Table 4: Spirometry has been removed from OLE Year 2 and OLE Year 3 and beyond. • Weight is now every 6 months starting at V10. • Footnote "b" (in Table 2 and Table 3) and "c" (in Table 4) were revised: Removed physical examination and weight assessments from the footnote as applicable because time points for these assessment were updated.	Spirometry is not required for safety or efficacy evaluations. Additional testing has been removed to reduce patient and site burden.
	• Footnote text added to indicate that "During the telemedicine (remote) visits, a WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status." Text was added to Table 2 footnote "i", Table 3 footnote "g", and Table 4 footnote "h."	Text added to clarify study procedures for WOCBP.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.3 SoA (Table 1) 6.3.1 Methods for Assigning Treatment Groups 8.8 Optional Genomics Initiative	The term "optional genetic(s)" was replaced with the term "optional genomics initiative"	Term was updated to align with AstraZeneca CSP template requirements.
1.3 SoA (Table 1)	The following revisions were made: • Complete HES physical examination was removed from V3-V8, flare, and IPD visits; retained at V1 and V9. • Brief physical examinations were added at V3-V8, flare, and IPD visits. • Weight was removed from V3-V8, flare, and IPD visits; retained at V1 and V9. • ECG was removed from V1, V12, V24, flare, and IPD visits; added to V3. • Clinical chemistry (central lab) was removed from V3-V8 and IPD visit; retained at V1, V9, and flare visit. • Serology (Hep B and C, HIV-1 and 2) removed from V9 and IPD visit; retained at V1.	Benralizumab has a well characterised safety profile in other indications; therefore, the frequency of monitoring safety labs, ECGs, and physical exams were decreased to reduce patient and site burden.
	• "Whole blood for immunophenotyping (all sites)" in CSP v7.0 was changed to "Whole blood for PBMC (NIH, NW) and SMART tubes (AZ)" in CSP v8.0. • "Whole blood for eosinophil phenotyping (select sites only)"in CSP v7.0 was changed to "Whole blood for eosinophil phenotyping (NW) (North America only)" in CSP v8.0. • Footnotes "y" and "z" were added (see below).	Text was revised to align with the laboratory manual and provide clarification regarding sample collection for the mechanistic sub-study.
1.3 SoA (Table 1)	The following footnotes were added or revised: • Footnote "j" in CSP v7.0: Results from historical echocardiogram conducted within 12 months of Visit 1, if available, assessed for clinical significance by the investigator. Now footnote "k" in CSP v8.0: For patients with known or suspected cardiac involvement, heart function should be assessed for clinical significance, either by an historical echocardiogram done within 12 months of Visit 1 or during screening if the historical echocardiogram is not available. • New text added to footnote "o": If a WOCBP is attending an onsite visit where a urine pregnancy test is not scheduled, she will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status. • New footnote "q": Serum pregnancy test to be performed at Visit 1 and subsequently only if the urine pregnancy (dipstick) test is positive. • Footnote "v" in CSP v7.0: Whole blood for eosinophil phenotyping will be selected sites only, while whole blood for DNA analysis and for immunophenotyping will be from all sites. Now footnote "x" in CSP v8.0: All blood samples related to the mechanistic sub-study apply to all sites, except for whole blood for eosinophil phenotyping, which is applicable to North America only. The other	Footnotes revised or added to clarify study procedures and/or to match protocol updates.

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Section Number and Name	Description of Change	Brief Rationale
	blood samples apply to all study sites and include 2 samples for PBMC analysis, one sample in SMART tubes for immunophenotyping, and one sample for DNA analysis. • New footnote "y": The NIH will perform PBMC analysis, Northwestern University will perform additional PBMC analysis and fresh eosinophil phenotyping, and AstraZeneca will perform the analysis of SMART tubes. If the PBMC sample collection is missed at Visit 1, the sample can be taken at Visit 4 or Visit 5 (not Visit 2 or Visit 3). • New footnote "z": (applicable to the sample for whole blood for DNA analysis to be collected for the mechanistic sub-study): DNA sample collection preferred at screening, but it can be taken at later time points.	
1.3 SoA (Table 2)	The following revisions were made: • Additional visits can now be done remotely: ° Optional remote visits in CSP v7.0: V17, V18, V20, and V21. ° Optional remote visits in CSP v8.0: V11, V12, V14, V15, V17, V18, V20, and V21.	Revisions made to reduce patient and site burden.
	• V10: Clinical chemistry and troponin (central lab) were added. • V11: Haematology, WBC with differential only, clinical chemistry, and troponin labs (central lab) were removed. • V14: Haematology, WBC with differential labs (central lab) were removed.	Revisions made to reduce patient and site burden and align laboratory assessments to mandatory onsite visits.
2.3 Benefit/Risk Assessment	Sentence removed: In total, 238 AEs were reported during the DB treatment period. New text added (underlined): Risk minimisation measures include exclusion of patients with life-threatening HES …, active or recent malignancy with certain exceptions, and exclusion of pregnant women (Section 5.2).	Sentence is not relevant to the topic. Text revision added for consistency with exclusion criterion 8 (see below).
4.1 Overall Design 6.3.2.1 Maintaining the Blind to the Patient's Eosinophil Counts	New text added: The site and patients will remain blinded after the primary DBL (ie, study conduct at the site and patient level remains the same throughout the DB period).	Text added for clarification to ensure that appropriate blinding procedures are followed during the conduct of the study. Revision ensures consistency between Sections 4.1 and 6.3.2.1.
4.1.1 Screening (Enrolment up to Randomisation)	New text was added: • For patients with known or suspected cardiac involvement, heart function should be assessed. • If no historical echocardiography results are available, an echocardiogram will be performed during screening.	Text added to clarify that heart function will only be assessed on patients with known and suspected cardiac involvement. The text also clarifies when an echocardiogram is to be performed during screening.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
4.1.3 Open-label Treatment Period (Week 24 to End of Treatment)	Text was added (new text is underlined and deleted text is strikethrough): • Patients will attend scheduled clinic visits at 4-week intervals throughout the OLE treatment period; however, to reduce patient burden and allow flexibility, patients will have the option to self-administer IP or have IP administered by their caregiver at home or at a remote location using an APFS after ~~Visit 16~~ Visit 10/Week 28 (Section 6.1.5). For these patients, some visits do not include extensive onsite assessments and can optionally be performed as remote visits through telephone/telemedicine contact as indicated in the SoA.	Further clarify the optional self-administration visit schedule in Section 6.1.5 for the OLE period.
	• Background therapy for HES may be adjusted after this time (Section 6.5.1), unless a modification is required for a HES clinical worsening/flare or an AE thought to be due to background therapy.	Text added to further clarify when HES background therapy may be adjusted and to ensure consistency with other sections of the CSP.
4.4 End-of-Study Definition	Clarified definition of the end of study according to European Union and Food and Drug Administration requirements.	Revisions made for consistency and alignment in terms of posting study results.
5.2 Exclusion Criteria	Exclusion criterion 8 was revised as follows: Previous CSP v7.0 text: 8 Current malignancy, or history of malignancy, except: (a) Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided the patient is in remission and curative therapy was completed at least 12 months prior to the date that informed consent, and assent when applicable, was obtained. (b) Patients who have had other malignancies are eligible provided the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained. New CSP v8.0 text: 8 Current or history of malignancy within 5 years before the screening visit with the following exceptions: (a) Patients treated for in situ carcinoma of the cervix who have completed curative therapy and are in remission for at least 12 months prior to signing the informed consent and (b) Patients with basal cell or superficial squamous skin cancer. (c) 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 the date informed consent was obtained.	Text amended as risks with superficial skin cancers have not been identified. Skin superficial cancers do not generally metastasise and are not difficult to diagnose. We do not expect an increased risk for these cancers.
5.2 Exclusion Criteria	Exclusion criterion 14 was revised as follows: Previous CSP v7.0 text: 14 Previously received benralizumab. New CSP v8.0 text: 14 Evidence of prior benralizumab treatment failure.	Text updated as prior benralizumab use will not affect study endpoints.

