Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3253C00001
Version	6.0
Date	06 Mar 2024

A Randomised, Double-blind, Active-controlled 52-week Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab Compared to Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in Patients Receiving Standard of Care Therapy (MANDARA Study)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2019-001832-77

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

Redacted for Public Disclosure

SUMMARY OF CHANGES TABLE

Document	Date of Issue
Amendment 5 (CSP version 6.0)	06 March 2024
Amendment 4 (CSP version 5.0)	11 April 2023
Amendment 3 (CSP version 4.0)	24 February 2021
Amendment 2 (CSP version 3.0)	04 August 2020
Amendment 1 (CSP version 2.0)	27 March 2020
Original protocol (Initial creation 1.0)	11 June 2019

Amendment 5: 06 March 2024

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 and in the EU Clinical Trial Regulation Article 2, 2(13), as 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 CSP has been amended to comply with the European Union Clinical Trials Regulation [EU CTR]: (EU) No 536/2014 requirements.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
CSP front page	EU CT Number was added on the CSP front page: 2023-510248-19-00.	Conformance with EU CTR.: Regulation (EU) No 536/2014.	Non-substantial
1.1 Schedule of Assessments; Table 5: Open-label Extension Period (Year 4 Onwards), if Applicable	Removal of ESR and CRP assessments requirement to perform on IPD/EOT visit.	Correction of error. The assessments were inadvertently added to the Table 5 which is not in line with expected study design. ESR and CRP assessments are not required after completion of first year OLE.	Non-substantial
6.2.3: Optional At-home or Remote-location Investigational Product Administration	Removal of obsolete statement about provision of urine pregnancy tests for patients' remote visits.	Correction of error. In CSP v5, requirement for urine pregnancy testing was restricted to on-site visits. In section 6.2.3 were inadvertently left references to urine	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
		pregnancy tests being provided to patients for home testing. Obsolete information was removed to align with the CSP SoA.	
6.5 Concomitant Therapy	IV, IM, SC corticosteroid therapy administration applicable to DB only	Clarification added on corticosteroid therapy administration during OLE.	Non-substantial
7.1 Discontinuation of Study treatment	Wording added: "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."	Clarification language added to discontinuation of Study treatment section.	Non-substantial
9.4.5 OLE Period Analyses	Information on additional analysis and final DBL present originally in section 4.1 Overall Design added to section 9 Statistical Considerations.	Clarification added on additional analysis and planned data cut-off for OLE period analyses, aligning with section 4.1	Non-substantial
Appendix A1: Regulatory and Ethical Considerations – Regulatory Reporting Requirements for SAEs	New CSP template text was added.	Clarification added on the process for reporting of SUSARs by the sponsor to Eudravigilance Database in accordance with EU CTR 536/2014.	Non-substantial
Appendix A4: Data protection Appendix A5: Dissemination of Clinical Study Data Appendix A6: Data Quality Assurance	New CSP template text was added.	Changes were made to comply with AstraZeneca new CSP template guidelines amended to adhere to the EU CTR: Regulation (EU) No 536/2014 requirements.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
Throughout	Minor editorial Changes.	Correction of typos, omissions, and grammatical errors.	Non-substantial

AE, adverse event; CRP, C-reactive protein; CSP, clinical study protocol; CTR, Clinical Trial Regulation; DB, double blind; DBL, database lock; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ESR, erythrocyte sedimentation rate; EU, European Union; IP, investigational product; IPD, IP discontinuation; IM, Intramuscular; IV, Intravenous; OLE, open-label extension; SAE, serious adverse event; SoA, Schedule of Assessments; SC, subcutaneous; SUSARs, suspected unexpected serious adverse reactions.

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1 PROTOCOL SUMMARY

1.1 Schedule of Assessments

This study comprises 2 distinct periods: a 52-week double-blind (DB) treatment period, during which patients will be randomised to receive either benralizumab or mepolizumab, and an OLE, during which all patients will receive benralizumab alone. The primary database lock will occur after all randomised patients have been followed up for the 52-week DB treatment period.

The SoA for the DB treatment period and for the first year of the OLE period of the study are provided in Table 1 and Table 2, respectively. The SoA for ePRO endpoints for the DB treatment period and the first year of the OLE period are provided in Table 6.

Patients may have the opportunity to participate in the OLE period of this study for at least one year following completion of the DB period on treatment (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, Table 4, and Table 5.

Table 1 Schedule of Assessments – Double-blind Treatment Period

Study procedures	Run in	Double-blind treatment period																		Details in CSP sections or Appendix
Visit	**V1 Screening**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17** [1]	**Unsch visit** [2]	**IPD** [4]	
Study week (calculated from V2)	**-4 to -1 wks (min)**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit windows		**± 3 days**		**± 7 days**					**± 3 days**		**± 7 days**									
General procedures																				
Informed consent (main study)	X																			5.1
Optional genetic research informed consent	X																			8.7
Demography/history	X																			5.1 and 5.2
Cardiovascular history and risk factors	X																			5.1 and 5.2
History of EGPA and treatment	X																			5.1 and 5.2
Height	X																			8.2.5.1
Weight	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.2.5.1
Inclusion/exclusion	X	X																		5.1 and 5.2
Randomisation criteria		X																		5.3
Eligibility check to enter OLE																	X			5.3.3
Efficacy assessments																				
DAILY corticosteroid medication usage [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
Record OCS dose and check compliance [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
BVAS	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.1.1.1

Table 1 Schedule of Assessments – Double-blind Treatment Period

Study procedures	Run in	Double-blind treatment period																		Details in CSP sections or Appendix
Visit	**V1 Screening**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17** [1]	**Unsch visit** [2]	**IPD** [4]	
Study week (calculated from V2)	**-4 to -1 wks (min)**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit windows		**± 3 days**		**± 7 days**					**± 3 days**		**± 7 days**									
VDI		X							X								X		X	8.1.1.3
Assess EGPA relapse [7]/remission		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.1.1.2
ePRO device dispensing/training	X																			8.1.1
ePRO assessments [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.1.1.4 to 8.1.1.11
Review ePRO completion and confirm compliance	X	X [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.1.1
Health resource use		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.10
Reversibility testing (post-BD FEV1)		X																		8.1.1.12
Spirometry (pre-BD FEV1)		X				X			X				X			X	X	X [2]	X	8.1.1.12
Safety assessments																				
Concomitant/ post IP medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam	X								X										X	8.2.2.1
Brief physical exam		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X [2]		8.2.2.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.2.3
ECG (triplicate recordings)	X															X			X	8.2.4
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3

Table 1 Schedule of Assessments – Double-blind Treatment Period

Study procedures	Run in	Double-blind treatment period																		Details in CSP sections or Appendix
Visit	**V1 Screening**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17** [1]	**Unsch visit** [2]	**IPD** [4]	
Study week (calculated from V2)	**-4 to -1 wks (min)**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit windows		**± 3 days**		**± 7 days**					**± 3 days**		**± 7 days**									
Laboratory assessments (always taken pre-dose at dosing visits)																				
Haematology, WBC w/differential [10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.2.1
Serum chemistry [11]	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.2.1
Lipoproteins (fasting) [12]		X															X			8.2.1
Hepatitis, HIV	X															X				8.2.1.2
Urinalysis central laboratory	X																			8.2.1
Troponin [13]	X																X			8.2.1
Urinalysis (dipstick) [14]		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.2.1
Serum pregnancy test [15]	X																			8.2.1.1
Urine pregnancy test (dipstick) [15]		X		X	X	X	X	X	X		X	X	X	X	X	X	X		X	8.2.1.1
ESR (local)	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	8.2.1
CRP	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X [2]	X	
FSH [16]	X																			8.2.1.1
MPO/PR3 (ANCA status)	X								X								X		X	8.2.1
Serum for biomarkers		X		X									X			X	X	X [2]		8.8
Total IgE, FEIA		X																		8.2.1
Nasal secretions [17]		X	X	X									X			X		X [2]		8.8

Table 1 Schedule of Assessments – Double-blind Treatment Period

Study procedures	Run in	Double-blind treatment period																		Details in CSP sections or Appendix
Visit	**V1 Screening**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17** [1]	**Unsch visit** [2]	**IPD** [4]	
Study week (calculated from V2)	**-4 to -1 wks (min)**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit windows		**± 3 days**		**± 7 days**					**± 3 days**		**± 7 days**									
PK [18]		X	X	X		X			X	X			X			X	X		X	8.5
ADA/nAb [19]		X				X			X				X			X	X		X	8.9
Whole blood for RNA		X														X				8.8
Optional genetic sample [20]		X																		8.7.1
Mechanistic sub-study procedures (if applicable)																				
Mechanistic sub-study informed consent	X																			
Tissue sample [21]		X														X		X [2]		8.8
Induced sputum [22]	X	X													X	X		X [2]		8.8
Whole blood for cell phenotyping [23]	X	X													X	X				8.8
Patient qualitative interviews sub-study procedures (if applicable)																				
Explain patient qualitative interview sub-study	X																			Appendix A
Patient qualitative interview sub-study ICF		X																		
Patient qualitative interview [24]		X														X			X	8.1.2
Other/administrative																				
IRT/RTSM transaction	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	6.3.1

Table 1 Schedule of Assessments – Double-blind Treatment Period

Study procedures	Run in	Double-blind treatment period																		Details in CSP sections or Appendix
Visit	**V1 Screening**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17** [1]	**Unsch visit** [2]	**IPD** [4]	
Study week (calculated from V2)	**-4 to -1 wks (min)**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**25**	**28**	**32**	**36**	**40**	**44**	**48**	**52**			
Visit windows		**± 3 days**		**± 7 days**					**± 3 days**		**± 7 days**									
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix A
Investigational product administration																				
Administer blinded IP at the site		X		X	X	X	X	X	X		X	X	X	X	X	X				6
Administer open-label benralizumab at the site (first dose of OLE)																	X			
Telephone contact for patients who discontinue early from IP and unwilling/unable to continue with clinic visits																				
Telephone contact			Telephone contact every 4 weeks from the date of last clinic visit, and to continue until the end of the double-blind treatment period ⟷																	7.1.1.1

1 Visit 17 is the last double-blind visit and the first OLE visit. All assessments at Visit 17 to be performed BEFORE administration of open-label benralizumab.
2 Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits, at the discretion of the Investigator.
3 If unscheduled visit is to assess the patient for potential EGPA relapse, include these additional assessments. Other assessments may be performed as clinically indicated.
4 In case of early discontinuation from IP, procedures of the IPD visit to be performed 4 weeks (± 7 days) after last dose of IP (replaces regular scheduled visit assessments).
5 The patient reports OCS medication usage each evening using the provided ePRO device (Visit 1-17).
6 Investigator/delegate to record the OCS dose in the eCRF at each study visit and check compliance against patient reported use between study visits.
7 In the event of an EGPA relapse, blood and urine to be collected. In addition, for patients participating in the mechanistic sub-study, a sputum and relevant biopsy sample (if possible) should be collected.
8 Visit 2 must be confirmed on the handheld device by a trained site personnel prior to baseline ePRO questionnaires completion by the patient. Sites should ensure patients complete all baseline ePRO assessments. For subsequent visits, the site should confirm the visit either on the web portal Study Works or on the device.
9 See Table 6 for all ePRO assessment details.
10 From baseline (Visit 2) until the second visit of the OLE (Week 56 [Visit 18]), eosinophil, basophil, and monocyte counts will be redacted from all central laboratory reports in order to maintain the blind.

[11] eGFR will be calculated according to the CKD-EPI formula at each visit where serum chemistry is collected.
[12] Patient must be in fasting state. If patient has not fasted, he/she may return to collect this sample as soon as possible. The period of fasting may be adjusted at the discretion of the Investigator for patients with relevant metabolic conditions (eg, diabetes mellitus).
[13] Investigators can perform additional troponin assessments using a central test as clinically indicated during other visits.
[14] Haematuria to be checked by dipstick test provided centrally.
[15] Only for WOCBP.
[16] FSH test done only for female patients to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for ≥ 12 months.
[17] Only sites with the required equipment will collect nasal secretion samples.
[18] On dosing visits, PK will be collected pre-dose.
[19] ADA/nAb analysis will only be done on samples from patients who received benralizumab. Neutralising antibody testing will be performed for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.
[20] Optional genetic sample: Sample collection is recommended at baseline (Visit 2) but may be drawn at any time after the patient is randomised.
[21] In patients with chronic rhinosinusitis with or without nasal polyps, a tissue biopsy sample should be taken from the nose (Week 0 and Week 52). Biopsies from other sites may be taken as per clinical judgment (unscheduled visit), these biopsies must remain blinded (refer to footnote 8).
[22] Spirometry is required as part of the sputum induction procedure as described in the separate laboratory manual.
[23] Sampling of whole blood for cell phenotyping at Visits 2 and 16 are applicable for all North American mechanistic sub-study sites and at Visits 1 and 15 only for the McMaster site.
[24] Each participating patient will be interviewed twice. The first interview will take place at least 7 and up to 21 days after Visit 2. The second will take place at least 7 and up to 21 days after Visit 16.

ADA, Anti-drug antibodies; AE(s), adverse event(s); ANCA, anti-neutrophil cytoplasmic antibodies; BD, bronchodilator; BVAS, Birmingham Vasculitis Activity Score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CSP, clinical study protocol; ECG, electrocardiogram; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; ePRO, electronic patient reported outcome; ESR, erythrocyte sedimentation rate; FEIA, fluorenzyme immunoassay; FEV1, forced expiratory volume in 1 second; FSH, follicle stimulating hormone; HIV, human immunodeficiency virus; IgE, Immunoglobulin E; IP, investigational product; IPD, IP discontinuation; IRT, Interactive Response Technology; min, minimum; MPO, myeloperoxidase; nAb, neutralising antibodies; OC,S oral corticosteroid; OLE, open-label extension; PK, pharmacokinetics; PR3, proteinase-3; RNA, ribonucleic acid; RTSM, Randomisation and Trial Supply System Management; SAE(s), serious adverse event(s); Unsch, unscheduled; V, Visit (number); VDI, Vasculitis Damage Index; WBC, white blood cells; Wks, weeks.