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Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion 17 was revised as follows: Previous CSP v7.0 text: 17 Receipt of any biologic product (monoclonal or polyclonal antibody) within 4 months or 5 half-lives prior to Visit 1, whichever is longer, and during the study period. New CSP v8.0 text: 17 Receipt of any marketed or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer. Patients on stable therapy for at least 3 months before randomisation who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study.	Updated text for clarification on the use of biologics and to align with benralizumab's safety profile.
5.2 Exclusion Criteria	Exclusion criterion 22 was revised (deleted text is strikethrough): 22 For women only: Currently pregnant, breastfeeding, or lactating women (a) Both urine and serum pregnancy tests will be done for WOCBP at Visit 1 ~~and a urine pregnancy test must be performed for WOCBP at each treatment visit prior to IP administration. A positive urine test result must be confirmed with a serum pregnancy test~~. If serum test is positive, the patient should be excluded.	Updated exclusion criterion #22 for clarity as this criterion is to confirm eligibility.
5.3 Criteria to be Confirmed/Reconfirmed Prior to Randomisation (Visit 3)	New text was added (underlined): ECG: No evidence of clinically significant abnormality from the ECG performed at Visit 3 (exclusion criterion 6).	Text added for clarification.
6.1.2 Medical Devices Including Combination Products with a Device Constituent 8.4.11 Medical Device Deficiencies Appendix E Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added section regarding combination products with a device constituent and third-party medical devices for use in the study. Updated current language regarding device deficiencies including definitions and reporting of medical device deficiencies. Updated language in the Appendix regarding intensity definitions for medical devices and language describing the processes to follow if device deficiencies fulfil the definition of an AE/SAE. Previous Appendix E 5 (in CSP v7.0) "Reporting of SAEs" was removed.	To comply with regulatory requirement(s) (eg, EU-CTR) and global company requirement in CSP template. Text removed because it is not relevant to the section.
6.1.5 Optional Self-Administration of Investigational Product	The following revisions were made: • The option for at-home self-administration of IP and remote visits was changed from "after Visit 16" to "after Visit 10." • Text added (underlined): … IP administered by their caregiver at home or at a remote location using the	To reduce patient and site burden, optional remote visits with IP administration will start earlier and pregnancy test was changed to quarterly tests.

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Section Number and Name	Description of Change	Brief Rationale
	APFS after Visit 10 where allowable by local health authorities and ethics committees. • Home pregnancy test in the OLE for WOCBP who are doing optional remote visits with IP self-administration (after Visit 16) was removed. • Text removed is strikethrough and text added is underlined: IP kits ~~and urine dipsticks for pregnancy testing (for WOCBP)~~ for the remote visits may be dispensed starting from ~~Visit 16 (Week 52)~~ Visit 10/Week 28 … • Text added: Urine pregnancy tests will be performed onsite per the SoA. • Text added (underlined): If the IP is administered by the patient or their caregiver, IP should be administered on the day of a scheduled visit after all remote visit assessments are completed. • Text added: A WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed. Testing can be used to confirm pregnancy status.	Patients doing optional remote visits with IP self-administration will have mandatory onsite visits quarterly; therefore, the pregnancy test can be done at the onsite visits per the SoA. This revision ensures PI/site alignment to inclusion criterion #9 (contraception methods) and lifestyle considerations (Section 5.4) on avoiding pregnancy.
6.5.3 Restrictions (Table 8)	The following text was added to "Any biologic product (monoclonal or polyclonal antibody)": Patients on stable therapy for at least 3 months before randomisation who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study (AstraZeneca should be informed when COVID-19 prevention or treatment is utilised).	Alignment with exclusion criterion 17 and the known benralizumab safety profile.
6.8 Treatment of Overdose 8.4.10 Reporting of Overdose	The following revisions were made: • Previous Section 8.4.3 "Overdose" in CSP v7.0 is now divided in 2 sections in CSP v8.0: 6.8 "Treatment of Overdose" and 8.4.10 "Reporting of Overdose" • Template text was added in Section 6.8 to explain what the investigator should do in case of an overdose. • Text in Section 8.4.10 was changed from "If an overdose on an AstraZeneca IP occurs in the course of the study …" to "If an overdose on an IP or AstraZeneca non-IP occurs in the course of the study …"	Revisions and new text were added to align with AstraZeneca CSP template requirements and reporting guidelines.
7.1 Discontinuation of Study Intervention	The following revisions were made: • Text deleted: Removed pregnancy as a reason for IPD	To align with Section 8.4.8.1 (Maternal exposure) of the CSP. Considering the life-treating nature of HES, this update would allow discussion between the investigator and study physician on benefit-risk before any IPD in the event of a pregnancy.

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Section Number and Name	Description of Change	Brief Rationale
	• Text added (underlined): Patients discontinuing from IP are strongly encouraged to continue in the study (without IP administration) up to the study completion …	Text was added for clarification.
7.1.1 Procedures for Early Discontinuation of Study Intervention and at End of Study	New text was added (underlined): The EOT visit is only used for ongoing patients following the last dose of IP when AstraZeneca declares the end of the study (Section 4.4).	Text was added for clarification.
7.1.1.1 Early Discontinuation of Study Treatment (IPD During DB Treatment Period)	The following revisions were made: • Text was slightly revised to indicate that after an IPD, patients who (a) opt to return to all scheduled site visits but without IP administration or (b) opt for the follow-up option that includes monthly telephone contact will exit the study after they complete Visit 9/Week 24. • Text added to indicate that patients who complete the DB period on treatment but are ineligible or unwilling to enter the OLE will have an IPD visit, after which they will exit the study.	Options to be offered to patients at the IPD visit were slightly revised to clarify study procedures after IPD.
7.1.1.2 End of Treatment Upon Notification of Closure of Study	New text was added: The IPD visit is used in all other cases when a patient discontinues IP during the OLE period.	Text added to clarify study procedures upon notification of study closure.
7.3 Lost to Follow-up	Minor revisions (ie, addition of template text) to the actions that must be taken if a patient fails to return to the site for required study visits were added.	Revisions and text were added to align with AstraZeneca CSP template requirements/ guidelines
8 STUDY ASSESSMENTS AND PROCEDURES	New text added: • Text regarding collection, handling, and storage of human biological samples. • Text indicating that alternate strategies for visits, assessments, etc. may be implemented in the event of a significant study-continuity issue (eg, caused by a pandemic). • Text indicating that laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel starting from randomisation/baseline (Visit 3/Week 0) until Visit 10/Week 28.	Revisions and new text were added to align with AstraZeneca CSP template requirements and for alignment across the CSP sections.
8.2.1.1 HES Physical Examinations	The following revisions were added: • Complete HES or brief physical examinations will now be performed. • System/organs to be assessed during a brief physical examination were added. • The following text was revised: Previous CSP v7.0 text: The Investigator will use the HES physical examination (Appendix H) to determine baseline HES physical examination … New CSP v8.0 text:	Revisions made to clarify study procedures.

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Section Number and Name	Description of Change	Brief Rationale
	The investigator will use the HES physical examination (Appendix H) to help identify specific organ involvement … • Text added: For flare visits, positive HES signs and symptoms should be reported.	
8.2.2 Haematologic Relapse	New text was added (underlined): At randomisation (Visit 3), patients must have an AEC < 1000 cells/µL, based on local laboratory assessment …	Text added for clarification.
8.3.1 Physical Examination	The following revisions were made: • New Section 8.3.1 was added with cross-reference to Section 8.2.1.1 "HES Physical Examinations." • Previous Section 8.2.5.1 "Height and Weight" in CSP v7.0 is now Section 8.3.1.1 in CSP v8.0. • Section 8.3.6 "Other Safety Assessments" removed; not needed anymore.	Revisions and section rearranged to comply with AstraZeneca template requirements/ guidelines.
8.3.3 Clinical Safety Laboratory Assessments (Table 9)	The following lab tests were removed: • Haematology: erythrocyte count, reticulocytes, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration. • Urinalysis: pH, glucose, haemoglobin/ erythrocytes/blood, protein/albumin, ketones, microscopic (WBC and RBC), urine sediment.	Benralizumab has a well characterised safety profile in other indications; therefore, the frequency of monitoring safety labs was decreased to reduce patient and site burden.
8.3.3.1 Pregnancy Tests	The following revisions were made: • Urine HCG (dipstick): Urine pregnancy tests will **NOT** be performed before each IP administration during the DB and OLE periods, at flare visits, or IPD visits. Urine pregnancy tests will now be performed at V1 and then quarterly as indicated in the SoA.	Alignment with Clinical Trials Facilitation and Coordination Group guidance on pregnancy testing in clinical trials.
	• Serum beta-HCG: Added that a serum pregnancy test will also be conducted if a urine pregnancy (dipstick) test is positive. • Urine HCG (dipstick): WOCBP who are doing optional remote visits with self-administration of IP will **NOT** be provided with urine pregnancy dipstick tests and advised to perform the test prior to IP self-administration. • New text added: If a WOCBP becomes pregnant, see Section 8.4.8 for additional information, including reporting requirements in case of a pregnancy during the study.	Revisions were made to reduce patient and site burden and clarify study procedures related to urine and serum pregnancy tests.
	• New note added: A WOCBP will be asked whether she may be pregnant to confirm that IP dosing may proceed if they are attending a remote visit with IP self-administration and at any onsite visit where a urine pregnancy test is not scheduled. Testing can be used to confirm pregnancy status.	Ensures PI/site alignment to inclusion criterion #9 (contraception methods) and lifestyle considerations (Section 5.4) on avoiding pregnancy.
8.3.4 Electrocardiograms	Text was revised to indicate that ECG will now be performed at baseline (V3) only and that a single ECG trace (not triplicate) will be obtained.	Revisions made to reduce patient and site burden. Electrocardiographic safety has been well

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Section Number and Name	Description of Change	Brief Rationale
		characterised from multiple studies conducted for product development.
8.3.5 Echocardiogram	The following revision was made: Previous CSP v7.0 text: Historical echocardiograms conducted within 12 months of Visit 1 (if available) will be assessed for clinical significance by the Investigator at screening. New CSP v8.0 text: For patients with known or suspected cardiac involvement, heart function should be assessed for clinical significance, either by a historical echocardiogram done within 12 months of Visit 1 or during screening if a historical echocardiogram is not available.	Text added to clarify which patients should be assessed for heart function and when the assessment will be performed.
8.4 AEs, SAEs, and Other Safety Reporting	The following revisions were made: • Heading changed from 8.3 "Adverse Events and Serious Adverse Events" to 8.4 "AEs, SAEs, and Other Safety Reporting". • Heading 8.3.1 "Method of Detecting Adverse Events and Serious Adverse Events" in CSP v7.0 was removed. Text is now under Section 8.4. • Template text regarding notification of symptoms by the patient and assessment of symptoms by the investigator was added. • AEs and SAEs variables to be collected were moved from Section 8.3.4 "Adverse Event Data Collection" in CSP v7.0 to Section 8.4 in CSP v8.0.	All changes were made to comply with current AstraZeneca template requirements.
8.4.1 Time Period and Frequency for Collecting AE and SAE Information	The following revision was made: Previous CSP v7.0 text: However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify AstraZeneca. New CSP V8.0 text: However, if the investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a treated patient, the investigator shall, without undue delay, report the SAE to AstraZeneca.	Revision was made to comply with current AstraZeneca CSP template requirements/ guidelines and AE/SAE reporting requirements.
8.4.3 Causality Collection 8.4.4 AEs Based on Examinations and Tests 8.4.5 AEs Based on Signs and Symptoms 8.4.7 Reporting of SAEs	Text was added as follows: • Section 8.4.3: For medical devices, a guide to the interpretation of the causality question can be found in Appendix E. • Section 8.4.4: The results from the protocol mandated laboratory tests and vital signs will be summarised in the CSR. • Section 8.4.5: "All AEs spontaneously reported by the patient or care provider …" was changed to "All signs or symptoms spontaneously reported by the patient or care provider …" • Section 8.4.7: When the EDC is temporarily not accessible, the AstraZeneca study representative should	All revisions were made to comply with current AstraZeneca CSP template requirements/ guidelines and AE/SAE reporting requirements.

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Section Number and Name	Description of Change	Brief Rationale
	confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC system when access resumes.	
8.4.8.1 Maternal Exposure	The following revision was made (deleted text is strikethrough and added text is underlined): The designated ~~Sponsor~~ 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 pregnancies associated with SAEs …	Text added for clarification and alignment with current AstraZeneca CSP template guidelines.
8.4.9 Medication Error, Drug Abuse, and Drug Misuse	Added Drug Abuse, Medication Error, and Drug Misuse definitions	Update required due to CT-3 regulation and corporate safety CAPA.
8.5 Pharmacokinetics	New text added: • To indicate that information about storage, reuse, and destruction of PK samples is found in Appendix C. • To indicate when PK samples will be disposed of. • To indicate that additional analyses may be conducted on the anonymised, pooled, or individual PK samples.	Revisions made to clarify proper use, reuse, storage, disposition, and destruction of PK samples. Revisions align with current AstraZeneca CSP template guidelines.
8.5 Pharmacokinetics	Section 8.5.1.3 Storage and Destruction of Pharmacokinetic Samples in CSP v7.0 was removed.	Revision was made to align with the current AstraZeneca CSP template. This information is now provided in Section 8.5 and Appendix C.
8.7 Immunogenicity Assessments	The following revision was made: Previous CSP v7.0 text: These samples will be tested by AstraZeneca or AstraZeneca's designee. New CSP v8.0 text: These samples will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.	Revision was made to comply with current AstraZeneca CSP template requirements/ guidelines.
	The following revision was made: Previous CSP v7.0 text: Samples may be stored for a maximum of 5 years (or according to local regulations) following the final CSR or publication associated with the study at a facility selected by AstraZeneca to enable further analysis of immune responses to benralizumab. New CSP v8.0 text: Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years post-CSR finalisation. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.	Language was revised to comply with current AstraZeneca CSP template and sample retention requirements/ guidelines.

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Section Number and Name	Description of Change	Brief Rationale
8.7 Immunogenicity Assessments	CSP template text added to indicate that • The laboratory manual has details regarding collection, labelling, storage, and shipment of samples. • Appendix C has details regarding storage, reuse, and destruction of ADA samples.	Revision was made to comply with current AstraZeneca CSP template requirements/ guidelines and provide the location of relevant information related to these samples.
8.8 Optional Genomics Initiative Appendix D Optional Genomics Initiative Sample	The following revision was made: • Heading title was changed from "Genetics" to "Optional Genomics Initiative."	Revision was made to align with current AstraZeneca CSP template guidelines/ requirements.
8.8 Optional Genomics Initiative	The following revisions were made: • Template text added to indicate that collection of the optional sample for Genomics Initiative research is also part of this study and is subject to agreement in the ICF addendum. • Heading 8.8.1 "Optional Exploratory Genetic Sample" was removed. • Section 8.8.2 "Storage and Destruction of Genetic Samples" was removed. • Text added to indicate that information about storage and destruction of genetic samples is found in Appendix D.	Revision was made to comply with current AstraZeneca CSP template requirements/ guidelines. Information about storage and destruction of genetic samples is provided in Appendix D.
8.9 Biomarkers	Template text added to indicate that consenting to participate in the study also means consenting to the mandatory research components of the study.	Text added for clarification and to align with current AstraZeneca CSP template requirements/guidelines.
	Section 8.7.3 Storage, Reuse, and Destruction of Biomarker Samples (in CSP v7.0) was removed and a cross-reference to Appendix C was added.	Change was made to align with AstraZeneca CSP template requirements/guidelines. This information is provided in Appendix C.
8.9.1 Biopsy	The following revisions were made: • Text added: Tissue biopsies will be collected as applicable (see below) according to the SoA (Table 1 and Table 2). • Text revised (new text is underlined, and text deleted is strikethrough): ° Local review of unscheduled biopsies is allowed only after Visit 10/Week 28 ~~the primary DBL~~ … ° Study personnel should remain blinded to the cell counts in biopsy reports obtained from randomisation/baseline (Visit 3), during the DB treatment period, and ~~until~~ for the first 4 weeks ~~in~~ of the OLE period (until Visit 10/Week 28).	To clarify study procedures and timing for sample collection of tissue biopsies and when unredacted results will be available.