Table 2 Schedule of Assessments – Open-label Extension Period (First Year)

Study procedure	Open-label extension period – first year															Details in CSP sections or Appendix
Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**Unsch visit [2]**	**IPD / EOT [4]**	
Study week (calculated from Visit 2) Visit windows: ± 7 days	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**			
Visit can be done remotely [1]							**X**	**X**		**X**	**X**					
General procedures																
Weight	X	X	X	X	X	X			X			X	X	X [2]	X	8.2.5.1
Efficacy assessments																
WEEKLY corticosteroid medication usage [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
Record OCS dose and check compliance [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
BVAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.1.1.1
VDI						X						X			X	8.1.1.3
Assessment of EGPA relapse [7]/remission	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.1.1.2
ePRO assessments [8]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.1.1.4 to 8.1.1.11
Review ePRO completion and confirm compliance	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.1.1
Health resource use	X	X	X	X	X	X	X	X	X	X	X	X	X		X	8.10
Spirometry (pre-BD FEV1)						X						X		X [2]		8.1.1.12
Safety assessments																
Concomitant/post IP meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam												X			X	8.2.2.1
Brief physical exam														X [2]		8.2.2.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.2.3
ECG (triplicate recordings)													X		X	8.2.4
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3

Table 2 Schedule of Assessments – Open-label Extension Period (First Year)

Study procedure	Open-label extension period – first year															Details in CSP sections or Appendix
Visit	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**Unsch visit [2]**	**IPD / EOT [4]**	
Study week (calculated from Visit 2) Visit windows: ± 7 days	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**			
Visit can be done remotely [1]							**X**	**X**		**X**	**X**					
Laboratory assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/differential	X	X		X		X						X		X [2]	X	8.2.1
Serum chemistry [9]	X			X		X			X			X	X	X [2]	X	8.2.1
Urinalysis (dipstick) [10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.2.1
Urine pregnancy test (dipstick) [11]	X	X	X	X	X	X			X			X	X		X	8.2.1.1
ESR (local)						X						X		X [2]	X	8.2.1
CRP	X	X		X		X			X			X	X	X [2]	X	8.2.1
Serum for biomarkers						X						X				8.8
PK [12]						X						X			X	8.5
ADA/nAb [13]						X						X			X	8.9
Other/ Administrative																
IRT/RTSM transaction	X	X	X	X	X	X	X	X	X	X	X	X	X		X	6.3.1
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix A
Benralizumab administration																
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X			6

1 These visits can optionally be conducted remotely by telephone contact for patients who are self-administering IP. Vital signs and urinalysis (dipstick) will not be assessed when a visit is conducted remotely.

2 Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits, at the discretion of the Investigator.

3 If unscheduled visit is to assess the patient for potential EGPA relapse, include these additional assessments. Other assessments may be performed as clinically indicated.

4 The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after decision to discontinue IP has been made, and at the latest 4 weeks ± 7 days after the last dose of IP. End of Treatment visit will only be scheduled following notification of closure of the study (Section 7.1.1.2), 4 weeks ± 7 days after the last dose of IP.

5 The patient reports OCS medication usage on a weekly basis using the provided ePRO device (Visit 18 through 30).

[6] Investigator/delegate to record the OCS dose in the eCRF at each study visit and check compliance against patient reported use between study visits.
[7] In the event of an EGPA relapse, blood and urine to be collected.
[8] See Table 6 for all ePRO assessment details.
[9] eGFR will be calculated according to the CKD-EPI formula.
[10] Haematuria to be checked by dipstick test provided centrally.
[11] Only for women of child-bearing potential.
[12] On dosing visits, PK will be collected pre-dose.
[13] Neutralising antibody testing 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; AE(s), adverse event(s); BD, bronchodilator; BVAS, Birmingham Vasculitis Activity Score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CSP, clinical study protocol; ECG, electrocardiogram; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ePRO, electronic patient reported outcome; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus; IP, investigational product; IPD, IP discontinuation; IRT, Interactive Response Technology; meds, medications; nAb, neutralising antibodies; OCS, oral corticosteroid; OLE, open-label extension; PK, pharmacokinetics; RTSM, Randomisation and Trial Supply System Management; SAE(s), serious adverse event(s); Unsch, unscheduled; V, Visit (number); VDI, Vasculitis Damage Index; WBC, white blood cells.

Table 3 Schedule of Assessments – Open-label Extension Period (Year 2), if Applicable

Study procedure	Open-label extension period – Year 2 (if applicable)															Details in CSP sections or Appendix
Visit	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study week (calculated from V2) Visit windows: ± 7 days	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**			
General procedures																
Weight														X [2]	X	8.2.5.1
Efficacy assessments																
Record OCS dose and check compliance [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
BVAS														X [2]	X	8.1.1.1
VDI													X	X	X	8.1.1.3
Clinical assessment of EGPA relapse/remission [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.1.1.2
Health resource use															X	8.10
Spirometry (pre-BD FEV1)														X [2]		8.1.1.12
Safety assessments																
Concomitant/ post IP meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam															X	8.2.2.1
Brief physical exam														X [2]		8.2.2.2
Vital signs						X						X		X [2]	X	8.2.3
ECG (triplicate recordings)												X			X	8.2.4
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Laboratory assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/differential [7]						X						X		X [2]	X	8.2.1
Serum chemistry [7,8]						X						X		X [2]	X	8.2.1
Urinalysis (dipstick) [9]						X						X		X	X	8.2.1

Table 3 Schedule of Assessments – Open-label Extension Period (Year 2), if Applicable

Study procedure	Open-label extension period – Year 2 (if applicable)															Details in CSP sections or Appendix
Visit	**V31**	**V32**	**V33**	**V34**	**V35**	**V36**	**V37**	**V38**	**V39**	**V40**	**V41**	**V42**	**V43**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study week (calculated from V2) Visit windows: ± 7 days	**108**	**112**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**			
Urine pregnancy test (dipstick) [10]						X						X			X	8.2.1.1
ESR (local)														X [2]		8.2.1
CRP														X [2]		8.2.1
PK [11]						X						X			X	8.5
ADA/nAb [12]						X						X			X	8.9
Other/ Administrative																
IRT/RTSM transaction	X	X	X	X	X	X	X	X	X	X	X	X	X		X	6.3.1
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix A
Benralizumab administration																
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X			6

1 These visits can optionally be conducted remotely by telephone contact for patients who are self-administering IP.
2 Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits, at the discretion of the Investigator.
3 If unscheduled visit is to assess the patient for potential EGPA relapse, include these additional assessments. Other assessments may be performed as clinically indicated.
4 The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after decision to discontinue IP has been made, and at the latest 4 weeks ± 7 days after the last dose of IP. EOT visit will only be scheduled following notification of closure of the study (Section 7.1.1.2), 4 weeks ± 7 days after the last dose of IP.
5 Investigator/delegate to record the OCS dose in the eCRF at each study visit.
6 Clinical assessment of relapse/remission based on Investigators' overall clinical assessment. In case of clinically suspected relapse, an unscheduled visit should be performed.
7 Haematology and chemistry samples may be collected more frequently if clinically indicated at Investigators' discretion.
8 eGFR will be calculated according to the CKD-EPI formula.
9 Haematuria to be checked by dipstick test provided centrally.
10 Only for women of child-bearing potential.
11 On dosing visits, PK will be collected pre-dose.
12 Neutralising antibody testing 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; AE(s), adverse event(s); BD, bronchodilator; BVAS, Birmingham Vasculitis Activity Score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CSP, clinical study protocol; ECG, electrocardiogram; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 second; IP, investigational product; IPD, IP discontinuation; IRT, Interactive Response Technology; meds, medications; nAb, neutralising antibodies; OCS, oral corticosteroid; PK, pharmacokinetics; RTSM, Randomisation and Trial Supply System Management; SAE(s), serious adverse event(s); Unsch, unscheduled; V, Visit (number); VDI, Vasculitis Damage Index; WBC, white blood cells.

Table 4 Schedule of Assessments – Open-label Extension Period (Year 3), if Applicable

Study procedure	Open-label extension period – Year 3 (if applicable)															Details in CSP sections or Appendix
Visit	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**V55**	**V56**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study week (calculated from Visit 2) Visit windows: ± 7 days	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**			
General procedures																
Weight														X [2]	X	8.2.5.1
Efficacy assessments																
Record OCS dose and check compliance [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
BVAS														X [2]	X	8.1.1.1
VDI													X	X	X	8.1.1.3
Clinical assessment of EGPA relapse/remission [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X [2]	X	8.1.1.2
Health resource use															X	8.10
Spirometry (pre-BD FEV1)														X [2]		8.1.1.12
Safety assessments																
Concomitant/ post IP meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam															X	8.2.2.1
Brief physical exam														X [2]		8.2.2.2
Vital signs						X						X		X [2]	X	8.2.3
ECG (triplicate recordings)												X			X	8.2.4
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Laboratory assessments (always taken pre-dose at dosing visits)																
Haematology, WBC w/differential [7]						X						X		X [2]	X	8.2.1
Serum chemistry [7,8]						X						X		X [2]	X	8.2.1
Urinalysis (dipstick) [9]						X						X		X	X	8.2.1

Table 4 Schedule of Assessments – Open-label Extension Period (Year 3), if Applicable

Study procedure	Open-label extension period – Year 3 (if applicable)															Details in CSP sections or Appendix
Visit	**V44**	**V45**	**V46**	**V47**	**V48**	**V49**	**V50**	**V51**	**V52**	**V53**	**V54**	**V55**	**V56**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study week (calculated from Visit 2) Visit windows: ± 7 days	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**		**X**	**X**	**X**	**X**	**X**		**X**			
Urine pregnancy test (dipstick) [10]						X						X			X	8.2.1.1
ESR (local)														X [2]		8.2.1
CRP														X [2]		8.2.1
PK [11]						X						X			X	8.5
ADA/nAb [12]						X						X			X	8.9
Other/administrative																
IRT/RTSM transaction	X	X	X	X	X	X	X	X	X	X	X	X	X		X	6.3.1
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix A
Benralizumab administration																
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X			6

1 These visits can optionally be conducted remotely by telephone contact for patients who are self-administering IP.
2 Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits, at the discretion of the Investigator.
3 If unscheduled visit is to assess the patient for potential EGPA relapse, include these additional assessments. Other assessments may be performed as clinically indicated.
4 The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after decision to discontinue IP has been made, and at the latest 4 weeks ± 7 days after the last dose of IP. EOT visit will only be scheduled following notification of closure of the study (Section 7.1.1.2), 4 weeks ± 7 days after the last dose of IP.
5 Investigator/delegate to record the OCS dose in the eCRF at each study visit.
6 Clinical assessment of relapse/remission based on Investigators' overall clinical assessment. In case of clinically suspected relapse, an unscheduled visit should be performed.
7 Haematology and chemistry samples may be collected more frequently if clinically indicated at Investigator's discretion.
8 eGFR will be calculated according to the CKD-EPI formula.
9 Haematuria to be checked by dip-stick test provided centrally.
10 Only for women of child-bearing potential.
11 On dosing visits, PK will be collected pre-dose.
12 Neutralising antibody testing 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; AE(s), adverse event(s); BD, bronchodilator; BVAS, Birmingham Vasculitis Activity Score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CSP, clinical study protocol; ECG, electrocardiogram; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 second; IP, investigational product; IPD, IP discontinuation; IRT, Interactive Response Technology; meds, medications; nAb, neutralising antibodies; OCS, oral corticosteroid; OLE, open-label extension; PK, pharmacokinetics; RTSM, Randomisation and Trial Supply System Management; SAE(s), serious adverse event(s); Unsch, unscheduled; V, Visit (number); VDI, Vasculitis Damage Index; WBC, white blood cells.

Table 5 Schedule of Assessments – Open-label Extension Period (Year 4 Onwards), if Applicable

Study procedure	Open-label extension period – Year 4 onwards (if applicable)															Details in CSP sections or Appendix
Visits	**V57/ 70/ 83**	**V58/ 71/ 84**	**V59/ 72/ 85**	**V60/ 73/ 86**	**V61/ 74/ 87**	**V62/ 75/ 88**	**V63/ 76/ 89**	**V64/ 77/ 90**	**V65/ 78/ 91**	**V66/ 79/ 92**	**V67/ 80/ 93**	**V68/ 81/ 94**	**V69/ 82/ 95**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study weeks (calculated from Visit 2) Visit windows: ± 7 days	**212/ 264/ 316**	**216/ 268/ 320**	**220/ 272/ 324**	**224/ 276/ 328**	**228/ 280/ 332**	**232/ 284/ 336**	**236/ 288/ 340**	**240/ 292/ 344**	**244/ 296/ 348**	**248/ 300/ 352**	**252/ 304/ 356**	**256/ 308/ 360**	**260/ 312/ 364**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**			
General procedures																
Weight														X [2]	X	8.2.5.1
Efficacy assessments																
Record OCS dose and check compliance [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.4
BVAS														X [2]	X	8.1.1.1
VDI												X		X	X	8.1.1.3
Clinical assessment of EGPA relapse/remission [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1.2
Health resource use															X	8.10
Safety assessments																
Concomitant/ post IP meds (only in case of SAE and relevant for SAE) [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam															X	8.2.2.1
Brief physical exam														X		8.2.2.2
Vital signs												X		X	X	8.2.3
ECG (triplicate recordings)															X	8.2.4
SAEs [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Laboratory assessments																
Haematology, WBC w/differential [9]												X		X	X	8.2.1
Serum chemistry [9,10]												X		X	X	8.2.1

Table 5 Schedule of Assessments – Open-label Extension Period (Year 4 Onwards), if Applicable

Study procedure	Open-label extension period – Year 4 onwards (if applicable)															Details in CSP sections or Appendix
Visits	**V57/ 70/ 83**	**V58/ 71/ 84**	**V59/ 72/ 85**	**V60/ 73/ 86**	**V61/ 74/ 87**	**V62/ 75/ 88**	**V63/ 76/ 89**	**V64/ 77/ 90**	**V65/ 78/ 91**	**V66/ 79/ 92**	**V67/ 80/ 93**	**V68/ 81/ 94**	**V69/ 82/ 95**	**Unsch visit [2]**	**IPD/ EOT [4]**	
Study weeks (calculated from Visit 2) Visit windows: ± 7 days	**212/ 264/ 316**	**216/ 268/ 320**	**220/ 272/ 324**	**224/ 276/ 328**	**228/ 280/ 332**	**232/ 284/ 336**	**236/ 288/ 340**	**240/ 292/ 344**	**244/ 296/ 348**	**248/ 300/ 352**	**252/ 304/ 356**	**256/ 308/ 360**	**260/ 312/ 364**			
Visit can be done remotely [1]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**			
Urinalysis (dipstick) [11]														X	X	8.2.1
Urine pregnancy test (dipstick) [12]												X			X	8.2.1.1
ESR (local)														X [2]		8.2.1
CRP														X [2]		8.2.1
PK															X	8.5
ADA/nAb [13]															X	8.9
Other/administrative																
IRT/RTSM transaction	X	X	X	X	X	X	X	X	X	X	X	X	X		X	6.3.1
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Appendix A
Benralizumab administration																
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X			6

1 These visits can optionally be conducted remotely by telephone contact for patients who are self-administering IP.
2 Unscheduled visits may be initiated as needed, and any additional assessments may be performed at these visits, at the discretion of the Investigator.
3 If unscheduled visit is to assess the patient for potential EGPA relapse, include these additional assessments. Other assessments may be performed as clinically indicated.
4 The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after decision to discontinue IP has been made, and at the latest 4 weeks ± 7 days after the last dose of IP. EOT visit will only be scheduled following notification of closure of the study (Section 7.1.1.2), 4 weeks ± 7 days after the last dose of IP.
5 Investigator/delegate to record the OCS dose in the eCRF at each study visit.
6 Clinical assessment of relapse/remission based on Investigators' overall clinical assessment. In case of clinically suspected relapse, an unscheduled visit should be performed.
7 Concomitant medications taken for and relevant for SAE or significant medical/adverse event should be recorded in the eCRF.
8 Only SAEs or significant medical/adverse events that lead to an intervention should be captured and recorded in the eCRF.
9 Haematology and chemistry samples may be collected more frequently if clinically indicated at Investigator's discretion.