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Section Number and Name	Description of Change	Brief Rationale
	° All unredacted biopsy results will be available upon request to the site personnel after ~~the primary DBL~~ Visit 10/Week 28.	
8.9.2 Mechanistic Sub-study 6.3.1 Methods for Assigning Treatment Groups	Text added or revised as follows: • To indicate that all blood samples related to the mechanistic sub-study apply to all sites, except for whole blood for eosinophil phenotyping. • Added the reason for not collecting the sample of whole blood for eosinophil phenotyping from all sites. • Number of samples required for PBMC analysis, immunophenotyping, and DNA analysis were added.	Revisions made to clarify study procedures related to the mechanistic sub-study.
8.10.2 Spirometry	Text revised to indicate that only patients with pulmonary involvement (not all patients) will undergo spirometry at screening.	Revision added to clarify spirometry test at screening and for consistency with the SoA (Table 1).
8.11 Healthcare Resource Utilisation	Text was added: • To indicate that protocol-mandated procedures, tests, and encounters are excluded. • To indicate what type of data may be collected.	Revisions were made to align with AstraZeneca CSP template requirements/guidelines.
8.12 Study Participant Feedback Questionnaire – Not Applicable	Heading added per CSP template. No content was added because the section is not applicable.	Revision was made to align with AstraZeneca CSP template requirements/guidelines.
9 STATISTICAL CONSIDERATIONS	Text was added: The SAP will be finalised prior to the primary DBL, and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.	Text added to align with AstraZeneca CSP template requirements/ guidelines and for clarification.
9.1 Statistical Hypotheses	Text was added (underlined): The primary endpoint will be tested at the CCI significance level using a stratified log-rank test adjusting for region and HES flare status at screening.	Text added for clarification and consistency across the statistical sections and the synopsis.
9.4.1 General Considerations	Text added: For all binary endpoints based on status at the end of the DB treatment period, to avoid potential bias in the estimation of treatment effect, analyses will be based only on the subset of patients who had the opportunity to complete the 24-week DB treatment period at the time of the primary analysis. Analyses will be repeated when the final patient competes the 24-week DB period (Section 4.1).	Text added to clarify how the analysis will incorporate the incomplete follow-up the final randomised patients may have at the time of the primary analysis.
9.4.2.1 Calculation or Derivation of Variable for Efficacy Analyses	The following revisions were made: • New text explaining how the endpoint "Number of HES worsening/flare events" will be calculated. • Added text to indicate that the endpoints "Change from baseline in PROMIS fatigue short form 7a" and "Proportion of patients who experience an HES worsening/flare over the DB treatment" are now key secondary endpoints.	In line with the reprioritisation of key secondary endpoints, additional details on key efficacy endpoint derivations have been added.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
9.4.2.3 Secondary Endpoints Analysis Methods	The following revisions were made: • The section was slightly revised to indicate which endpoints are now "key secondary endpoints". • Text was added to explain how the proportion of patients with HES worsening/flare in the DB period and the number of flare events during the DB period will be calculated.	In line with the reprioritisation of key secondary endpoints, additional details on efficacy analysis methods for key secondary endpoints have been added.
9.4.3 Safety Analyses	ECG analyses will only be conducted for patients with post-baseline ECG data collected.	ECG no longer collected post-baseline.
9.5 Interim Analyses	Text was revised (text deleted is strikethrough, and text added is underlined): AstraZeneca's internal personnel or its designees will monitor the overall rate of HES worsening/flare (blinded to treatment assignment) to ensure that the final sample size will be adequate to provide the ~~47~~ approximately 38 events needed for the ~~final~~ primary analysis.	Text added for clarification. The primary analysis is no longer the "final" DB analysis.
Appendix A 1 Regulatory and Ethical Considerations	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches"	Update required to comply with regulatory requirement (eg, EU-CTR) and global company requirement.
Appendix A 6 Dissemination of Clinical Study Data	Updated information about timelines for submission of trial results summaries to EU CTIS.	Update required to comply with EU-CTR.
Appendix A 7 Data Quality Assurance	The following revisions were made to Appendix A 7: • Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations.	Update required to comply with EU-CTR and global company requirement.
	• Added CSP template text indicating that AstraZeneca or designee is responsible for medical oversight of the study and that monitoring details describing clinical reviews of study are included in the monitoring plan.	Text added to align with AstraZeneca CSP template requirements/ guidelines.
Appendix A 9 Study and Site Start and Closure	Definitions for study start date were added.	Text added to align with AstraZeneca CSP template requirements/ guidelines.
Appendix B 4 Medication Error, Drug Abuse, and Drug Misuse	Added detailed Drug Abuse and Drug Misuse definition and examples.	Update required due to CT-3 regulation and corporate safety CAPA.
Appendix C Handling of Human Biological Samples	The following revisions were made to Appendix C 1 "Chain of Custody": • Added information about retention timelines for appropriately consented human biological samples (ie, for maximum 15 years from last patient last visit). • Other minor updates regarding records of sample arrival, processing information, and retention were made.	Language updated to align with current AstraZeneca CSP template requirements/ guidelines and AstraZeneca standard retention timelines.
Appendix D 2 Genetic Research Plan and Procedures	The following revisions were made: • An exclusion from this genetic research was added: Healthy volunteers and paediatric patient samples will not be collected for the Genomics Initiative. • Informed consent text was revised (new text is underlined and deleted text is strikethrough): To	Language added or revised to align with the current AstraZeneca CSP template guideline/company requirements.

List of Non-substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
	participate in the genetic component of the study, the patient must sign and date both the consent form for the main study and the ~~genetic component of the study~~ optional genetic research information ICF.	
	• Section "Statistical Methods and Determination of Sample Size" (present in CSP v7.0) was deleted.	Content is not applicable to this section.
Appendix H HES Examination	Footnotes added: • A brief physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, and abdomen. • For flare visits, positive HES signs and symptoms should be reported.	Footnotes added to clarify study procedures.
Appendix K Protocol Amendment History	Summary of CSP v7.0 modifications (Amendment 6) was moved to Appendix K.	Updated in align with current AstraZeneca CSP template requirements/ guidelines.

ADA(s) = anti-drug antibody(ies); ADE(s) = adverse device effect(s); AE(s) = adverse event(s); AEC(s) = absolute eosinophil count(s); APFS = accessorised prefilled syringe; AZ = AstraZeneca; CAPA = corrective and preventive actions; COVID-19 = coronavirus disease 2019; CSP = clinical study protocol; CSR = clinical study report; CT-3 = Detailed guidance on the collection, verification, and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use; DB = double-blind; DBL = database lock; DNA = deoxyribonucleic acid; ECG(s) = electrocardiogram(s); EDC = electronic data capture; EOT = end of treatment; EudraCT = European Union Drug Regulating Authorities Clinical Trials Database; EU CT number = European Union clinical trial number; EU CTIS = European Union Clinical Trials Information System; EU-CTR = European Union-Clinical Trial Regulation; EU/EEA= European Union/European Economic Area; HCG = human chorionic gonadotropin; Hep = hepatitis; HES = hypereosinophilic syndrome; HIV = human immunodeficiency virus; ICF = informed consent form: IP = investigational product; IPD = IP discontinuation; NIH = National Institutes of Health; non-IP = non-investigational product; NW = Northwestern; OLE = open-label extension; PBMC(s) = peripheral blood mononuclear cell(s); PK = pharmacokinetics; PROMIS = Patient-reported Outcomes Measurement Information System; PSSR = pre-startup safety review; RBC(s) = red blood cell(s); SADE(s) = serious adverse device effect(s); SAE(s) = serious adverse event(s); SAP = statistical analysis plan; SoA = schedule of activities; USADE(s) = unanticipated serious adverse device effect(s); V(x) = study visit(number); v7/v8 = version 7/ version8; WBC(s) = white blood cell(s); WOCBP = woman/women of childbearing potential.

K 2 Amendment 6 (29 June 2022)

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

Overall Rationale for the Amendment

The primary reason for this amendment is to modify inclusion criterion #6 regarding HES flares to allow enrolment of those with a history of 2 or more HES worsenings/flares in the preceding 12 months as these patients are at risk of having future HES flares. There is evidence from a previous Phase III HES study with a different product that this new cohort of patients is biologically and clinically similar to currently enrolled patients with active flare. Considering the unmet medical need in patients with a history of HES worsenings/flares, AstraZeneca has included this study population as they may benefit from benralizumab treatment.