[10] eGFR will be calculated according to the CKD-EPI formula.
[11] Haematuria to be checked by dip-stick test provided centrally.
[12] Only for women of child-bearing potential.
[13] Neutralising antibody testing 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; BVAS, Birmingham Vasculitis Activity Score; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CSP, clinical study protocol; ECG, electrocardiogram; eCRF, electronic case report form; eGFR, estimated glomerular filtration rate; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ESR, erythrocyte sedimentation rate; IP, investigational product; IPD, IP discontinuation; IRT, Interactive Response Technology; meds, medications; nAb, neutralising antibodies; OCS, oral corticosteroid; PK, pharmacokinetics; RTSM, Randomisation and Trial Supply System Management; SAE(s), serious adverse event(s); Unsch, unscheduled; V, Visit (number); VDI, Vasculitis Damage Index; WBC, white blood cells.

Table 6 Schedule of Assessments for ePRO Endpoints (Double-blind Period and Open-label Extension Period – First Year)

PRO assessment	Double-blind treatment period (V1-V17) After Visit 2, all assessments may be completed at home. If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.	OLE period – first year (V18-V30) All assessments will be completed at Visit 18. After Visit 18, all assessments may be completed at home. If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.
Corticosteroid medication usage	V1-V17: daily at home in the evening Unscheduled visit [a]: at site IPD visit: at site	After V18: every 7 days (± 2 days) until V30 IPD visit: at site EOT visit: at site
ACQ-6	V1: at site V2: at site After V2: every 7 days (± 2 days) until V17 Unscheduled visit [a]: at site IPD visit: at site	After V18: every 28 days (± 2 days) until V30 IPD visit: at site EOT visit: at site
Sino-nasal questionnaire	V1: at site V2: at site After V2: every 7 days (± 2 days) until V17 Unscheduled visit [a]: at site IPD visit: at site	After V18: every 28 days (± 2 days) until V30 IPD visit: at site EOT visit: at site
SNOT-22	V1: at site V2: at site After V2: every 28 days (± 2 days) until V7 After V7: every 84 days (± 2 days) until V17 IPD visit: at site	After V18: every 84 days (± 2 days) until V30 IPD visit: at site EOT visit: at site
SF-36v2	V1: at site V2: at site V3: 7 days (± 2 days) after V2 After V3: every 28 days (± 2 days) after V2 until V7 After V7: every 84 days (± 2 days) until V17 IPD visit: at site	After V18: every 84 days (± 2 days) until V30 IPD visit: at site EOT visit: at site

Table 6 Schedule of Assessments for ePRO Endpoints (Double-blind Period and Open-label Extension Period – First Year)

PRO assessment	Double-blind treatment period (V1-V17) **After Visit 2, all assessments may be completed at home.** **If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.**	OLE period – first year (V18-V30) **All assessments will be completed at Visit 18. After Visit 18, all assessments may be completed at home.** **If any assessment has not been completed prior to the site visit, it will be completed at the site prior to other study procedures.**
PGIC	After V2: every 7 days (± 2 days) for 28 days	Not applicable
PGIS	V1: at site V2: at site After V2: every 7 days (± 2 days) until V17 IPD visit: at site	Not applicable
WPAI-GH	V1: at site V2: at site After V2: every 28 days (± 2 days) until V7 After V7: every 84 days (± 2 days) until V17 IPD visit: at site	After V18: every 84 days (± 2 days) until V30 IPD visit: at site EOT visit: at site

[a] Only if the unscheduled visit is to assess the patient for potential EGPA relapse.

ACQ-6, Asthma Control Questionnaire (6-item version); EOT, end of treatment; ePRO electronic patient reported outcome; IPD, investigational product discontinuation; OLE, open-label extension; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PRO, patient reported outcome; SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22, Sino-nasal Outcome Test-22; V, visit (number); WPAI, Work Productivity and Activity Impairment Questionnaire (General Health version 2.0).

1.2 Synopsis

International Coordinating Investigator

PPD

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Protocol Title

A Randomised, Double-blind, Active-controlled 52-Week Study with an Open-label Extension to Evaluate the Efficacy and Safety of Benralizumab Compared to Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in Patients Receiving Standard of Care Therapy (MANDARA Study)

Rationale

Eosinophilic granulomatosis with polyangiitis (EGPA) (formerly Churg-Strauss syndrome) is a rare disease characterised by potentially life-threatening systemic eosinophilic small-vessel vasculitis in association with asthma, sinusitis, and pulmonary infiltrates. Eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome (HES) have distinct, but partly overlapping clinical and histologic features, including target organs. Because eosinophilia is central to the pathophysiology of EGPA, it is hypothesised that direct or indirect depletion of eosinophils could also treat EGPA.

Benralizumab (FASENRA™ [1]) is a humanised, afucosylated monoclonal antibody (mAb) (immunoglobulin G subclass 1 [IgG1], immunoglobulin G1 kappa isotype [IgG1κ]) that binds to the human interleukin-5 receptor alpha subunit (IL-5Rα) with high affinity and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the fragment crystallizable (Fc) domain of benralizumab results in high affinity for FcγRIII receptors on immune effector cells such as natural killer cells leading to depletion by apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity. The direct eosinophil-depleting ability of benralizumab has been shown to be effective in eosinophilic asthma and in steroid-dependent asthma. Benralizumab has also shown potential for benefit in HES, a group of diseases with persistent blood eosinophilia and evidence of eosinophil-mediated end-organ damage.

This Phase III study in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy includes a 52-week double-blind (DB) period in which the efficacy and safety of benralizumab will be compared with an active comparator, mepolizumab, which has regulatory approval in several markets for use in

[1] FASENRA (benralizumab) is a trademark of the AstraZeneca group of companies.

patients with EGPA. The study also includes an open-label extension (OLE) period intended to allow each patient at least one additional year of treatment with open-label benralizumab, which will provide an opportunity to assess long-term safety and tolerability of benralizumab in this patient population.

Overall Design

The objectives and endpoints for the DB treatment period and the OLE period of the study are presented in Table 7 and Table 8, respectively.

Table 7 Study Objectives – Double-blind Period

The following objectives/endpoints are for the double-blind period (double-blind) of the study.	
Primary objective:	**Endpoint/variable:**
To assess the durability of response to treatment with benralizumab compared with mepolizumab in patients with relapsing or refractory EGPA who are receiving standard of care therapy, assessed by the proportion of patients in remission at both Weeks 36 and 48	Primary endpoint: Proportion of patients with relapsing or refractory EGPA, achieving remission, defined as BVAS = 0 and OCS dose ≤ 4 mg/day (main remission definition) at both Weeks 36 and 48 Supportive endpoint: Proportion of patients who have achieved remission defined by BVAS = 0 and OCS dose ≤ 7.5 mg/day (supportive remission definition) at both Weeks 36 and 48
Secondary objectives:	**Endpoint/variable:**
To assess the efficacy of benralizumab compared with mepolizumab on duration of clinical remission, defined as accrued duration in weeks where a patient achieves remission	Total accrued duration of remission for the following categories: 0 wk, > 0 to < 12 wk, 12 to < 24 wk, 24 to < 36 wk, ≥ 36 wk. Analysis will be repeated based on main and supportive remission definitions
To assess the efficacy of benralizumab compared with mepolizumab on time to first relapse	Time from randomisation to first EGPA relapse, where relapse is defined as any of the following: • Active vasculitis (BVAS > 0); OR • Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR • Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting **any** of the following: ° An increased dose of OCS therapy to > 4 mg/day prednisolone total daily dose; **OR** ° An increased dose or addition of immunosuppressive therapy; **OR** ° Hospitalisation related to EGPA worsening

Table 7 Study Objectives – Double-blind Period

To assess the effect of benralizumab on corticosteroid dose required during Weeks 48 through 52 compared to mepolizumab	Based on the average daily prednisolone/prednisone dose during Weeks 48 through 52: • Proportion of patients in each category: 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg, and > 7.5 mg. • Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25% reduction; 25 to < 50% reduction; 50 to < 75% reduction; 75 to < 100% reduction; 100% reduction. • Proportion of patients with ≥ 50% reduction from baseline. • Proportion of patients with 100% reduction from baseline. • Proportion of patients with ≤ 4 mg in average daily dose.
To assess the clinical benefit of benralizumab compared to mepolizumab	Proportion of patients who have achieved any clinical benefit when meeting any of the criteria below. Proportion of patients who have achieved complete response when meeting all of the criteria below. • Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the double-blind treatment period • ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52 • EGPA relapse free during the double-blind treatment period. Analysis will be repeated for the supportive remission definition.
To assess the annualised relapse rate in patients receiving benralizumab compared to mepolizumab	Annualised relapse rate
To assess the proportion of patients who achieve remission within the first 24 weeks and remain in remission for the remainder of the double-blind period in patients receiving benralizumab compared to mepolizumab	Proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period. Analysis will be repeated based on main and supportive remission definitions.
To assess additional measures of the efficacy and health status/health-related quality of life in patients receiving benralizumab compared to mepolizumab	BVAS, VDI, pulmonary function testing, asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT-22 questionnaire), health-related quality of life (SF-36v2), PGIS, WPAI, and blood eosinophil counts will be assessed as change from baseline over the 52-week double-blind treatment period. PGIC will be assessed as response proportions at each weekly assessment between Visits 2 and 4.

Table 7 Study Objectives – Double-blind Period

Safety objectives:	**Endpoint/variable:**
To assess the safety and tolerability of benralizumab compared to mepolizumab	Safety and tolerability will be evaluated based on AEs, vital signs, physical exam, clinical laboratory, and ECG. 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
To assess the pharmacokinetics and immunogenicity of benralizumab	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralising antibodies
Exploratory objectives:	**Endpoint/variable:**
To assess the cumulative OCS use in response to treatment with benralizumab compared to mepolizumab	Cumulative OCS use, as measured by AUC for daily prednisolone/prednisone dose, over the 52-week double-blind treatment period
To evaluate the effect of benralizumab compared to mepolizumab on health care resource utilisation due to EGPA	Number of EGPA-related hospitalisations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers of inflammation	Biomarkers of inflammation, eg, CRP and ESR
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers related to the MoA, eosinophilic inflammation, and EGPA disease pathogenesis, as well as baseline predictors of response to benralizumab or mepolizumab	Exploratory biomarkers in: • Serum • Whole blood • Nasal secretions • Tissue biopsies and sputum (mechanistic sub-study only)
To characterise the patient-reported experience and treatment benefits of benralizumab compared with mepolizumab through patient interviews	Patient interviews to characterise patient-reported experience and treatment benefits (sub-study)

ACQ-6, Asthma Control Questionnaire (6-item version); AE(s), adverse event(s); AUC, area under the curve; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; ECG, electrocardiogram; EGPA, eosinophilic granulomatosis with polyangiitis; ER, emergency room; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IP, investigational product; MoA, mechanism of action; OCS, oral corticosteroid; OLE, open-label extension; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; SAE(s), serious adverse event(s); SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22, Sino-nasal Outcome Test-22; VDI, Vasculitis Damage Index; WPAI, Work Productivity and Activity Impairment Questionnaire; wk, weeks

Table 8 Study Objectives for Open-label Extension Period

The following objectives/endpoints are for the open-label extension portion of the study:	
Objectives:	**Endpoint/variable:**
To evaluate the effect of benralizumab on remission, relapse, and OCS use [a]	Remission, relapse (as defined in Table 7 [c]), OCS use
To assess patient reported outcomes in patients receiving benralizumab [b]	Asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT-22 questionnaire), health-related quality of life (SF-36v2), and WPAI
To assess the safety and tolerability of benralizumab [a]	Safety and tolerability will be evaluated based on AEs, vital signs, physical exam, clinical laboratory, and ECG. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by the Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To assess the pharmacokinetics and immunogenicity of benralizumab [d]	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralising antibodies
To evaluate the effect of benralizumab on health care resource utilisation due to EGPA [b]	Number of EGPA-related hospitalisations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test)
To assess biomarkers of inflammation [b]	Biomarkers of inflammation, eg, CRP and ESR
To assess biomarkers related to the MoA of benralizumab, eosinophilic inflammation, and EGPA disease pathogenesis [b]	Exploratory biomarkers in serum

[a] Applicable to full duration of OLE.
[b] Applicable to first year of OLE only.
[c] Applicable to first year of OLE only. From the second year, the definitions of remission and relapse will be based on the Investigator's overall clinical assessment.
[d] Applicable to OLE Year 1-3.

ACQ-6, Asthma Control Questionnaire (6-item version); AE(s) adverse event(s); CRP, C-reactive protein; ECG, electrocardiogram; EGPA eosinophilic granulomatosis with polyangiitis; ER, emergency room; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IP, investigational product; MoA, mechanism of action; OCS, oral corticosteroids; OLE, Open-label extension PK, pharmacokinetics; RNA, ribonucleic acid; SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22, Sino-nasal Outcome Test-22; WPAI, Work Productivity and Activity Impairment Questionnaire.

Overall Design

This is a randomised, DB, active-controlled, parallel group, multicentre 52-week Phase III study to compare the efficacy and safety of benralizumab 30 mg versus mepolizumab 300 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W) in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy.

The target population is adult female or male patients aged 18 years and above who have documented EGPA diagnosis plus documentation of at least 2 additional features of EGPA and a history of relapsing or refractory disease. After initial enrolment and confirmation of entry criteria (Visit 1), potentially eligible patients will enter a screening period of up to 4 weeks (minimum of one week) and will be required to be on a stable dose of oral corticosteroids (OCS) ≥ 7.5 mg/day prednisolone/prednisone (but not > 50 mg/day), for at least 4 weeks prior to baseline (Visit 2) (see Appendix K for Belgium). Patients on immunosupressive therapy must be on a stable dose for at least 4 weeks prior to baseline (Visit 2) and should remain on the same dose until the end of the DB period (if the patient does not enter the OLE) or until completion of the first 6 months of the OLE period (if the patient continues into the OLE). Dose reductions for safety reasons will be permitted. Note that the dose of immunosuppressive therapy must not exceed the maximal doses used in clinical practice.

Study Period

Estimated date of first patient enrolled: third quarter 2019

Estimated date of last patient completed: third quarter 2024.

Number of Patients

Approximately 140 eligible patients will be randomised in a 1:1 ratio to either the benralizumab 30 mg or mepolizumab 300 mg treatment groups, respectively.

Treatments and Treatment Duration

Patients who meet the eligibility criteria at Visit 1 and criteria needing to be confirmed/reconfirmed at baseline (Visit 2) will be randomised to a 52-week treatment period with investigational product (IP) Q4W. Patients will receive either one SC injection of benralizumab 30 mg plus 3 SC injections of placebo to mepolizumab, or 3 injections of mepolizumab 100 mg SC plus one SC injection of placebo to benralizumab at each dosing visit. In the DB treatment period, patients will receive IP Q4W, starting from Week 0 and ending at Week 48; the DB treatment period will end at Week 52. All patients who complete the 52-week DB treatment period on IP may be eligible to continue into an OLE period. The OLE period is intended to allow every patient at least one year of treatment with open-label benralizumab 30 mg administered SC every fourth week.

Statistical Methods

The primary database lock will occur after all randomised patients have been followed up for the 52-week DB treatment period. The study will remain blinded until the primary database lock. The primary analysis will include all data captured during the DB treatment period (intention-to-treat approach). Safety data from the open-label period available at the time of the primary database lock will also be reported. Additional analyses may be performed after the primary database lock to analyse the data that were not available in the primary analysis. The final database lock will occur after the last patient has completed at least one year in the OLE and when the end of the study has been declared.

The primary efficacy endpoint is the proportion of patients who achieve EGPA main remission at both Week 36 and Week 48 of the DB period. The primary analysis is to demonstrate non-inferiority (NI) of benralizumab versus mepolizumab in terms of durability of response to treatment based on the primary endpoint of remission using a logistic regression model adjusted for treatment arm, baseline dose of prednisone, baseline BVAS, and region. From this model, the absolute difference in remission rates (benralizumab - mepolizumab) will be estimated, with the associated two-sided 95% confidence interval. If the primary analysis demonstrates NI (further detail below), a formal test of superiority between benralizumab and mepolizumab will be assessed. In addition, to assess external validity of the study, an indirect comparison of benralizumab to historic placebo will be evaluated using remission rate.

For NI of benralizumab compared to mepolizumab to be demonstrated for the primary endpoint, the lower 95% confidence limit for the absolute difference between benralizumab and mepolizumab needs to be above the NI margin of -25%.

The study sample size is based on the assumption that mepolizumab and benralizumab each have a remission rate of 32%; 140 patients will provide ~90% power to demonstrate NI with a NI margin of -25% at the 2.5% one-sided significance level.

Secondary efficacy endpoints of the DB period include comparison of benralizumab to mepolizumab in terms of the following: duration of clinical remission accrued in weeks where a patient achieves remission (assessed for main and supportive remission definitions, separately); time from randomisation to first relapse; average daily dose of OCS required during Weeks 48 through 52; percent reduction from baseline in average daily prednisolone/prednisone dose during Weeks 48 through 52; proportion of patients who have achieved any clinical benefit and complete response during the double-blind treatment period; annualised relapse rate; proportion of patients achieving remission within the first 24 weeks and remaining in remission for the remainder of the DB period (main and supportive remission, separately); and durability of response assessed by the proportion of patients in supportive remission at both Week 36 and Week 48.

Logistic regression will be used to analyse the average daily prednisolone/prednisone dose ≤ 4 mg/day during Weeks 48 through 52, ≥ 50% (and 100% seperately) reduction from baseline in average daily prednisolone/prednisone dose during Weeks 48 through 52, any clinical benefit, complete response, and remission within the 24 weeks and remaining in remission for the remainder of the DB period. A negative binomial model will be used to analyse annualised relapse rate. The Cox-proportional hazards model will be used to analyse time to relapse. A proportional odds model will be used to analyse accrued duration of remission, the average of daily prednisolone/prednisone dose during Weeks 48 through 52 (with categories 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg, and > 7.5 mg), and percentage reduction from baseline in average prednisolone/prednisone dose during Weeks 48 through 52 (with categories no reduction or premature discontinuation from treatment before Week 48, < 25% reduction, 25 to < 50% reduction, 50 to < 75% reduction, 75 to < 100% reduction, and 100% reduction).

Further secondary endpoints include additional measures of efficacy and health status/health-related quality of life (HRQoL) assessed as change from baseline over the 52-week DB period as follows: Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (VDI), pulmonary function testing, asthma symptoms (Asthma Control Questionnaire, 6-item version) [ACQ-6]), sino-nasal symptoms (including Sino-nasal Outcome Test-22 [SNOT-22]), HRQoL (Short Form 36-Item Health Survey, version 2 [SF-36v2]), and blood eosinophil counts. The change from baseline in these continuous secondary endpoints will be analysed using a mixed effect model for repeated measures (MMRM) analysis. Descriptive statistics will be provided for Patient Global Impression of Severity (PGIS) and Work Productivity and Activity Impairment questionnaire (WPAI) to assess change from baseline over the 52-week DB period. In addition, Patient Global Impression of Change (PGIC) responses will also be assessed between Visits 2 and 4.

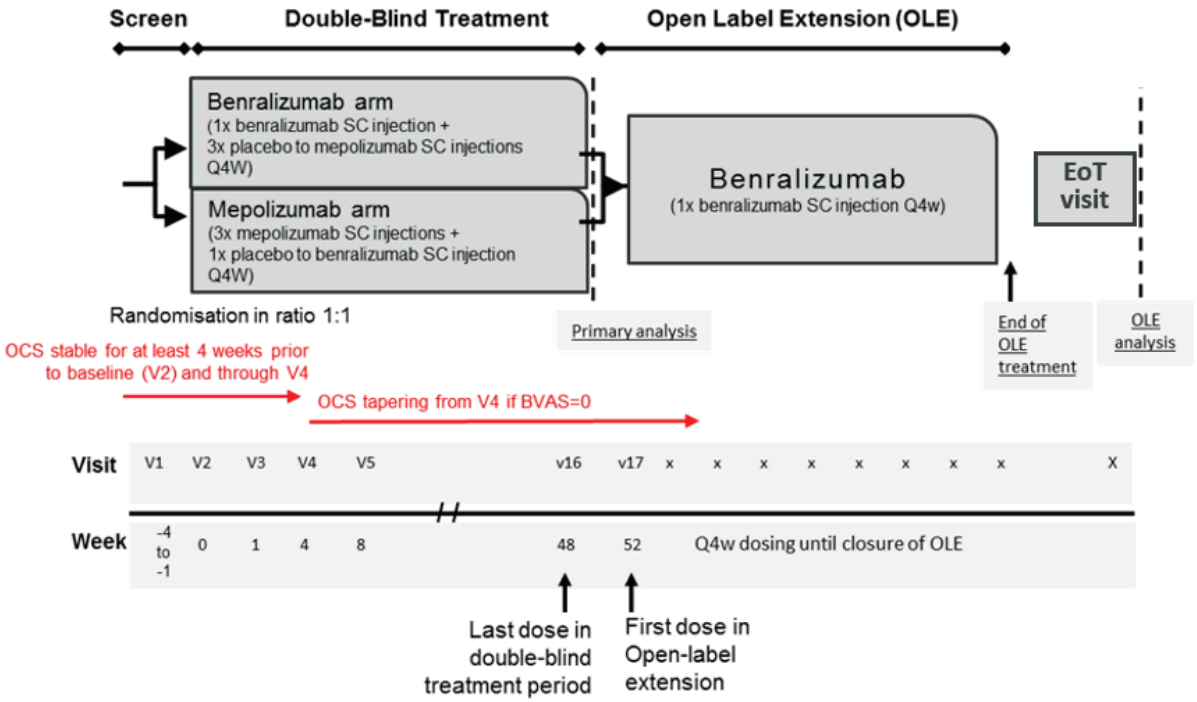
In addition, safety and tolerability of the benralizumab and mepolizumab treatments will be assessed for the DB period, and relevant endpoints will be summarised descriptively and reported in the primary analysis based on the safety analysis set. The pharmacokinetics (PK) and immunogenicity of the benralizumab treatment during the DB period will be reported based on the safety analysis set.

A further assessment of safety, tolerability, efficacy, PK, and immunogenicity will be reported after the final database lock including summaries of data from the OLE period only based on descriptive summaries.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



BVAS, Birmingham vasculitis activity score; OCS oral corticosteroids; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; V, Visit (number).

2 INTRODUCTION

2.1 Study Rationale

The aim of this randomised, double blind, active-controlled, parallel group, multicentre 52-week Phase III study is to compare the efficacy and safety of benralizumab 30 mg versus mepolizumab 300 mg administered by SC injection Q4W in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy. Because eosinophilia is central to the pathophysiology of EGPA, it is hypothesised that direct or indirect depletion of eosinophils could treat EGPA. A reduction in eosinophils could be achieved through blockade of IL-5 or the IL-5 receptor (specifically expressed on the surface of eosinophils and basophils) because IL-5 is the major hematopoietin regulating the life cycle of eosinophils (Clutterbuck et al 1989, Lopez et al 1988, Rothenberg and Hogan 2006).

Benralizumab (FASENRA™ [2]) is a humanised, afucosylated mAb (IgG1, IgG1κ) that binds to the human IL-5Rα subunit with high affinity and specificity. 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). Preliminary evidence of the efficacy of benralizumab in HES is also available from a Phase IIa investigator-initiated study (Kuang et al 2019). An IL-5 cytokine inhibitor, mepolizumab was recently approved for treatment of EGPA in several countries including the US, Canada, Japan, Australia, and Israel, based on a single Phase III study conducted in the EU and RoW countries (MIRRA study; Wechsler et al 2017). Although, mepolizumab increased the accrued time that patients were in remission compared with placebo in this registrational study (results summarised in Section 2.2.1), 47% of patients treated with mepolizumab did not meet the primary endpoint definition of remission in the study. This suggests that although an IL-5 cytokine-depleting approach is of benefit in patients with EGPA, an unmet need remains.

Potential advantages of benralizumab compared with mepolizumab for treatment of EGPA patients may be the direct near complete depletion or apoptosis of eosinophils. By inducing direct, near complete depletion of eosinophil levels in blood and tissue, it is believed that benralizumab will deliver at least similar efficacy to mepolizumab as measured through EGPA remission with a comparable safety profile. In accordance with increasing scientific discussion regarding comparative effectiveness studies and US FDA regulatory guidance that patients with EGPA should be given access to approved therapies, this study is designed to compare the efficacy and safety of benralizaumab with mepolizumab in the treatment of relapsing or refractory EGPA.

[2] FASENRA (benralizumab) is a trademark of the AstraZeneca group of companies.

2.2 Background

2.2.1 EGPA Disease and Current Approaches to Disease Management

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) is a rare disease characterised by potentially life-threatening systemic eosinophilic small vessel vasculitis in association with asthma, sinusitis, and pulmonary infiltrates. Multiple organs can be affected including the heart, lungs, skin, gastrointestinal tract, kidneys, and nervous system (Keogh et al 2006, Holle and Gross 2009, Vaglio et al 2012). The mean age of diagnosis of EGPA is 48 years, with a gender ratio of approximately 1:1 (Pagnoux et al 2007); the incidence has been estimated as 1-4 per million per year (Lane et al 2005). Eosinophilic granulomatosis with polyangiitis pathophysiology remains only partly understood, but it is associated with a positive status for ANCAs usually directed against MPO or PR3 on enzyme-linked immunosorbent assay in approximately 40% of patients (Holle and Gross 2009, Sinico et al 2005). Two different phenotypes of EGPA are described: ANCA positive and ANCA negative. Data show differences in clinical disease presentation based on ANCA status and indicate that ANCA-positive patients should be treated more aggressively (Sokolowska et al 2014).

Before the use of corticosteroids for EGPA, more than 50% of patients died within 3 months of diagnosis; with the advance in treatment strategies, patient survival has been reported as > 90% at one year and 60% to 97% at 5 years (Baldini et al 2010).

The current approach to the management of EGPA is based on reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications. Systemic corticosteroid therapy is the cornerstone therapy for the treatment of EGPA patients. However, use of corticosteroids, particularly longer term, is associated with significant adverse effects, including weight gain, osteoporosis, hyperglycaemia, depression, and increased risk of infection, which can limit the treatment benefits (Poetker and Reh 2010). Furthermore, although remission can be achieved in a proportion of patients with corticosteroid therapy alone, addition of more potent immunosuppressive therapies (eg, azathioprine, methotrexate, or mycophenolate mofetil) to maintain remission is commonly required (Baldini et al 2010, Vaglio et al 2012, Dunogué et al 2011, Holle and Gross 2009, Mukhtyar et al 2009a). In general, although the use of these treatments is effective for establishing remission, patients remain vulnerable to either the complications of long-term use of these therapies or the risk of relapse, particularly if the dose of corticosteroid or immunosuppressant is reduced or stopped. A relapse rate of 30% to 40% is reported, which increases with time (Busse et al 2019). Furthermore, recurrent relapse is considered to place the patient at risk of permanent tissue and/or organ damage secondary to the vasculitic process. Therefore, the key goal in the treatment of EGPA is to induce and maintain remission whilst reducing the burden of corticosteroid usage and other immunosuppressive therapies.

Mepolizumab (NUCALA® [3]) is a fully humanised mAb (Ig G1, IgG1κ mAb) that binds specifically to human IL-5 and thus blocks binding of human IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface (Pavord et al 2012, Stein et al 2006, Rothenberg et al 2008, Nair et al 2009). In the Phase III MIRRA study, 136 patients with relapsing or refractory EGPA were assigned to mepolizumab or placebo administered SC Q4W plus standard care for 52 weeks (Wechsler et al 2017). A significantly higher percentage of patients treated with mepolizumab were in remission at both Week 36 and Week 48 compared to placebo (32% vs 3%). Remission was defined as BVAS of 0 and the receipt of prednisolone or prednisone at a dose of 4.0 mg or less per day. A total of 44% of the patients in the mepolizumab group, as compared with 7% of those in the placebo group, had an average daily dose of prednisolone or prednisone of 4.0 mg or less per day during Weeks 48 through 52. Even so, only approximately half the patients treated with mepolizumab had protocol-defined remission (Wechsler et al 2017). Based on these data, mepolizumab has recently been approved in several countries as treatment for EGPA (Section 2.1).

Clinical benefit was defined post hoc in the MIRRA study as follows: remission at any time (2 definitions used), 50% or greater OCS dose reduction during Weeks 48 through 52, or no EGPA relapse. The 2 remission definitions were BVAS of 0 plus prednisolone or prednisone at a dose of 4.0 mg or less per day (main remission) or 7.5 mg/d or less (supportive remission). With mepolizumab versus placebo, 78% versus 32% of patients experienced clinical benefit 1, and 87% versus 53% of patients experienced clinical benefit 2 (both $p < 0.001$) (Steinfeld et al 2019).