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
1.1 Synopsis	Updated the address of the International Co-ordinating investigator	For administrative reasons	Non-substantial
	Added short title.	To align with current AstraZeneca CSP template	
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 4.1.4 Open-label Treatment Period (Week 24 to End of Treatment) 4.4 End of Study Definition	Specified that the minimum length of the OLE will be 2 years in adolescents and revised the end of study definition to encompass this change.	To comply with European Medicines Agency Paediatric Committee requirement (EMEA-001214-PIP04-19)	Substantial
1.1 Synopsis 3 Objectives and Endpoints Section 9.1 Statistical Hypotheses 9.4.1 Efficacy Analyses	Added estimand description for the primary and secondary endpoints. The addition of estimand descriptions does not entail a change to the analysis approach for the primary or secondary endpoints.	To align with current AstraZeneca CSP template	Non-substantial
1.1 Synopsis	HES flare status at screening added as stratification factor for randomisation, covariate for analyses of the primary and secondary	To align with expanded inclusion criterion	Substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
6.3.1 Methods for Assigning Treatment Groups 9.4.1.2 Primary Endpoint 9.4.1.3 Secondary Endpoints 9.4.7 Subgroup Analysis	endpoints, and subgroup for subgroup analyses of the primary endpoint. Specification of geographic regions used for stratification added.	allowing patients without an HES flare at screening	
1.1 Synopsis 1.3 Schedule of Activities 4.1 Overall Design 9.2 Sample Size Determination 9.4.1 Efficacy Analyses	Revised “and all randomised patients have been followed up for the 24-week DB treatment period” to “and all randomised patients have had the opportunity to be followed up for the 24-week DB treatment period” when describing the time point of the primary DB lock	For accuracy and clarity as patients who, eg, withdraw from the study prior to the end of the DB treatment period will not be followed up for the full 24-week DB treatment period	Non-substantial
1.2 Study schema	Updated study schema figure and associated footnotes.	To clarify and remove redundancy.	Non-substantial
1.3 Schedule of Activities (Table 1, Table 2) 8.2.1 Clinical Safety Laboratory Assessments (Table 9)	“Creatine phosphokinase” removed from central laboratory assessments.	To remove redundancy as creatine kinase also listed as a central laboratory assessment and is the same as creatine phosphokinase	Non-substantial
1.3 Schedule of Activities (Table 1)	Changed “PBMC flow cytometry” to “immunophenotyping”.	To cover analyses based on peripheral blood mononuclear cells as well as analyses based on whole leukocytes	Non-substantial
1.1 Synopsis 1.3 Schedule of Activities (Table 1) 4.1 Overall Design 4.1.2 Screening (Enrolment up to Randomisation) 5.1 Inclusion Criteria (inclusion criterion 8)	Specified “prednisone/prednisolone” when mentioning OCS for assessment of corticosteroid responsiveness prior to randomisation and for treatment of HES worsening/flares. Added that other OCSs in equivalent doses are permitted and Appendix I listing equivalent doses.	To clarify and add further details to guide use of OCS for assessing corticosteroid responsiveness and for treatment of HES worsening/flares	Non-substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
6.1.4 Sponsor-provided Oral Corticosteroids for Assessment of Corticosteroid Responsiveness 8.1.1 Hypereosinophilic Syndrome Worsening/flare 9.4.1.1 Calculation or Derivation of Variable for Efficacy Analyses Appendix I			
1.3 Schedule of Activities (Table 1 to 4)	Changed footnote "Spirometry will be performed in all patients at Visit 1. Spirometry at other scheduled visits is required only in patients with pulmonary involvement or abnormal spirometry at Visit 1" to "Spirometry will be performed only in patients with pulmonary involvement" for Table 1 and 2. Added this footnote to Table 3 and 4, where it had been inadvertently omitted.	To reduce patient burden and simplify	Non-substantial
1.3 Schedule of Activities (Table 4)	Changed title from "Schedule of Assessments for the Open-Label Extension (Year 3)" to "Schedule of Assessments for the Open-Label Extension (Year 3 and Beyond)". Added footnote to title stating "After Year 3, assessments should be performed with a similar schedule and frequency as for Year 3; eg, the assessments at the first visit of Year 3 (Visit 36/Week 132) should be performed at the first visit of Year 4 (Visit 49/Week 184)."	To encompass an open-label period potentially longer than 3 years	Non-substantial
4.1.3 Double-blind Treatment Period (Randomisation to Week 24) 4.1.4 Open-label Treatment Period (Week 24 to End of Treatment) 8.1.1 Hypereosinophilic	Revised statement that patients not able to get to the site due to the HES worsening/flare "may visit their local physician…" to "are strongly recommended to visit their local physician…"	To strengthen the recommendation to subjects to visit their local physician if they cannot visit the site when having an HES worsening/flare	Non-substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
Syndrome Worsening/flare			
5 Study population	Revised "In this protocol, "enrolled" patients are defined as those who sign informed consent/assent" to "In this protocol, "enrolled" patients are defined as those patients who have signed (or whose legally acceptable representative have signed) informed consent/assent."	For consistency across CSP	Non-substantial
5.1 Inclusion Criteria (inclusion criterion 6)	Revised inclusion criterion 6 from "Signs or symptoms of HES worsening/flare and/or laboratory abnormalities indicative of HES worsening/flare (other than isolated eosinophilia) at Visit 1" to "Signs or symptoms of HES worsening/flare and/or laboratory abnormalities indicative of HES worsening/flare (other than isolated eosinophilia) at Visit 1 **OR** A documented history of 2 or more HES worsening/flares within 12 months prior to Visit 1 requiring an escalation in therapy. • At least one flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare."	To allow enrolment of those with a history of 2 or more HES worsenings/flares in the preceding 12 months as these patients are at risk of having future HES flares.	Substantial
5.2 Exclusion Criteria (exclusion criterion 17) 6.5.3 Restrictions	Revised "…any marketed or investigational biologic product…" to "…any biologic product…"	To simply and clarify the distinction between existing language that covers investigational products and language that covers biologics	Non-substantial
5.5.1 Re-screening	Revised to state that patients screen-failed for not meeting corticosteroid responsiveness criteria can be re-screened only once, while patients screen-failed for other reasons may be re-screened more than once.	To clarify the requirements and frequency of re-screening	Non-substantial
6.3.2 Methods for Ensuring Blinding – Double-Blind Treatment Period 8.8.1 Biopsy	Added instructions that AstraZeneca's prior permission is required in the rare instances where local review of a tissue biopsy is needed before Visit 10 and that all necessary precautions including redaction of reports should be exercised to maintain blinding.	To allow local review of biopsy before Visit 10	Non-substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
8.1.1 Hypereosinophilic Syndrome Worsening/flare	Added description of HES worsening/flare assessment for patients entering the study without an HES worsening/flare.	To align with the revision of inclusion criterion 6	Non-substantial
	Revised description of length of blinded period from "until Week 36 (Visit 12)" to "until Week 28 (Visit 10)"	To correct typo in visit/week number and align with the rest of the CSP	Non-substantial
	Added to the definition of HES worsening/flare that "To be considered as a separate HES worsening/flare, the start date of an HES worsening/flare must be at least 14 days apart from the stop date of the preceding HES worsening/flare."	To clarify the classification of multiple HES worsening/flares occurring within a short time frame	Non-substantial
	Revised "In such cases, an HES symptoms interview with the patient may be conducted by the site staff via telephone, if possible" to "In such cases, the investigator-led HES symptom interview with the patient is strongly recommended to be conducted by the site staff via telephone."	To strengthen the recommendation to sites that an HES symptoms interview be conducted by the site staff via telephone if the subject cannot visit the site when experiencing an HES worsening/flare	Non-substantial
8.4.2 Pregnancy	Added that pregnancies in the partner of male participants are exempt from the requirement to report all pregnancies and outcomes of pregnancy to AstraZeneca.	To align with current AstraZeneca position that collection of data on a male's partner's pregnancy is no longer required in benralizumab studies	Non-substantial
Appendix A3	Deleted "If the patient's partner becomes pregnant, despite prevention, state that the partner will be asked to sign an ICF for pregnant partners. If a patient's partner becomes pregnant during or within 12 weeks after the study, the partner will be asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly."		
8.4.3 Overdose	Deleted "For overdoses associated with an SAE, the standard reporting timelines apply; see Section 8.3.2. For other overdoses, reporting must occur within 30 days." Added "If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives	To align with current AstraZeneca CSP template	Non-substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	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 (Section 8.3.9) and within 30 days for all other overdoses."		
8.4.4 Medical Device Deficiencies	Added section.	To align with current AstraZeneca CSP template	Non-substantial
8.4.4 Device Constituent Deficiencies	Deleted section.	To align with current AstraZeneca CSP template and remove redundancy as covered by new Section 8.4.4 Medical Device Deficiencies	Non-substantial
8.4.5 Serious Adverse Device Effect Reporting	Deleted section.		
8.5.3 Pharmacodynamics	Added section, which states that pharmacodynamic parameters will be evaluated using biomarkers with cross-reference to Section 8.6.	To align with current AstraZeneca CSP template	Non-substantial
8.7.2 Mechanistic Sub-study	Revised "A second whole blood sample will also be collected from all study sites, for a more in-depth phenotypic analysis of lymphocytes and other leukocytes, by flow cytometry of peripheral blood mononuclear cells" to "A second whole blood sample will also be collected from all study sites, for a more in-depth phenotypic analysis of lymphocytes and other leukocytes"	To cover analyses based on peripheral blood mononuclear cells as well as analyses based on whole leukocytes	Non-substantial
9.4.1.1 Calculation or Derivation of Variable for Efficacy Analyses	Revised the censoring rules for HES worsening/flare and haematologic relapse to state that patients who have not experienced the event "during the DB treatment period will be right censored at the time of DB study completion or withdrawal from the study during the DB treatment period."	To clarify and add specificity	Non-substantial
9.4.2 Safety Analyses	Revised "Laboratory data will be summarised by presenting shift tables using normal ranges and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges)" to	To add flexibility in data presentation	Non-substantial

Section # (in Current CSP) and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	"Laboratory data will be summarised by presenting shift tables (if applicable) using normal ranges and by presenting summary statistics of observed and change from baseline values."		
Appendix C3	Updated IATA category definitions, URLs, and packing guidelines	To align with current AstraZeneca CSP template and up-to-date IATA information	Non-substantial
Appendix E	Added appendix describing definitions and procedures for recording, evaluating, follow-up, and reporting of medical device AEs, ADEs, SAEs, SADEs, USADEs, and medical device deficiency.	To align with current AstraZeneca CSP template	Non-substantial
Appendix H	Added "Specify" under "If yes/abnormal…" to those items with no other specific instructions	For clarity	Non-substantial
Throughout	Added "during the DB treatment period" when mentioning the 47 patients with first HES worsening/flare event included in the primary analysis	To clarify the time period during which HES worsening/flares will be counted for the primary analysis	Non-substantial
Throughout	Minor editorial, formatting, and organisational (eg, to the order of subsections or appendices) changes.	To clarify text, improve consistency, and align with the current AstraZeneca CSP template and style conventions.	Non-substantial

K 3 Amendment 5 (16 February 2021)

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

Overall Rationale for the Amendment

The primary rationale for this amendment is to introduce the possibility of self/at-home administration of benralizumab and remote visits during the open-label extension of the study.