2.2.2 Role of Interleukin-5 in Pathogenesis of EGPA

Interlukin-5 is the major hematopoietin regulating the life cycle of eosinophils (Clutterbuck et al 1989, Lopez et al 1988, Rothenberg and Hogan 2006). In EGPA, the mechanism of tissue injury is poorly understood, but the degree of blood and tissue eosinophilia appears to be associated with disease pathogenesis (Schnabel et al 1999). In a series of in vitro studies, it has been shown that circulating levels of IL-5 are increased in patients with active EGPA, that PBMCs are the likely source of elevated circulating IL-5 in the disease, and that T-cell activation is required for increased IL-5 release by PBMCs (Shonermarck et al 2000, Kiene et al 2001, Hellmich et al 2005, Hellmich et al 2003). Of particular interest with regard to the pathogenesis of EGPA and associated vasculitis is the ability of IL-5 to promote the adhesion of eosinophils to vascular endothelium and CC chemokine receptor 3-dependent migration of eosinophils from the vasculature (Shahabuddin et al 2000). Thus, the elevated production of IL-5 by PMBCs in EGPA may be relevant pathogenetically for the development of vasculitis by promoting transvascular migration and functional activation of eosinophils.

[3] NUCALA is a registered trademark of the GlaxoSmithKline group of companies.

2.2.3 Mechanism of Action of Benralizumab and Evidence Supporting Potential as a Treatment for EGPA

Benralizumab (FASENRA) is a humanised, afucosylated mAb (IgG1, IgG1κ). Benralizumab binds to the human IL-5Rα with high affinity and specificity. The IL-5 receptor is specifically expressed on the surface of eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIII receptors on immune effector cells such as natural killer cells leading to depletion by apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (Humbles et al 2011, Kolbeck et al 2010.

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). Benralizumab has also shown benefit in HES (Kuang et al 2019). Eosinophilic asthma is recognised as an important subphenotype of asthma, and asthma is a common feature across patients with EGPA and the main feature of the prodromal phase of EGPA (Baldini et al 2010). Hypereosinophilic syndrome is a group of diseases with persistent blood eosinophilia and evidence of eosinophil-mediated end-organ damage. Although any organ system can be involved, HES commonly involves the skin, heart, lungs, gastrointestinal tract or central nervous system, and shares clinical and histologic features with EGPA (Baldini et al 2010). Eosinophilic granulomatosis with polyangiitis and HES have distinct but partly overlapping clinical and histologic features, including target organs (Wu et al 2018). Studies in asthma and HES therefore provide relevant evidence for the potential benefit of benralizumab's eosinophil-depleting MoA in treating EGPA.

The safety and efficacy of benralizumab in patients with HES was evaluated in a single centre, Phase IIa, DB, placebo-controlled, investigator-initiated study (Kuang et al 2019). The primary objective of the study was to determine the efficacy of benralizumab in reducing eosinophilia at Week 12. Patients received SC benralizumab 30 mg or placebo monthly for a 12-week DB period (Week 1 to 12), after which all patients received active benralizumab for a 12-week open-label treatment period (Weeks 13 to 24) and a 24-week OLE period (Weeks 25 to 48). Tapering of background therapy was allowed in the OLE period of the study. The study population was 20 platelet-derived growth factor receptor alpha-negative HES patients with eosinophil counts of greater than or equal to 1000 cells/µL. The mean baseline absolute eosinophil count was 2331 cells/µL in the benralizumab group and 2535 cells/µL in the placebo group. One patient had a diagnosis of EGPA. Benralizumab depleted eosinophils at Week 12 compared with placebo: 9 of 10 patients treated with benralizumab had a 50% reduction in absolute eosinophil counts (the primary endpoint of the study) with the majority reaching almost complete depletion of eosinophil counts compared with 3 of 10 patients treated with placebo that met the primary endpoint. Benralizumab also resulted in near-complete depletion of eosinophils in the bone marrow and tissues in most patients at Week 12. The effect was sustained in most patients for 48 weeks. Eosinophil

reduction was associated with clinical improvement and the ability to taper background therapy, including OCS.

The results of this Phase IIa study of benralizumab in HES patients provide further evidence of benralizumab's significant eosinophil-depleting capabilities and suggest that benralizumab may also be effective for the treatment of EGPA.

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

2.3 Benefit/Risk Assessment

2.3.1 Benralizumab

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 for exposures up to approximately one year. The most commonly reported AEs included nasopharyngitis, asthma, and upper respiratory tract infections. Most AEs were mild to moderate in nature. Fewer patients in the benralizumab group reported SAEs compared with placebo. Longer-term safety studies have been conducted in asthma patients who completed one of the predecessor studies for up to an additional one year (adults) and 2 years (adolescents). In general, the safety results (Busse et al 2019) were commensurate with the predecessor studies.

Safety and tolerability data from the Phase IIa 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. In total, 238 AEs were reported during the DB treatment period. Total AEs, Grade 3 AEs, and the numbers of patients reporting an AE were similar between the benralizumab and placebo arms. No new safety signals for benralizumab were identified in this study in patients with HES, and the safety profile of benralizumab was similar to that in the asthma pivotal studies.

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.

Based on benralizumab's MoA and evidence of benefit in other eosinophil driven diseases (asthma and HES), there is a potential for benralizumab to provide benefits in patients with EGPA. In addition, given the extensive safety data already available, the benefit risk profile in patients with EGPA is expected to be favourable, commensurate with that observed in the benralizumab asthma pivotal trials. Risk minimisation measures include exclusion of patients with diagnosed granulomatosis with polyangiitis, microscopic polyangiitis, or organ- or life-threatening EGPA, untreated parasitic infection, a history of anaphylaxis to any biologic therapy, active or recent malignancy, and exclusion of pregnant women. Risk minimisation measures will be maintained during the conduct of this study, in conjunction with the performance of the 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 Investigator's Brochure.

2.3.2 Mepolizumab

The benefit/risk profile of mepolizumab is supported by the previously demonstrated increase in remission in patients with EGPA (Wechsler et al 2017) and known safety profile. No additional AEs were identified in the mepolizumab study in patients with EGPA compared to those reported in the mepolizumab severe asthma trials (refer to the mepolizumab core Reference Safety Information). Mepolizumab is currently approved for EGPA in several countries including the US, Canada, Japan, Australia, and Israel. In addition, mepolizumab is approved for severe asthma in US, the EU, and other countries.

Risk minimisation measures in this study, in respect of treatment with mepolizumab, are as listed above for benralizumab, in conjunction with the performance of routine pharmacovigilance activities.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the DB treatment period and the OLE period of the study are presented in Table 9 and Table 10, respectively.

Table 9 Study Objectives – Double-blind Period

The following objectives/endpoints are for the double-blind period of the study	
Primary objective:	**Endpoint/variable:**
To assess the durability of response to treatment with benralizumab compared with mepolizumab in patients with relapsing or refractory EGPA who are receiving standard of care therapy, assessed by the proportion of patients in remission at both Weeks 36 and 48	Primary endpoint: Proportion of patients with relapsing or refractory EGPA, achieving remission, defined as BVAS = 0 and OCS dose ≤ 4 mg/day (main remission definition) at both Weeks 36 and 48. Supportive endpoint: Proportion of patients who have achieved remission defined by BVAS = 0 and OCS dose ≤ 7.5 mg/day (supportive remission definition) at both Weeks 36 and 48.
Secondary objectives:	**Endpoint/variable:**
To assess the efficacy of benralizumab compared with mepolizumab on duration of clinical remission, defined as accrued duration in weeks where a patient achieves remission	Total accrued duration of remission for the following categories: 0 wk, > 0 to < 12 wk, 12 to < 24 wk, 24 to < 36 wk, ≥ 36 wk. Analysis will be repeated based on main and supportive remission definitions.
To assess the efficacy of benralizumab compared with mepolizumab on time to first relapse	Time from randomisation to first EGPA relapse, where relapse is defined as any of the following: • Active vasculitis (BVAS > 0); OR • Active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 score; OR • Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting **any** of the following: ° An increased dose of OCS therapy to > 4 mg/day prednisolone total daily dose; **OR** ° An increased dose or addition of immunosuppressive therapy; **OR** ° Hospitalisation related to EGPA worsening.

Table 9 Study Objectives – Double-blind Period

To assess the effect of benralizumab on corticosteroid dose required during Weeks 48 through 52 compared to mepolizumab	Based on the average daily prednisolone/prednisone dose during Weeks 48 through 52: • Proportion of patients in each category: 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg, and > 7.5 mg. • Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25% reduction; 25 to < 50% reduction; 50 to < 75% reduction; 75 to < 100% reduction; 100% reduction. • Proportion of patients with ≥ 50% reduction from baseline. • Proportion of patients with 100% reduction from baseline. • Proportion of patients with ≤ 4 mg in average daily dose.
To assess the clinical benefit of benralizumab compared to mepolizumab	Proportion of patients who have achieved any clinical benefit when meeting any of the criteria below. Proportion of patients who have achieved complete response when meeting all of the criteria below. • Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the double-blind treatment period • ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52 • EGPA relapse free during the double-blind treatment period. • Analysis will be repeated for the supportive remission definition.
To assess the annualised relapse rate in patients receiving benralizumab compared to mepolizumab	Annualised relapse rate
To assess the proportion of patients who achieve remission within the first 24 weeks and remain in remission for the remainder of the double-blind treatment period in patients receiving benralizumab compared to mepolizumab	Proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of the double-blind treatment period. Analysis will be repeated based on main and supportive remission definitions.
To assess additional measures of the efficacy and health status/health-related quality of life in patients receiving benralizumab compared to mepolizumab	BVAS, VDI, pulmonary function testing, asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT 22 questionnaire), health-related quality of life (SF 36v2), PGIS, WPAI and blood eosinophil counts will be assessed as change from baseline over the 52-week double-blind treatment period. PGIC will be assessed as response proportions at each weekly assessment between Visits 2 and 4.

Table 9 Study Objectives – Double-blind Period

Safety objectives:	**Endpoint/variable:**
To assess the safety and tolerability of benralizumab compared to mepolizumab	Safety and tolerability will be evaluated based on AEs, vital signs, physical exam, clinical laboratory, and ECG. 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
To assess the pharmacokinetics and immunogenicity of benralizumab	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralising antibodies
Exploratory objectives:	**Endpoint/variable:**
To assess the cumulative OCS use in response to treatment with benralizumab compared to mepolizumab	Cumulative OCS use, as measured by AUC for daily prednisolone/prednisone dose, over the 52-week double-blind treatment period
To evaluate the effect of benralizumab compared to mepolizumab on health care resource utilisation due to EGPA	Number of EGPA-related hospitalisations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test)
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers of inflammation	Biomarkers of inflammation, eg, CRP and ESR
To evaluate the effect of benralizumab compared to mepolizumab on biomarkers related to the MoA, eosinophilic inflammation and EGPA disease pathogenesis, as well as baseline predictors of response to benralizumab or mepolizumab.	Exploratory biomarkers in: • serum • whole blood • nasal secretions • tissue biopsies and sputum (mechanistic sub-study only)
To characterise the patient-reported experience and treatment benefits of benralizumab compared with mepolizumab through patient interviews	Patient interviews to characterise patient-reported experience and treatment benefits (sub-study)

ACQ-6, Asthma Control Questionnaire (6-item version); AE(s), adverse event(s); AUC, area under the curve; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; ECG, electrocardiogram; EGPA, eosinophilic granulomatosis with polyangiitis; ER, emergency room; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IP, investigational product; MoA, mechanism of action; OCS, oral corticosteroid; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PK, pharmacokinetics; SAE(s), serious adverse event(s); SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22, Sino-nasal Outcome Test-22; VDI, Vasculitis Damage Index; WPAI, Work Productivity and Activity Impairment Questionnaire; wk, week(s).

Table 10 Study Objectives for Open-label Extension Period

The following objectives/endpoints are for the open-label extension portion of the study:	
Objectives	**Endpoint/variable:**
To evaluate the effect of benralizumab on remission, relapse, and OCS use [a]	Remission, relapse (as defined in Table 9 [c]), OCS use
To assess patient reported outcomes in patients receiving benralizumab [b]	Asthma symptoms (ACQ-6), sino-nasal symptoms (including SNOT-22 questionnaire), health-related quality of life (SF-36v2) and WPAI
To assess the safety and tolerability of benralizumab [a]	Safety and tolerability will be evaluated in terms of AEs, vital signs, physical exam, clinical laboratory, and ECG Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by the Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP • Other significant AEs
To assess the pharmacokinetics and immunogenicity of benralizumab [d]	Serum benralizumab concentrations Anti-benralizumab antibodies and neutralising antibodies
To evaluate the effect of benralizumab on health care resource utilisation due to EGPA [b]	Number of EGPA-related hospitalisations; length of hospital stay; ICU days; number of EGPA-related ER visits; number of EGPA-related outpatient visits (by type); number of EGPA-related procedures/tests (by specific procedure/test)
To assess biomarkers of inflammation [b]	Biomarkers of inflammation, eg, CRP and ESR
To assess biomarkers related to the MoA of benralizumab, eosinophilic inflammation and EGPA disease pathogenesis [b]	Exploratory biomarkers in serum

[a] Applicable to full duration of OLE
[b] Applicable to first year of OLE only
[c] Applicable to first year of OLE only. From the second year, the definitions of remission and relapse will be based on the Investigator's overall clinical assessment.
[d] Applicable to OLE Year 1-3.

ACQ-6, Asthma Control Questionnaire (6-item version); AE(s), adverse event(s); CRP, C-reactive protein; ECG, electrocardiogram; EGPA, eosinophilic granulomatosis with polyangiitis; ER, emergency room; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IP, investigational product; MoA, mechanism of action; OCS, oral corticosteroids; OLE, open-label extension; PK, pharmacokinetics; RNA, ribonucleic acid; SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); SNOT-22, Sino-nasal Outcome Test-22; WPAI, Work Productivity and Activity Impairment Questionnaire.

4 STUDY DESIGN

4.1 Overall Design

This is a randomised, double blind, active-controlled, parallel group, multicentre 52-week Phase III study to compare the efficacy and safety of benralizumab 30 mg versus mepolizumab 300 mg administered by SC injection Q4W in patients with relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy.

The target population is adult female or male patients aged 18 years and above who have documented EGPA diagnosis plus documentation of at least 2 additional features of EGPA and a history of relapsing or refractory disease. In addition, potentially eligible patients will enter a screening period of up to 4 weeks (minimum of one week) and will be required to be on a stable dose of OCS ≥ 7.5 mg/day prednisolone/prednisone (but not > 50 mg/day), for at least 4 weeks prior to baseline (Visit 2) (see Appendix K for Belgium). If dose adjustment is necessary during the screening period, or the Investigator determines that the patient has not maintained a stable dose, the patient will be screen failed. Patients on immunosuppressive therapy must be on a stable dose for at least 4 weeks prior to baseline (Visit 2) and should remain on the same dose until the end of the DB period (if the patient does not enter the OLE) or until completion of the first 6 months of the OLE period (if the patient continues into the OLE). Dose reductions for safety reasons will be permitted. For full details on the study population and inclusion and exclusion criteria, refer to Section 5.

Approximately 140 eligible patients will be randomised 1:1 at baseline (Visit 2), to receive benralizumab or mepolizumab Q4W for a 52-week DB treatment period. Randomisation will be stratified by region (North America, Western Europe, Japan). A minimum of approximately 25% patients will be included in a mechanistic sub-study to explore the PD response and MoA of benralizumab compared to mepolizumab (Section 8.8.4). The number of patients with ANCA-positive status or an eosinophil count < 150 cells/μL (< 0.15×10^9/L) will be restricted to approximately 10% and 40%, respectively, of the total number of randomised patients. Approximately 45 patients will participate in a non-interventional interview to collect data on HRQoL and the patients' experience during the DB portion of the study (Section 8.1.2).

Between baseline (Visit 2) and Week 4, patients will be required to maintain a stable oral prednisolone/prednisone dose of ≥ 7.5 mg/day (but not > 50 mg/day). If necessary, upward adjustments are permitted for clinical management of the patient. From Week 4 onward, if the patient's BVAS = 0 their oral prednisolone/prednisone dose should be tapered downwards according to standard-of-care practice. A recommended tapering schedule is provided in Appendix H and enables a reduction in OCS dose every 2 weeks, with the intention of achieving a prednisone/prednisolone dose of 4 mg/day or less. For details on prednisolone/prednisone tapering, see Section 6.5.1.

The final dose of the DB treatment period will be given at Week 48 and the DB treatment period will complete at Week 52.

All patients who complete the 52-week DB treatment period on IP may be eligible to continue into an OLE period. The OLE period is intended to allow each patient at least one year of treatment with open-label benralizumab 30 mg administered SC every fourth week (earlier enrolled patients may therefore be in the OLE for longer than one year). AstraZeneca may choose to extend the study depending on the overall development program and reserves the right of terminating the OLE early.

The primary database lock will occur after all randomised patients have been followed up for the 52-week DB treatment period. The study will remain blinded until the primary database lock. The primary analysis will include data from the DB period of the study (intention-to-treat approach). Safety data from the open-label period available at the time of the primary database lock will also be reported. Additional analyses may be performed after the primary database lock to analyse the data that were not available in the primary analysis. The final database lock will occur after the last patient has completed at least one year in the OLE and when the end of the study has been declared. Data from the OLE period of the study will be presented in an addendum to the primary analysis CSR, and/or a separate OLE period CSR.

In this study, 2 definitions of EGPA remission will be investigated as: (i) main remission definition: BVAS = 0 plus OCS dose of prednisolone/prednisone ≤ 4 mg/day, and (ii) supportive remission definition: BVAS = 0 plus OCS dose of prednisolone/prednisone ≤ 7.5 mg/day.

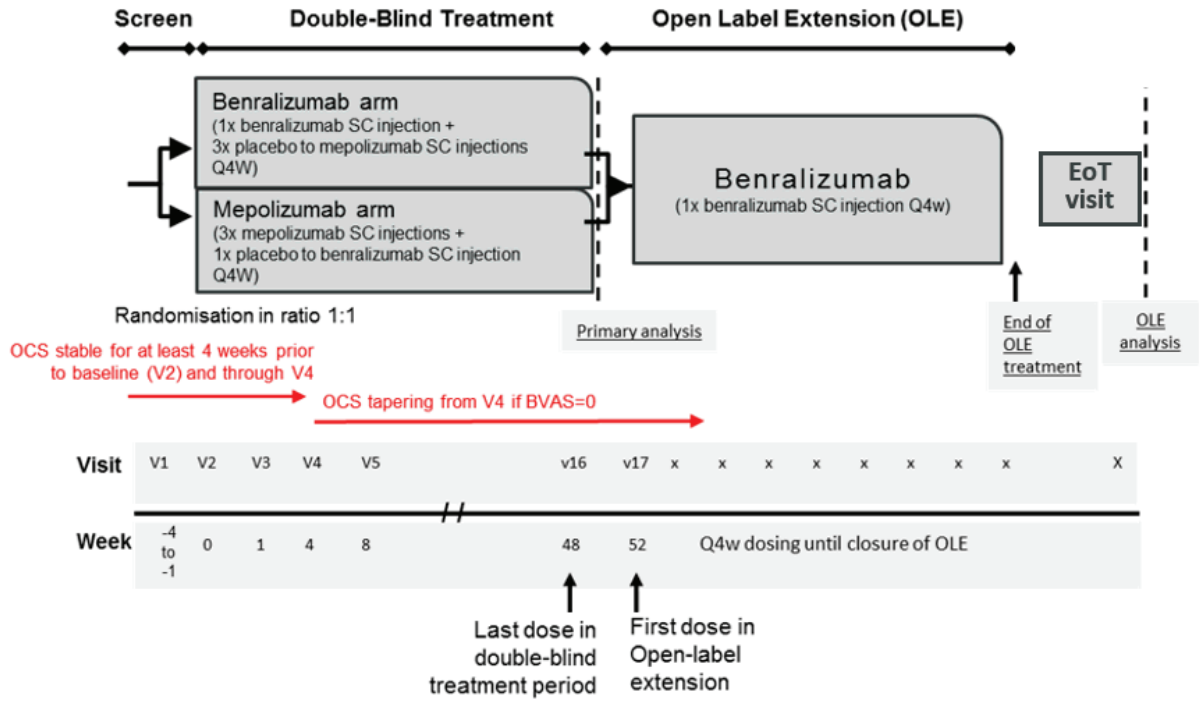
The primary efficacy endpoint is the proportion of patients who achieve EGPA main remission at both Week 36 and Week 48 of the DB period. The primary analysis is to demonstrate NI of benralizumab versus mepolizumab in terms of durability of response to treatment based on the primary endpoint of remission using a logistic regression model adjusted for treatment arm, baseline dose of prednisone, baseline BVAS, and region. If the primary analysis demonstrates NI, a formal test of superiority between benralizumab and mepolizumab will be assessed. In addition, to assess external validity of the study an indirect comparison of benralizumab to historic placebo will be evaluated using remission rate.

For full details of all objectives and endpoints for the DB period and the OLE period, refer to Section 3.

This study will be conducted at approximately 80 sites in 9 countries.

The general study design is summarised in Figure 2.

Figure 2 Study Design



BVAS, Birmingham vasculitis activity score; OCS, oral corticosteroids; OLE, open-label extension; Q4W, every 4 weeks; SC, subcutaneous; V, Visit (number).

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

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

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with 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/reconsent for the mitigation procedures (note, in the case of verbal consent/ reconsent the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened 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 (would only be applicable during the OLE): 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 G.

4.2 Scientific Rationale for Study Design

As detailed in Section 2, the central role of eosinophilia in the pathophysiology of EGPA suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of EGPA. In addition to benralizumab's proven efficacy in eosinophilic asthma (Bleecker et al 2016, Fitzgerald et al 2016) and in steroid-dependent asthma (Nair et al 2017), the efficacy results of benralizumab in HES patients (Kuang et al 2019) provide further evidence of benralizumab's significant eosinophil-depleting capabilities and suggest that benralizumab will also be effective for the treatment of EGPA.

Key features of this study include: a 52-week DB active-controlled period; an adult study population with documented relapsing or refractory EGPA on corticosteroid therapy with or without stable immunosuppressive therapy; use of mepolizumab 300 mg SC Q4W as comparator to benralizumab 30 mg SC Q4W; and the definition of the proportion of patients who achieve remission at both Weeks 36 and 48 as the primary efficacy endpoint. These features are consistent with the mepolizumab Phase III EGPA study conducted in the EU and in RoW countries (Wechsler et al 2017); the labelled dosing regimen for mepolizumab in markets where it has been approved for treatment of patients with EGPA; general regulatory guidance for design of efficacy studies; and the outcomes of pre-Phase III regulatory interactions between AstraZeneca and the US FDA.

The DB portion of this study is designed to compare the efficacy and safety of benralizumab to mepolizumab while the OLE will primarily provide an opportunity to assess long-term safety and tolerability of benralizumab in this patient population.

Fifty-two weeks of DB treatment is sufficient duration to observe EGPA remission and relapse based on the Phase III study of mepolizumab in a very similar population of patients with relapsing or refractory EGPA (Wechsler et al 2017).

The study sample size in this study is based on the assumption that mepolizumab and benralizumab each have a remission rate of 32% (as previously shown for mepolizumab [Wechsler et al 2017]); therefore, 140 patients will provide ~90% power to demonstrate NI with a NI margin of -25% at the 2.5% one-sided significance level. For the study to be positive, the lower 95% confidence limit for the difference between benralizumab and mepolizumab needs to be above the NI margin of -25%.

4.3 Justification for Dose

The dose of mepolizumab chosen, 300 mg SC Q4W is consistent with the labelled dosing regimen in markets where mepolizumab has been approved for EGPA and is the dose of mepolizumab studied in the Phase III study conducted in EU and RoW countries in patients with EGPA (Wechsler et al 2017).

Given it is not feasible to conduct formal dose ranging in EGPA (as it is a rare condition) and that depletion of eosinophils in the circulation as well as in the tissues of patients is considered critical for control of EGPA, the proposed dosing regimen for benralizumab in this study is 30 mg SC Q4W. Key clinical information supporting this proposed dosing regimen is summarised below.

The approved dosing regimen of benralizumab in severe asthma is 30 mg administered 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 EGPA generally have a greater blood and tissue eosinophil burden than patients with severe asthma and are more akin to those observed in HES (Wu et al 2018). In an investigator-initiated Phase IIa study of patients with HES, benralizumab 30 mg Q4W was the regimen studied (Kuang et al 2019). The Q4W dose was effective in reducing blood and tissue eosinophilia in patients with several clinical subtypes of HES, with an acceptable safety profile. Thus, this more frequent regimen (30 mg Q4W) was selected as an appropriate Phase III dose to ensure blood eosinophil depletions in EGPA patients with higher eosinophil burden.

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:

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

FDA requirements define two 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 (for example, last patient's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

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

As patients may be offered the opportunity to participate in an OLE of at least one year after completing the DB period of the study on IP, the end of study is initially planned to be when the last randomised patient completes one year in the OLE (approximately third quarter of 2024).

However, as AstraZeneca may choose to extend the OLE period and reserves the right to terminate the OLE early (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).

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

See Appendix A 5 for guidelines for the dissemination of study results.

5 STUDY POPULATION

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

To compare the efficacy and safety of benralizumab with mepolizumab, this study's population is intended to be consistent with the population studied in the mepolizumab MIRRA Phase III study conducted in EU and RoW countries in patients with EGPA (Wechsler et al 2017). Each patient should meet all the inclusion criteria and none of the

exclusion criteria for this study in order to be assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

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

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

5.1 Inclusion Criteria

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

In addition, as some eligibility criteria cannot be confirmed at Visit 1, these must be verified at the end of the screening period (ie, at baseline [Visit 2]) prior to randomisation (Section 5.3).

Informed consent/age/gender

1 Provision of signed and dated, written ICF prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

2 Patient; males and females must be 18 years of age and older at the time of signing the ICF.

Type of patients and disease

3 Patients who **have documented EGPA diagnosis:** patients who have been diagnosed with EGPA for at least 6 months before screening visit (Visit 1) date based on the history or presence of: asthma plus documented eosinophilia (> 1.0×10^9/litre and/or > 10% of leukocytes) **plus documentation of at least 2 of the following** additional features of EGPA:

   (a) A biopsy showing histopathological evidence of eosinophilic vasculitis, OR perivascular eosinophilic infiltration, OR eosinophil-rich granulomatous inflammation

   (b) Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)

   (c) Pulmonary infiltrates, non-fixed

   (d) Sino-nasal abnormality

   (e) Cardiomyopathy (established by echocardiography or magnetic resonance imaging)

(f) Glomerulonephritis (haematuria, red cell casts, proteinuria)

(g) Alveolar haemorrhage (by bronchoalveolar lavage)

(h) Palpable purpura

(i) Positive test for ANCA immunofluorescence and/or positive test for MPO and/or PR3 antibodies

4 History of relapsing OR refractory disease defined as:

Relapsing disease: Patients must have a history of at least one confirmed EGPA relapse (ie, requiring increase in investigator-initiated OCS dose, initiation/increased dose of immunosuppressive therapy or hospitalisation) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 milligram per day (mg/day).

Japan-only definition of relapsing disease: patients must have a past history of at least one confirmed EGPA relapse (ie, requiring increase in investigator-initiated OCS dose, initiation of IV prednisolone [or equivalent], initiation /increased dose of immunosuppressive therapy, initiation/increased dose of IV Ig or hospitalisation) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥ 7.5 mg/day.

Refractory disease:

Either: Failure to attain remission within the 6 months prior to Visit 1 (BVAS [scale 0-63] = 0 and OCS dose ≤ 7.5 mg/day prednisolone or equivalent) following induction treatment with a standard regimen, administered for at least 3 months.

Note:

(a) Patients who have received CYC induction regimen may be included a minimum of 2 weeks after the last dose of daily oral CYC, or 3 weeks after the last dose of pulsed IV CYC prior to baseline (Visit 2), if their total WBC is ≥ 4×10^9/L (tested at local laboratory if necessary) prior to randomisation.

(b) Patients who have received an azathioprine, methotrexate, or mycophenolate mofetil induction regimen may be included if on a stable dose for at least 4 weeks prior to baseline (Visit 2).

(c) Patients who have received an induction regimen comprising corticosteroids alone may be included only if they have failed to attain remission after 3 months of treatment **and** the corticosteroids dose is ≥ 15 mg/day prednisolone for the 4 weeks prior to baseline (Visit 2).

OR: Within 6 months prior to screening (Visit 1), recurrence of symptoms of EGPA (not necessarily meeting the protocol definition of relapse) while tapering OCS, occurring at any dose level ≥ 7.5 mg/day prednisolone or equivalent.

5 Therapy with corticosteroids: The prescribed dose of oral prednisolone or prednisone must be stable (ie, no adjustment of the dose) and must be ≥ 7.5 mg/day but not > 50 mg/day) for at least 4 weeks prior to baseline (Visit 2). Stable doses of OCS other than prednisolone or prednisone may be acceptable, but must be discussed with the AstraZeneca study physician (see Appendix K for Belgium).

6 Immunosuppressive therapy: If receiving immunosuppressive therapy (excluding CYC), the dosage must be stable for the 4 weeks prior to baseline (Visit 2). Note: The dose of immunosuppressive therapy must not exceed the maximal doses used in clinical practice.

7 ECG evaluation at screening (Visit 1): QTcF < 450 msec or QTcF < 480 msec for patients with bundle branch block
   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula
   - For purposes of data analysis, QTcF will be used as primary though data using both correction formulas will be collected and analysed.
   - The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief recording period.
   - QTcF will be used for patient eligibility.

Reproduction

8 Negative serum pregnancy test for WOCBP at screening (Visit 1)

9 WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration and for at least 12 weeks after last dose of IP. Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:
   - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion
   - 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.)
   - 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)

- Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for ≥ 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
  - 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 in the postmenopausal range. Until FSH is documented to be within menopausal range, treat the patient as WOCBP.
  - 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

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

Patients should be excluded from the study if any of the following criteria apply:

Medical conditions

1 Diagnosed with **granulomatosis with polyangiitis** (previously known as Wegener's granulomatosis) or **microscopic polyangiitis**.