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
1.1 Schedule of Assessments (Table 1)	Deleted footnote x from Table 1	Footnote was redundant.	Non-substantial
	Updated the new footnote x (previously footnote y) in Table 1 to add that spirometry will be performed in all patients at Visit 1.	To clarify that spirometry at Visit 1 will be performed for all patients.	Non-substantial
1.1 Schedule of Assessments (Table 3 [formerly Table 9 in Appendix H], Table 4 [formerly Table 10 in Appendix H])	Moved tables from Appendix H to Section 1.1 Schedule of Assessments	To keep all schedules of assessments in one place and improve navigability	Non-substantial
1.1 Schedule of Assessments (Table 2, Table 3 [formerly Table 9 in Appendix H], Table 4 [formerly Table 10 in Appendix H]) 4.1.4 Open-label treatment period (Week 24 to end of treatment) 6.1.1 Investigational Products 6.1.3 Optional Self-Administration of Investigational Product (newly added section) 6.2.1 Preparation and handling of investigational product 8.2.1.1 Pregnancy Tests	Introduced the option of IP self-administration (or administration by a caregiver) during the OLE. Introduced the option of remote visits during the OLE for patients who opt for IP self-administration (optional remote visits: V17, V18, V20, V21, V23, V24, V26, V27, V29, V30, V32, V33, V35, V36, V38, V39, V41, V42, V44, V45, and V47). Frequency of some onsite safety and laboratory assessments changed to quarterly and some assessments moved to adjacent visits to accommodate the new option for remote visits and self-administration of IP. Instructions on pregnancy test before IP administration and observation after IP	To reduce patient burden and allow flexibility during the OLE	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
	administration revised to accommodate the option of IP self-administration.		
4.1.2 Screening (Enrolment up to Randomisation)	Added "NOTE: OCS dose variations within ± 5 mg are acceptable if needed to allow dosing with locally available OCS formulation. If calculated OCS dose for steroid responsiveness assessment exceeds maximum locally approved daily dose, or in the investigator's opinion exceeds maximum tolerable dose for the patient, it can be reduced to maximum locally approved/tolerable dose at the discretion of the investigator; the decision and justification should be documented."	To clarify dosing of OCS for steroid responsiveness assessment including in patients with higher body weight.	Non-substantial
2.3 Benefit/risk Assessment 6.1.1 Investigational Products 8.4.7 Management of Investigational Product-related Drug Reactions Appendix E Anaphylaxis: Definition, Signs, Symptoms, and Management	Changed from a minimum of 1 hour of observation on site after IP administration to state that the patient should be observed in line with clinical practice. Changed guidance on treatment of acute anaphylactic reactions to state that appropriate drugs should be available at study sites rather than must be immediately available.	To align with clinical practice	Non-substantial
1.1 Schedule of Assessments (Table 2, Table 3 [formerly Table 9 in Appendix H], Table 4 [formerly Table 10 in Appendix H]) 7.1.1 Procedures for Early Discontinuation of Study Treatment and at End of Study 7.1.1.2 End of Treatment upon Notification of Closure of Study (formerly Discontinuation of Treatment Upon Notification of Closure of Study)	Revised "IPD visit" to "IPD/EOT visit" in the schedules of activities for the open-label extension. Added clarifications that EOT visit will be used only following the last dose of IP when AstraZeneca declares the end of the study while the IPD visit will be used in all other cases when a patient discontinues IP. Revised header of Section 7.1.1.2.	To clarify when "IPD" versus "EOT" visits are used.	Non-substantial
8.1.3.1 PROMIS Fatigue	Removed the list of questions included in the PROMIS Fatigue Short Form 7a and added information on the calculation and interpretation of the scores.	To provide relevant information on PROMIS Fatigue Short Form 7a.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
8.1.3.3 Patient Global Impression of Severity 8.1.3.4 Patient Global Impression of Change	Added the scores to which the minimum/maximum responses correspond.	To clarify the scales.	Non-substantial
8.2.3 Electrocardiograms	Revised the description of ECG triplicate completion to state that it is recommended they are performed no more than 2 minutes apart and that it is recommended that the full set of triplicates be completed within 5 minutes.	To clarify ECG timings.	Non-substantial
8.9.2 Patient Qualitative Interview Sub-Study	Revised "Interview transcripts will be completed for each interview in the language in which they are conducted. Transcripts will then be coded using ATLAS.ti in the language in which interviews were conducted" to "Interview transcripts will be completed for each interview in the language in which they are conducted and translated into English (if necessary). Translated transcripts will be coded using qualitative data analysis software."	Clarification and change in qualitative analysis methodology for interview transcripts	Non-substantial
8.9.3 Spirometry	Revised "At Visit 9 and Flare visits, spirometry will be required only for patients with pulmonary involvement or an abnormal spirometry at screening" to "At other scheduled visits and Flare visits, spirometry will be required only for patients with pulmonary involvement or an abnormal spirometry at screening."	Correction/ clarification as there are additional scheduled visits with spirometry assessments after Visit 9.	Non-substantial
9.4.1.1 Calculation or Derivation of Variable for Efficacy Analyses	Revised "The raw score will be summed for the 7 questions of the PROMIS Fatigue Short Form 7a. Change from baseline will be calculated at each visit over 24 weeks" to "Change from baseline in the PROMIS Fatigue Short Form 7a standardised total score will be calculated at each visit over 24 weeks".	To calculate standardised scores that allow for comparability with other PROMIS tools and/or disease areas.	Non-substantial
	Revised "The PGIC responders are categorised according to the following responses" to "Patients will also be categorised according to the following improvement categories post-baseline".	To clarify PGIC categorisation.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial / Non-substantial
9.4.1.3 Secondary Endpoints	Revised "The primary analysis will fit a MMRM model using the data collected up to and including the Week 24/IPD time point" to "The primary analysis will fit a MMRM model using the data collected up to and including the Week 24 time point."	Typo; corrected for clarity and consistency with the rest of the CSP and statistical analysis plan.	Non-substantial
Throughout	Minor editorial and formatting changes.	To clarify text, improve consistency, and align with current templates and style conventions.	Non-substantial

K 4 Amendment 4 (06 August 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 patient is not able to visit a study site during cases of civil crisis, natural disaster, or public health crisis to ensure that the clinical trial can continue whilst minimising risk to the patient, maintaining compliance with Good Clinical Practice, and minimising risks to the study integrity. The protocol has also been amended to clarify spirometry and mechanistic sub-study procedures, align with current AstraZeneca safety recommendations in studies with benralizumab, clarify inclusion/exclusion criteria, and revise, add, or remove minor text as needed to increase clarity or correct interpretation of the protocol.

Section # and Name	Description of Change	Brief Rationale
1 Protocol summary 1.1 Schedule of Assessment 1.2 Synopsis (overall design) 1.2 Synopsis (statistical methods) 4.1 Overall design 9.4.1 Efficacy analyses	Text was added: "Patients will not continue to be recruited after 47 patients have had their first HES worsening/flare."	Clarification when recruitment will be discontinued.

Section # and Name	Description of Change	Brief Rationale
Table 1 Schedule of Assessment	Footnote "m" was updated with: "Urinalysis by the central laboratory will be conducted at Visits 1 and 3 and any flare visit; urinalysis will be conducted by dipstick testing at all visits, except Visit 2 and Visit 3".	Clarification of timing of urine dipstick assessment.
Table 1 Schedule of Assessment	Footnote "v" was updated "Whole blood for eosinophil phenotyping will be selected sites only, whilst whole blood for DNA analysis and for PBMC flow cytometry will be from all sites"	Clarification of assessments being conducted by all sites and those done by selected sites.
Table 1 Schedule of Assessment	Spirometry (pre-bronchodilator FEV1 and FVC) footnote "x" was added to Visit 9. Description to footnote "x" was added: "Visit 9 spirometry is required only in patients with pulmonary involvement or abnormal spirometry at Visit 1. " Description to footnote "y" was added: "Spirometry at scheduled visits is required only in patients with pulmonary involvement or abnormal spirometry at Visit 1 Spirometry (pre-bronchodilator FEV1 and FVC was removed from IPD Visit)	Clarification that post-baseline spirometry is required only for patients with pulmonary involvement.
Schedule of Assessments (Tables 1, 2, 9, and 10)	Clinical chemistry – Statement "(incl. AST, ALT, total bilirubin, uric acid, creatinine)" was removed.	Specification of local chemistry assessment is provided in section 8.2.1.
Table 1 Schedule of Assessment	Mechanistic Sub-study Procedures – "Whole blood for cell phenotyping flow cytometry (selected sites only)" was changed to "whole blood for PBMC flow cytometry (all sites)"	Clarification of intended use of whole blood samples.
Table 1 Schedule of Assessment	Mechanistic Sub-study Procedures - Addition of "Whole blood for eosinophil phenotyping" and new sample collection was added to this point at Visit 1 and Flare Visit	A new addition to the assessments.
Schedule of Assessments (Table 2, 9, and 10)	Table 2: Footnote "j" was updated. Wording" "but is not mandatory" was removed Table 9 and 10: Footnote "h" was updated. Wording" "but is not mandatory" was removed	Clarification of biopsy sample processing.
Table 2	Description to footnote "k" was added: "Spirometry at scheduled visits is required only in patients with pulmonary involvement or abnormal spirometry at Visit 1	Clarification that post-baseline spirometry is required only for patients with pulmonary involvement.
1.2 Synopsis	New address of International coordinating was added	ICI address was changed from August 2020.