2 **Organ-threatening EGPA:** organ-threatening EGPA as per the European League against Rheumatism criteria (Yates et al 2016), ie, organ failure due to active vasculitis, creatinine > 5.8 mg/dL (> 513 µmol/L) within 3 months prior to screening (Visit 1) and through randomisation (Visit 2).

3 **Life-threatening EGPA:** imminently life-threatening EGPA disease defined as any of the following within 3 months prior to screening (Visit 1) and through randomisation (Visit 2).
  - Intensive care required
  - Severe alveolar haemorrhage or haemoptysis requiring transfusion or ventilation or haemoglobin < 8 g/dL (< 80 g/L) or drop in haemoglobin > 2 g/dL (> 20 g/L) over a 48-hour period due to alveolar haemorrhage
  - Rapidly progressive glomerulonephritis with creatinine > 2.5 mg/dL (> 221 µmol/L) or rise in creatinine > 2 mg/dL (> 177 µmol/L) over a 48-hour period
  - Severe gastrointestinal involvement, for example, gangrene, bleeding requiring surgery

- Severe central nervous system involvement
- Severe cardiac involvement, for example, life-threatening arrhythmia, cardiac failure: ejection fraction < 20%, NYHA Class III/IV (NYHA 2012), acute myocardial infarction.

4 **Malignancy:** current malignancy, or history of malignancy, except:
- Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to screening (Visit 1).
- 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

5 **Liver disease:** unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

6 **Cardiovascular**: patients who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment including but not limited to:
- Known ejection fraction < 30%, OR
- Severe heart failure that meet NYHA Class IV (NYHA 2012), OR
- Hospitalised in the 12 months prior to screening (Visit 1) for severe heart failure meeting NYHA Class III (NYHA 2012), OR
- Angina diagnosed within 3 months prior to screening (Visit 1) and through randomisation (Visit 2).

7 **Infectious disease**: chronic or ongoing active infectious disease requiring systemic treatment.

8 **Parasitic infection**: a helminth parasitic infection diagnosed within 6 months prior to screening (Visit 1) and through randomisation (Visit 2) that has not been treated with or has failed to respond to standard of care therapy.

9 **Hepatitis status:** chronic stable hepatitis B and C (including positive testing for HBsAg 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, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

10 **Immunodeficiency:** A history of known immunodeficiency disorder including a positive HIV test.

11 History of known allergy, intolerance, or anaphylaxis to any biologic therapy or vaccine.

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

13 **Other concurrent medical conditions:** patients who have known, preexisting, clinically significant endocrine, autoimmune, metabolic, neurologic, renal, gastrointestinal, hepatic, haematological, respiratory or any other system abnormalities that are not associated with EGPA and are uncontrolled with standard treatment. Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the Investigator, may put the patient at risk, because of his/her participation in the study, or may influence the results of the study, or the patients' ability to complete entire duration of the study.

Prior/concomitant therapy

14 **Prohibited medications:** patients receiving any of the following:

- **OCS:** patient requires an OCS dose of > 50 mg/day prednisolone/prednisone in the 4-week period prior to baseline (Visit 2)
- **IV, IM, or SC corticosteroids** in the 4-week period prior to baseline (Visit 2)
- O**malizumab** within 130 days prior to screening (Visit 1)
- **CYC:** oral CYC within 2 weeks prior to Baseline (Visit 2) and IV CYC within 3 weeks prior to baseline (Visit 2).
- **Rituximab** within 6 months prior to screening (Visit 1); in addition, the patient must have shown recovery of peripheral B-cell count to within the normal range.
- **IV or SC immunoglobulin** within 30 days prior to screening (Visit 1)
- **Interferon-α** within 6 months prior to screening (Visit 1)
- **Anti-tumour necrosis factor therapy** within 12 weeks prior to screening (Visit 1)
- **Anti-CD52 (alemtuzumab)** within 6 months prior to screening (Visit 1)
- Any prior or current treatment with **mepolizumab, reslizumab, dupilumab, or benralizumab** either as a marketed or investigational biologic.
- Receipt of any other marketed or investigational biologic products within 4 months or 5 half-lives prior to screening, whichever is longer.

Other exclusions

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

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

17 Previous randomisation in the present study.

18 Patient is currently participating in any other interventional clinical study (**text addition for France** (Appendix K)**:** , with the exception of "registry"/ "cohort" trials which may include periodic biological sampling and/or patient questionnaires but in which no other un-licenced investigational product is administered).

19 For women only: Currently pregnant, breastfeeding, or lactating. Patients should not be enrolled if they plan to become pregnant during the time of study participation. A serum pregnancy test will be done for WOCBP at screening (Visit 1) and a urine pregnancy test must be performed for WOCBP at each treatment visit prior to IP administration.

20 Other laboratory parameter exclusions at screening (Visit 1) and on repeat testing (if applicable) prior to Visit 2:

- Creatinine > 2.5 mg/dL (221 μmol/L)
- WBC < 4×10^9/L
- Platelet count < 120000/mm^3
- Haemoglobin < 8 g/dL (< 80 g/L)

21 **Alcohol/substance abuse:** a history (or suspected history) or alcohol misuse or substance abuse within 2 years prior to screening (Visit 1).

22 **Other investigational non-biologic product:** receipt of any investigational non-biologic product within 30 days or 5 half-lives prior to screening (Visit 1), whichever is longer.

23 **Adherence:** patients who have known evidence of lack of adherence to prescribed medications and/or ability to follow physician's recommendations.

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

25 Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the Investigator, may put the patient at risk, because of his/her participation in the study, or may influence the results of the study, or the patients' ability to complete entire duration of the study. Any other medical illness that precludes study involvement

26 Receipt of blood products within 30 days prior to screening (Visit 1).

27 Receipt of live attenuated vaccines 30 days prior to screening (Visit 1).

5.3 Criteria to be Confirmed/Reconfirmed at Baseline (Visit 2) and Prior to Entry to OLE

At the end of the screening period, study patients must fulfil the following additional criteria in order to be randomised to study treatment at baseline (Visit 2):

5.3.1 Inclusion Criteria to be Confirmed/Reconfirmed at Baseline (Visit 2)

The following criteria must be verified prior to randomisation.

- **Corticosteroid and immunosuppressive therapy:** oral prednisolone/prednisone (≥ 7.5 mg/day) and immunosuppressive therapy (if being taken) have been stable for a period of at least 4 weeks prior to baseline (Visit 2) (see Appendix K for Belgium).
- **Laboratory abnormality:** no evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at screening (Visit 1), as judged by the Investigator.

Exception: Only for patients who have received a CYC induction regimen may be randomised a minimum of 2 weeks after the last dose of daily oral CYC, or 3 weeks after the last dose of pulsed IV CYC, if their total WBC is ≥ 4×10^9/L (tested at the local laboratory, if necessary; results must be available prior to baseline (Visit 2) and recorded only in the source documentation).

- **Liver Function Tests**: obtained at screening (Visit 1) or on repeat testing prior to Visit 2 if applicable:
  - ALT < 3 × ULN
  - AST < 3 × ULN
  - Alkaline phosphatase ≤ 2.0 × ULN
  - Bilirubin ≤ 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
- **ECG over-read:** no evidence of significant abnormality in the triplicate 12-lead ECG over-read from the screening visit (Visit 1).
- **Refractory disease:**
  - Patients who have received an azathioprine, methotrexate, or mycophenolate mofetil induction regimen may be included if on a stable dose for at least 4 weeks prior to baseline (Visit 2).
  - Patients who have received an induction regimen comprising corticosteroids alone may be included only if they have failed to attain remission after 3 months of treatment AND the corticosteroid dose is ≥ 15 mg/day prednisolone for the 4 weeks prior to baseline (Visit 2).

5.3.2 Exclusion Criteria to be Confirmed/Reconfirmed at Baseline (Visit 2)

- Prohibited medications: patients receiving any of the medications listed in exclusion criterion 14 between screening (Visit 1) and baseline (Visit 2).
- Other laboratory parameter exclusions as defined in exclusion criterion 20 on repeat testing (if applicable) prior to Visit 2.

5.3.3 Criteria to be Confirmed Prior to Commencing OLE at Visit 17

Patients that complete the DB period of the study on treatment may be eligible to continue into the OLE. If a patient had been randomised in error but the Investigator considers participation in the OLE to be safe and in the best interests of the patient, the Investigator should discuss the potential entry of the patient into the OLE with the AstraZeneca study physician. In order to confirm suitability to continue into the OLE at Visit 17, hepatitis status and immunodeficiency must be reconfirmed at Visit 16 (exclusion criteria 9 and 10, Section 5.2), and ECG (inclusion criterion 7, Section 5.1) at Visit 16.

5.4 Lifestyle Restrictions

Restrictions on strenuous exertion and dietary considerations are required prior to spirometry measurements, as described in Section 8.1.1.12.

Women of child-bearing potential must use a highly effective contraceptive method from randomisation throughout the study and for at least 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 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 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 and is based on the criteria below:

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, etc), patients may potentially be rescreened. These cases must be discussed with the AstraZeneca study physician prior to rescreening and documented in the Investigator study file.

Rescreening of a patient for any other reason (eg, the OCS dose is not stable during run-in period) will also be allowed only upon approval of the AstraZeneca study physician and only once. 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. It means that patient should keep the same E-code as was originally assigned.

Rescreened patients should sign a new ICF. All procedures from the screening/run-in period should be repeated (with the exception of testing for HIV-1 and HIV-2, hepatitis B and C, and FSH).

For re-screening during a study disruptions due to cases of civil crisis, natural disaster, or public health crisis, see Section 4.1.1.

5.5.2 Withdrawal From Study Due to Recruitment Cap

In order to limit the total number of 'ANCA-positive' patients (ie, ANCA immunofluorescence and/or positive test for MPO and/or PR3 antibodies) in the trial, after approximately 10% of the total number of randomised patients are determined to be ANCA positive (based on PR3 or MPO positive result of assessment at screening [Visit 1]), further ANCA-positive patients will not be randomised into the study and will be considered screen failures. Disposition will be recorded as 'Development of Study-Specific Withdrawal Criteria' and the reason given as 'withdrawn prior to randomisation due to ANCA +ve cap'.

In addition, in order to limit the total number of patients in the trial with a screening (Visit 1) eosinophil count of < 150 cells/μL (< 0.15×10^9/L), after approximately 40% of the total number of randomised patients with an eosinophil count of < 150 cells/μL (based on result of assessment at screening [Visit 1]) are randomised, further patients with an eosinophil count of < 150 cells/μL will not be randomised into the study and will be considered screen failures. Disposition will be recorded as 'Development of Study Specific Withdrawal Criteria', and the reason given as 'withdrawn prior to randomisation due to eosinophil cap'.

6 STUDY TREATMENT

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study patient according to the study protocol. Study treatment in this study refers to benralizumab, mepolizumab, placebo to benralizumab, and placebo to mepolizumab. Placebo to mepolizumab and placebo to benralizumab is used only to ensure blinding for the study treatments.

Investigational product will be administered Q4W from baseline (Visit 2) until Week 48 (Visit 16) in a DB fashion. Those patients that complete the DB treatment period on IP, will

receive open-label benralizumab administered Q4W from Week 52 (Visit 17) onwards (until the end of the study or early discontinuation).

Investigational product administration should ideally occur at approximately the same time of day, throughout the study, within the same patient.

6.1 Treatments Administered

6.1.1 Investigational Products

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

Study treatments are outlined in Table 11. Preparation, handling, storage, and accountability is covered in Section 6.2.

Table 11 Study Treatments

	Treatment 1		Treatment 2	
Study treatment name	**Benralizumab**	**Placebo to mepolizumab [a, b] (0.9% sodium chloride)**	**Mepolizumab [a, b]**	**Placebo to benralizumab**
Dosage formulation	30 mg/mL solution for injection in APFS; 1 mL fill volume	Matching placebo: solutions for injection in 1 mL polypropylene syringes (3 syringes will be used on each dosing occasion). Injection volume per syringe is 1 mL.	3 × 100 mg vials of powder for solution for injection reconstituted into 3 separate 1 mL polypropylene syringes for administration on each dosing occasion. Injection volume per syringe is 1 mL.	Matching placebo solution for injection in APFS; 1 mL fill volume.
Route of administration	SC injection	SC injection	SC injection	SC injection
Dosing instructions	Benralizumab active solution will be administered to patients by healthcare professionals, patients, or their caregivers SC using an APFS in this clinical study.	Placebo solution will be administered to patients by healthcare professionals SC using a syringe in this clinical study.	Mepolizumab active solution will be administered to patients by health care professionals SC using a syringe in this clinical study.	Placebo solution will be administered to patients by health care professionals SC using an APFS in this clinical study.

Table 11 Study Treatments

	Treatment 1		Treatment 2	
Packaging and labelling	Refer to pharmacy manual	Refer to pharmacy manual	Refer to pharmacy manual	Refer to pharmacy manual
Provider	AstraZeneca	Study site	AstraZeneca	AstraZeneca

[a] Mepolizumab is sourced locally in Japan.
[b] Mepolizumab/placebo to mepolizumab in Japan will be administrated with a 2-3 mL polypropylene syringe and 21-27 gauge needle.
APFS, accessorised prefilled syringe; 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 accessorised pre-filled syringe (status: investigational)

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

- 12-lead ECG/spirometer device

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 the third party device.

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 8.4.4) and appropriately managed by AstraZeneca.

6.2 Preparation/Handling/Storage/Accountability of Investigational Product

6.2.1 Preparation and Handling of IP

Up to and including on Visit 23, the IP will be administered at the study site on treatment visits and within visit windows as specified in the schedule in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5). After Visit 23, IP may be administered within the visit windows as described in Table 2, Table 3, Table 4, and Table 5 either on-site by an HCP or, optionally, at home or a remote location by the patient or their caregiver. Self-administration of the IP requires assessment and training by the Investigator (Section 6.2.3).

Investigational product will be supplied to the site in a kit with either benralizumab or placebo to benralizumab or mepolizumab. Placebo to mepolizumab consists of 0.9% sodium chloride and is to be supplied and prepared by each study site. For further details, see the separate pharmacy manual.

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

Prior to each IP administration:

- The Investigator/authorised delegate will assess the injection site as per the standards of medical care.
- For WOCBP, a serum pregnancy test will be performed at screening (Visit 1) and a urine pregnancy test before every subsequent dose of IP, except for those visits in the OLE which can be done remotely, where no pregnancy testing will be performed. Investigational product will be administered (and the patient randomised) only if the result of the test is negative.