Section # and Name	Description of Change	Brief Rationale
	Study period – estimated date of first patient enrolled was changed to: “third quarter 2020” Study period- estimated date of last patient completed changed to "third quarter 2024"	Revision in projected new first subject enrolled date. Revision in projected date of last patient completed.
Table 3	Exploratory Objectives the evaluation of HES clinical sub-types was added.	Clarification of the purpose of the exploratory biomarker objectives.
4.1.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis	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.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimising risk to the patient, maintaining compliance with GCP, and minimising risks to study integrity. These changes will only be initiated at a time of study disruption.
4.4 End of study definition	Wording “approximately 2Q2023” was removed.	Projected completion date removed to allow flexibility with estimated study completion date.
5.1 Inclusion Criterion #9 5.4 Lifestyle restriction Table 6 Allowed, restricted, and prohibited medications Appendix A A3 Informed consent process	“5 half-lives” was removed. 16 weeks was changed to 12 weeks.	These changes were implemented to follow current Sponsor safety recommendations in studies with benralizumab. Twelve weeks is consistent with 5 half-lives of benralizumab.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Criterion 9-Reproduction – text was updated: “Highly effective methods of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include”.	Updated as per current PSSR. To be compliant with CTFG guidance.
5.2 Exclusion Criteria	Medical conditions Criterion 1 (a)-word “OR” was removed from the paragraph 1 (b) The following text was added for history of thrombotic complications, stroke, or significant cardiac damage related to HES: "if the respective events were life threatening and currently represent a risk of life-threatening disease complications. Events that occurred in the past but considered resolved or stable, can be accepted if per investigator’s judgment, participation in the study will not put the patient at risk"	Clarification that past cardiovascular events are only excluded if life-threatening or currently pose a risk to the patient per investigator’s judgment.
5.2 Exclusion Criteria	Criterion 3 – “Clinical” was changed to “Definitive”.	Clarification of population being excluded.
5.2 Exclusion Criteria	Criterion 6 revised to indicate that clinically significant echocardiography and ECG findings prior to V1 or clinically significant ECG at Screening are exclusionary in opinion of the investigator.	Clarification of cardiovascular exclusion criteria.
5.3 Criteria to be confirmed/re-confirmed prior to randomisation (Visit 3)	Reference to central ECG deleted and statement updated: No evidence of significant abnormality from the local ECG performed at Visit 1. (Exclusion 6)”. ECG - removed "OVER - read" from the text.	Correction as no central-over read of ECG at Visit 1.
6. Study treatments	Wording was added “utilised by a study patient according to the study protocol”.	This was changed per new template wording.
6.1.2 Investigational product administration rescheduling	Text in paragraph "Re- scheduled IP" was updated. The word “The HES” was removed. Text: “For WOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative (see Section 8.4.2).” was added.	Clarification of procedures that must be performed before administering IP at an unscheduled visit.
6.2.3 Accountability	The word “Unblinded” was removed.	Corrective change as an unblinded monitor is not applicable.
6.3.2 Methods for ensuring blinding – double-blind treatment period	List of personnel which will have access to the randomisation list during the study, prior to the primary DB was updated. Text was added: “Drug Safety Services Representatives (Data Entry Site case handlers)”	Updated to be consistent with Unblinding Plan.

Section # and Name	Description of Change	Brief Rationale
	"the Data Safety Monitoring Board (DSMB) " "Unblinded Programmer" "Unblinded Medical Monitor" Text was removed: "Patient safety department at the Sponsor".	
6.3.3 Methods for unblinding – double-blind period	"Medical Monitor" was changed to "Study Physician"	This was changed per new template wording
Table 6 Allowed, restricted, and prohibited medications	Usage instructions were updated for – Live attenuated vaccines- text was removed: "or for adolescent patients from the European Union within 4 months or within 5 half-lives prior to the date informed consent, and assent when applicable, is obtained, whichever is longer." -Any investigational product – text was removed "30 days or 5 half-lives (whichever is longer)". -Any marked or investigational biologic (monoclonal or polyclonal antibody) "4 months or 5 half-lives (whichever is longer)" text was removed. -Allergen immunotherapy: Text was added: "if on stable maintenance regimen during the treatment period.	These changes were implemented to follow current sponsor safety recommendations in studies with benralizumab. Clarification that allergen immunotherapy is allowed if patient is on a stable regimen during the treatment period.
7.1.1.1 Early discontinuation of study treatment	- Wording in bullet point 3 was updated: words "continue" and "have" were added; "unwilling" and "whichever is later" were removed - Bullet point 4 was added	Clarification of patient discontinuation instructions.
8.1.3.3 Patient global impression of severity	Text revised to indicate that the PGIS is to capture the patient's perception of overall symptom severity over the past week, not at the time of completion of the assessment.	Correction to align with the intended recall period
8.2.1 Clinical safety laboratory assessments	Wording in: - Bullet point 1: text was updated, "including" word was added: "Local haematology (including WBC with differential) will be assessed at Visit 1 to confirm AEC per inclusion criterion 7 and at Visit 2 to support inclusion criterion 8. - Bullet point 2: text was updated, "including" word was removed before AST and wording was added. Local clinical chemistry (AST, ALT, total bilirubin, uric acid, and creatinine) and troponin will be assessed at Visit 1 to inform safety aspects of patients' eligibility.	Clarifications of Clinical Safety Laboratory assessments.

Section # and Name	Description of Change	Brief Rationale
	Additional local laboratory parameters may be included at discretion of the investigator. -bullet point three was updated to clarify requirements for urine analysis performed by central laboratory and urine dipstick - bullet point four was updated: "Optional blood sample(s) for local clinical chemistry can be taken at the discretion of the investigator at Visit 2 (e.g., to follow-up on any abnormalities found during the screening period) at flare visit or unscheduled visit (e.g., for immediate medical decisions)."	
Table 7 Laboratory safety variables	The word "Central" was added before Laboratory safety variables in the title of the table.	Editorial change.
8.2.1.2 Serology	Text was updated: "Local HIV express test will be performed at Visit 1 to inform eligibility. The sample from Visit 1 will also be sent to the central laboratory for HIV-1 and HIV-2 antibodies (along with p24 Antigen) assessment. "	Clarification that local testing will be general HIV. HIV1/2 will be assessed in central laboratory.
8.2.4 Echocardiogram	Text was added: " Historical echocardiograms conducted within 12 months of Visit 1 (if available) will be assessed for clinical significance by the investigator at screening."	Clarification regarding the use of historical echocardiograms.
8.3.5 Spirometry	Was moved to section 8.9.3 please refer in history of changes to point 8.9.3 for updated chapter	Spirometry is not a safety endpoint.
8.4.2.1 Maternal exposure	For patients who may become pregnant during the study, wording "discontinued immediately." regarding IP was removed Text added "temporarily withheld, and a conversation between the investigator and a Study Physician has to take place to determine whether continuation on IP or discontinuation of IP is in the best interest of the patient."	These changes were implemented to follow current sponsor safety recommendations in studies with benralizumab.
8.4.3 Overdose	Text added: "For this study, any does of benralizumab greater than 200 mg will be considered as an overdose.	Clarification regarding definition of overdose of benralizumab.
8.4.4 Malfunction of accessorised prefilled syringe	The title of the section was changed to "Device Constituent Deficiencies" from "Malfunction of accessorised prefilled syringe". The whole section was added.	To ensure compliance with new regulatory guidance.
8.4.5 SADE Reporting	The whole section was added.	To ensure compliance with new regulatory guidance.

Section # and Name	Description of Change	Brief Rationale
8.5.1 Determination of drug concentration	(Pharmacokinetic samples) was added to the title of Section 8.5.1 paragraph.	Editorial change.
8.5.1 Determination of drug concentration	Revised wording to clarify that all PK samples from patients assigned to benralizumab treatment group will be analysed but not in patients randomised to placebo in DB period and PK samples from all patients at other time points in OLE will be analysed.	Clarification of time points and treatment groups for PK sample analysis.
8.6 Immunogenicity	The bullet points were updated with the wording "ADA samples will be analysed in all patients at all time points".	Corrected to align with internal guidelines.
8.8.1 Biopsy	Text updated to clarify biopsy collection procedures and clarify population for these procedures.	Clarification that biopsies will be collected only in adults during the study unless it is contraindicated as judged by the investigator or refused by the patient. Clarification of biopsy sample processing.
8.8.2 Mechanistic sub-study	Text added to clarify that mechanistic sub-study analyses will only be conducted in adults and clarification of the total number of whole blood samples and intended use of samples.	Clarification of age group or mechanistic sub-study and intended use of whole blood samples.
8.9.3 Spirometry	The paragraph was moved to this section and updated to clarify spirometry requirements and clarify population for these assessments.	Clarification that post-baseline spirometry will be mandated only for patients with pulmonary involvement. Clarification for how spirometry will be performed if medication restrictions are not feasible.
8.9.4 Patient Testing Due to Public Health Crisis	Section included if patient testing is performed due to the public health crisis, the results may be documented for this study.	Section added for the test results secondary to public health crisis to be collected allowing for an evaluation of the public health crisis on the study.
9.4.1.1 Calculation or derivation of	Table 8: PGIS – wording was updated.	Correction to align with the intended recall period.

Section # and Name	Description of Change	Brief Rationale
variable for efficacy analyses		
9.4.1.3 Secondary endpoints	Wording was changed “adjusted rate differences” was removed, “odds ratio” was added. Paragraph related to The HRQoL Wording was added “endpoint's baseline”.	Clarification of statistical methodology and grammatical errors.
9.4.4 Methods for multiplicity control	First bullet point: word “relapse” was replaced by “first HES worsening”.	Clarification of the null hypothesis
Appendix A1 Regulatory and Ethical Considerations	Paragraph added Regulatory and Ethical Considerations text was updated Regulatory Reporting Requirements for SAEs. Text was added: “AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.” “The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.” Paragraph “Regulatory Reporting Requirements for SAEs” was added. Paragraph and bullet point to “The investigator will be responsible for the following was removed. Text: “The study will be performed in accordance with the Sponsor policy on Bioethics and Human Biological Samples.” was removed.	Provision of appropriate statements that describe Regulatory Reporting Requirements for SAEs in AZ studies. Correction to align with CSP template 5.0
A 3 Informed consent process	Text was added “and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study”.	Correction to align with CSP template 5.0.
Appendix A4 Data Protection	Text was updated: “The level of disclosure and use of their data must also be explained to the patient in the informed consent”.	Additional wording needed to address EU GDPR.

Section # and Name	Description of Change	Brief Rationale
Appendix A6 Dissemination of Clinical Study Data	Updated to correct web link; A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com	Previously link not correct.
Appendix A7 Data Quality Assurance	Updated: "The investigator is responsible for verifying that data entries are accurate and correct electronically signing the eCRF".	eCRF is signed electronically.
Appendix A7 Data Quality Assurance	Text was added "Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the [Monitoring Plan] [contracts]." And "The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)."	Correction to align with CSP template 5.0
Appendix A8 Source Documents	Updated; "reported on" was removed "entered in" was added.	Editorial changes.
Appendix A9 Study and Site Start and Closure	Added Common Text regarding sponsor responsibilities on premature termination/suspension of the study.	To comply with EU Clinical Trials Regulation No 536/2014 requirements (38) for definition of start of recruitment and ct.gov definition of study start.
Appendix D 1 Use/analysis of DNA	Text: "The samples will be retained while research on benralizumab continues but no longer than 15 years or other period as per local requirements." was removed.	This wording was removed in CSP template v. 5.0
Appendix E 1 Introduction	Wording was updated "analysis for serum tryptase will be performed at a local or central laboratory." The word "Central" was added.	Clarifications of clinical safety laboratory assessments.
Appendix F Medical device incidents: definition and procedures for recording, evaluation, follow-up, and reporting	Appendix F was removed. List of remaining CSP appendixes was updated.	Appendix F is not applicable for the Study CSP, since Benra APFS is a drug device combination product. Appropriate wording was updated in Sections 8.4.4 and 8.4.6.
Appendix G (previously appendix H) Hypereosinophilic	Question about photographs deleted.	There is no intent to collect a central collection of photography in this study.

Section # and Name	Description of Change	Brief Rationale
syndrome physical examination		
Appendix H (previously Appendix I) Table 9 Schedule of assessments for open-label extension Years 2 and 3	Spirometry (pre-bronchodilator FEV1 and FVC) was removed from IPD Visit.	Clarification that post-baseline spirometry is required only for patients with pulmonary involvement.
Appendix I (previously appendix J) Abbreviations	Abbreviations were added: "PBMC- Peripheral blood mononuclear cells" "SOP - Standard Operating Procedure" "ePRO"- patient-reported outcome was removed "eCOA" - Electronic clinical outcomes assessments was added "SADE" – Serious adverse device effect"	Omitted abbreviations were added and removed terms were deleted.
Appendix J	New appendix added: Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimising risk to the patient maintaining compliance with GCP, and minimising risks to study integrity. These changes will only be initiated at a time of study disruption.
Throughout	Minor editorial changes.	To align with the language and terminology used in the latest Clinical Study Protocol template and/or to clarify text and improve consistency.

K 5 Amendments 3 (27 September 2019), 2 (26 August 2019) and 1 (13 August 2019)

Version 4.0, 27 September 2019

In this amendment to the protocol:

- Synopsis, Sections 4.1, 5.1, 5.5.1 & 6.5.1:
  - Requirement of stable dose of HES medication updated from 1 month to 4 weeks to ensure consistency throughout the protocol.
- Table 1:
  - Correction that cell phenotyping (sub-study sampling) will be at selected sites, not just in USA.
- Section 5.1 Inclusion criteria:
  - #3: Revised to clarify the diagnosis of HES.
  - #9 & 10: Reference point for contraception requirements updated from 'randomisation' to 'enrolment'.
- Section 5.2 Exclusion criteria:
  - #16: Clarification of exemptions to interventional trials that are allowed concurrently with participation in this trial.
- Section 5.4 Lifestyle restrictions:
  - Revision to ensure that acceptable form(s) of contraception are adhered to from enrolment rather than randomisation.
- Section 5.5.1: Re-screening:
  - Clarifications to the procedures for re-screening, and addition of acceptable reasons to re-screen:
    - After 4 weeks if patient is not corticosteroid responsive during Screening.
    - If AEC <1000 cells/µl at visit 1.
- Section 5.5.1, 6.1.2, 6.4, 6.5.3, 7.1, 7.1.2:
  - Added that the study sponsor physician can designate an alternate contact under various circumstances.
- Section 6.3.2 Methods for ensuring blinding – double-blind treatment period:
  - Emphasize that unredacted eos may be ordered only in case of medical emergency.
- Section 6.5.1 Hypereosinophilic syndrome background therapy:
  - Updated to address rare cases of patients with no current background HES therapy that will require evidence of prior HES therapy and reason for discontinuation.

- Clarification that background medications can be changed after a patient has their first HES worsening/flare (also updated in Section 4.1.2).
- Reference to section 6.5.1 added to Inclusion criterion #5 and Section 4.1 (paragraph 5).

- Section 7.1 Discontinuation of investigational product:
  - Clarifications when considering early discontinuation of IP.
- Section 8.1.1 Hypereosinophilic syndrome worsening/flare:
  - Clarifications to evaluation of HES worsening/flare when patient is not able to come to the study site.
- Table 7 Laboratory safety variables:
  - Microscopy included in all central laboratory urinalyses, not just at Visit 3.
  - Pregnancy dipstick test removed from urinalysis as it is described in Section 8.2.1.1.
- Section 8.2.1.1 Pregnancy tests:
  - Pregnancy dipstick test schedule clarified.
- Section 8.2.5 Spirometry:
  - Clarification of which medications to withhold on days(s) when lung function testing is performed.
- Section 8.5.1 Determination of drug concentration:
  - Removal of random testing of PK from patients assigned to placebo.
- Section 8.6 Immunogenicity:
  - as well as removed ADA testing in placebo patients.
- Section 8.7.1 Optional exploratory genetic sample:
  - Clarified that samples for DNA isolation will only be taken from adult patients.
- Tables 2, 9 & 10:
  - Added central urinalysis at flare visits in the OLE.
- Appendix A5 Committees structure:
  - Correction of data shared with DSMB and clarifications to procedures
- Typographical errors and inconsistencies in wording also updated in various sections of the protocol.

Version 3.0, 26 August 2019

In this amendment to the protocol:

- Table 1 Schedule of assessments for the double-blind treatment period PK and ADA/nAb testing at Visit 4 (Week 4) was added.
- Mechanistic sub-study will be conducted in selected sites not limited to US.

Version 2.0, 13 August 2019
In this amendment to the protocol: • Section 8.1.2 haematologic relapse was added. • Subsequent sections were renumbered.
Version 1.0, 17 July 2019
Initial creation

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