6.2.2 Administration of IP at the Study Site

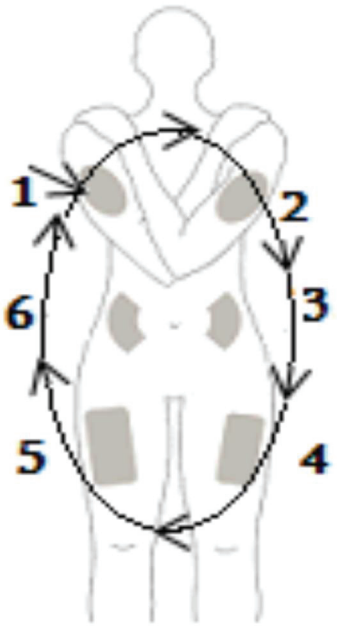
6.2.2.1 Injection Site Guidance

As 2 different IPs will be administered at each dosing visit during the DB period of the study, the anatomical injection site for each IP should be different in order to minimise risk of injection site reactions: For example, if benralizumab/placebo to benralizumab is administered in the arm, then mepolizumab/placebo to mepolizumab should be administered in the opposite arm, the thigh, or the abdomen. It is recommended that the site of injection is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, or hardened.

6.2.2.2 Benralizumab/Placebo to Benralizumab Administration

The benralizumab/placebo to benralizumab will be administered by the Investigator/authorised delegate using the supplied APFS into the upper arm, thigh, or the abdomen (Figure 3). It is recommended that the site of injection is rotated such that the patient receives IP at a different anatomical site at each treatment visit.

Figure 3 Suggested Schema of Rotation of Injection Sites for Benralizumab/ Placebo to Benralizumab



6.2.2.3 Preparation and Administration of Mepolizumab/Placebo to Mepolizumab

The mepolizumab/placebo to mepolizumab will be reconstituted/prepared by an unblinded site pharmacist, or suitably qualified delegate, and administered by the Investigator/authorised delegate. Reconstitution of mepolizumab, and preparation of the placebo to mepolizumab is described in a separate pharmacy manual.

6.2.2.4 Administration of Mepolizumab/Placebo to Mepolizumab

Administer the mepolizumab/placebo to mepolizumab SC into the upper arm, thigh, or abdomen as three separate SC injections. It is recommended that the individual injections be administered at least 5 cm (approximately 2 inches) apart. Further details on IP administration are described in the IP Handling Instruction provided to study sites. Investigational product administration must be carried out in line with the instruction.

6.2.2.5 After Investigational Product Administration

After IP administration at the study site, the patient should be observed in case of any acute drug reactions in line with clinical practice (Section 8.4.7).

See warnings and precautions information in the core Reference Safety Information for mepolizumab.

6.2.3 Optional At-home or Remote-location Investigational Product Administration

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 23 (Week 76). The Investigator 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 and documentation of IP administration will be provided.

After Visit 23, some visits do not include extensive on-site assessments and can optionally be performed as remote visits through telephone/telemedicine contact (see Table 2, Table 3, Table 4, and Table 5) for patients who opted for IP self-administration. IP kits for the remote visits may be dispensed starting from Visit 23 as described in Study Instructions for Self-Administration of Investigational Product by the Patient and/or Caregiver. After Visit 23, on-site visits will occur as per SoA, and patients may be dispensed IP kits to perform self-administration in between.

If the IP is administered by the patient or their caregiver, IP should be administered on a day of scheduled visit after all 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. WOCBP will be asked about any concerns for pregnancy.

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 on-site visit instead of an at-home visit or for an on-site unscheduled or flare visit, as necessary, and perform additional unscheduled assessments in case of medical need.

6.2.4 Conditions Requiring Investigational Product Administration Rescheduling

If any of the following occur, the Investigator should not administer IP, and **either** reschedule the visit within the allowed visit window (Table 1, Table 2, Table 3, Table 4, and Table 5) **OR** the dose of IP should be delayed or skipped, as considered appropriate by the investigator:

- The patient has an intercurrent illness that in the opinion of the Investigator may compromise the safety of the patient in the study (eg, viral illnesses).
- The patient, in the opinion of the Investigator, is experiencing an acute or emerging asthma exacerbation/EGPA relapse.

See Section 6.4 for further instructions on delayed or missed doses. It is recommended that the Sponsor study physician, or designee, be contacted in case of any questions.

6.2.5 Storage

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

6.2.6 Accountability

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

An unblinded AstraZeneca site monitor will account for all study treatments received at the site, for unused study treatments, 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 AstraZeneca and institution procedures.

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

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Patient Enrolment and Randomisation - Double-blind Period

All patients will be centrally assigned to randomised study treatment using an IRT/RTSM. Before the study is initiated, the log-in information and directions for the IRT/RTSM will be provided to each site.

The Investigator(s) will:

At screening (Visit 1)

1 Obtain signed informed consent 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') via the IRT/RTSM.

3 Confirm whether patient consented at screening (Visit 1) to participate in the mechanistic sub-study (applicable only for sites participating in mechanistic sub-study).

At baseline (Visit 2)

1 Determine patient eligibility for randomisation at baseline (Visit 2)

2 Confirm stable dose of OCS for at least 4 weeks before baseline (Visit 2)

3 Confirm ANCA status ('positive' or 'negative') (Section 5.5.2)

4 Confirm eosinophil count < 150 or ≥ 150 cells/μL (Section 5.5.2)

5 Confirm whether patient consented to participate in the patient interview sub-study (applicable only for countries participating in patient interview sub-study)

6 Randomise the eligible patient at baseline (Visit 2) via the IRT/RTSM. The IRT/RTSM will assign the patient with a unique randomisation code.

7 Confirm Visit 2 on the handheld device prior to ePRO questionnaire completion by the patient. Ensure patients complete all baseline ePRO assessments.

Patients will be allocated to treatment arms in a 1:1 ratio. The randomisation will be stratified by region:

- Patients recruited in North America
- Patients recruited in Japan
- Patients recruited in Western Europe

Randomisation codes will be assigned PPD 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 by PAREXEL Informatics on behalf of AstraZeneca (AZRand).

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

6.3.2 Methods for Ensuring Blinding – Double-blind Period

The first 52 weeks of this study is a DB design: AstraZeneca staff involved in the study, the patients, and the Investigators involved in the treatment of patients or in their clinical evaluation and monitoring of the patients will not be aware of the treatment allocation.

Placebo to benralizumab solution will be visually matched with benralizumab solution. Placebo to mepolizumab solution will be visually matched with mepolizumab solution.

All packaging and labelling of the IP will be done in such way as to ensure blinding for all AstraZeneca and investigational site staff.

Placebo to mepolizumab (0.9% sodium chloride) will prepared and dispensed by the study site using labels provided by the unblinded site pharmacist, for labelling instructions see the pharmacy manual.

Due to the need to reconstitute the mepolizumab shortly before administration, and for the study sites to supply, and prepare the placebo to mepolizumab, each site will need an appropriately qualified unblinded pharmacist/suitably qualified delegate to prepare IP during the DB period of the study. The unblinded pharmacist/delegate must not communicate with AstraZeneca, the Investigator, or any other site staff about the patient treatment allocation. An AstraZeneca unblinded 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 staff must be notified promptly by the Investigator before unblinding (if possible).

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 Contract Research Organisation 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 Blood Eosinophil Counts

While not entirely specific, patients on both benralizumab and mepolizumab treatment are expected to have lower blood eosinophil counts, but the degree of depletion may be different. In order to mitigate potential unblinding on this basis, per protocol haematology will be run by the central laboratory. From baseline (Visit 2) until the second visit of the OLE, Week 56

(Visit 18), eosinophil, basophil and monocyte counts will be redacted from any central laboratory reports sent to investigative sites to prevent the Principal Investigator/designee from possibly deducing the 'eosinophil + basophil + monocyte' contribution to the complete blood count. 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 differential count.

6.3.2.2 Handling of Clinical Laboratory Results Obtained During the Double-blind Period but Ordered Outside of the Clinical Trial

During the DB period of the study until Week 56 (Visit 18), site staff who are directly involved in the patient's management should remain blinded to any eosinophil, basophil and monocyte results included as part of outside lab reports. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil and monocyte results prior to the report being handed over to the site staff involved in the patient's management and prior to filing as a source document. Similarly, eosinophil and basophil results must be redacted from all communications with AstraZeneca. In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues he/she may order these tests. AstraZeneca should be notified of all such cases, but should not be informed about lab results.

6.3.2.3 Maintaining the Blind to the Patient's Induced Sputum Cell Count Analysis – Double-blind Period

For patients who consent to participate in the optional mechanistic sub-study, the induced sputum analysis will be run by the central laboratory.

Except for the Visit 2 sputum cell count, results will not be reported back to the site until after the primary database lock.

6.3.3 Methods for Unblinding – Double-blind Period

The IRT/RTSM will provide the IP kit identification number(s) to be allocated to the patient at each dispensing visit to the unblinded site pharmacists/delegate. Blinded and unblinded access and notifications will be controlled using the IRT/RTSM. Investigators will remain blinded to each patient's assigned study treatment until the primary database lock. To maintain this blind, an otherwise uninvolved third party (site personnel, eg, pharmacist or qualified delegate) will be unblinded and responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomisation.

The unblinded pharmacist/delegate's study-related activities will be monitored by unblinded site monitors, all of whom will have no further role in the management of study patients, or data collection, and will not have access to the study database.

Detail on how to unblind a patient's treatment allocation will be described in the IRT/RTSM user manual provided to each study site. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator should document and report the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. 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 Open-label Extension Period – Benralizumab Administration Only

Patients will keep the same E-Code in the OLE as assigned in the DB period of the study. Open-label IP administration will begin at Week 52 (Visit 17). The IRT/RTSM will continue to allocate IP kit number for each dosing visit of the OLE.

6.4 Treatment Compliance

The administration of all study treatments (both in the DB and OLE period 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.

Investigational product will be administered at the study site on treatment visits, at approximately the same time of day as administered at baseline (Visit 2), and within visit windows as specified in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5). Any change from the dosing schedule (dose interruptions or dose discontinuations) should be recorded in the eCRF. It should be noted that dose reductions are prohibited. It is recommended that the Sponsor study physician, or designee, be contacted in case of any questions.

Investigational product dosing should only occur within the allowed visit windows specified in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5). Conditions requiring re-scheduling of IP administration are described in Section 6.2.4. Subsequent doses should be scheduled according to the original schedule (counted from baseline (Visit 2).

When IP dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for IP administration) are still performed within the visit window.

Re-scheduled IP dose can then be administered at an unscheduled visit. Vital sign assessments, brief physical exam, and urine test for WOCBP 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 re-scheduled 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 2 doses of IP (consecutively or non-consecutively) at any time within a calendar year, it is strongly recommended that a conversation between the Investigator and the AstraZeneca study physician takes place to review the patient's adherence to treatment and decide on the patient's further disposition.

The date and time of all IP administrations, as well as any delayed or missed doses, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant Therapy

The Investigator must be informed as soon as possible about any medication(s) taken from the time of screening until the end of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF, along with:

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

For corticosteroids (prednisolone/prednisone) and immunosuppressive therapy, the dose must be recorded as well as all dose changes (see Appendix K for Belgium). Specific guidance on the dose /adjustment of dose of OCS is provided in Section 6.5.1. Patients will be required to record the dose of prednisolone/prednisone taken each day during the DB period on an electronic diary (ePRO device). During the first year of the OLE, the frequency of recording OCS use in the electronic diary will be reduced to weekly recall.

The following medication(s) are restricted as indicated in Table 12:

Table 12 Restricted Medications

Medication/class of drug:	Usage (including limits for duration permitted and special situations in which it is allowed)
Inactive/killed vaccinations (eg, inactive influenza)	Not allowed within the 7 days before or within 7 days after any IP dosing study visit
Allergen immunotherapy	Allowed if on stable therapy started 30 days prior to V1; no change during the treatment period
Immunosuppressive therapy (see Section 6.5.2)	Patients who have received a methotrexate, azathioprine, or mycophenolate mofetil induction regimen may be included if on a stable dose for at least 4 weeks prior to baseline (V2). If on immunosuppressive therapy, the dosage must be stable for the 4 weeks prior to baseline (V2) until the end of the double-blind period (if the patient does not enter the OLE), or until completion of the first 6 months of the OLE period (if the patient continues into the OLE). Dose reductions for safety reasons will be permitted). Note: The dose of immunosuppressive therapy must not exceed the maximal doses used in clinical practice. The following maximal doses are allowed: Azathioprine: 250 mg/day Methotrexate: 25 mg/week (PO or SC) Mycophenolate mofetil: 3000 mg/day Mycophenolic acid: 1440 mg/day
Therapy with oral corticosteroids	Patient must be on stable dose of oral prednisolone or prednisone of ≥ 7.5 mg/day (but not > 50 mg/day for at least 4 weeks prior to baseline (V 2). Tapering may occur starting at Week 4 as detailed in Section 6.5.1 and Appendix H.
Live attenuated vaccines	Not allowed from 30 days prior to screening (V1), during the treatment period, and for 12 weeks after the last dose of the IP
Blood products	Not allowed from 30 days prior to screening until randomisation. May be allowed during the study for the treatment of co-morbidities for which no alternative treatment is available.
Marketed biologic products	Generally disallowed with the exception for the treatment of co-morbidities for which no alternative treatment is available. The patient must be on stable therapy at the start of and throughout the study. A discussion with the AstraZeneca study physician should take place before including the patient in the study.

IP, investigational product; OLE, open-label extension; PO, oral; SC, subcutaneous(ly); V, visit (number).

The following medications are not permitted prior to Screening (Visit 1) or during the study in accordance with the following specified washout periods (Table 13):

Table 13 Prohibited Medications With Defined Washout Periods before Screening (Visit 1)

Prohibited medication/class of drug	Washout period
Mepolizumab, benralizumab, dupilumab and reslizumab	Previous receipt either as a marketed or investigational biologic at any time prior to Visit 1
Omalizumab	130 days
Rituximab	6 months prior to screening (in addition, the patient must have shown recovery of peripheral B-cell count to above the lower level for the normal reference limit or above pre-rituximab [first treatment] level).
IV or SC immunoglobulin	30 days
Interferon-α	6 months
Anti-tumour necrosis factor therapy	12 weeks
Anti-CD52 (alemtuzumab)	6 months

IV, intravenous; SC, subcutaneous.

In addition, the following medications are also prohibited during the study (with washout period noted below as applicable):

- **IV, IM, or SC corticosteroid therapy**: Prohibited during the 4 weeks prior to baseline (Visit 2). Applicable for DB only.
- **CYC**: Patients who have received CYC induction regimen may be included a minimum of 2 weeks after the last dose of daily oral CYC, or 3 weeks after the last dose of pulsed IV CYC prior to baseline (Visit 2), if their total WBC is $\geq 4 \times 10^9$/L (tested at local laboratory if necessary) prior to randomisation.
- **Other investigational agents (biologic or non-biologic)**: Investigational applies to any drug not approved for sale in the country in which it is being used.
- **Acetaminophen**: Prohibited in patients with acute viral hepatitis.
- Receipt of any non-biologic investigational product within 30 days or 5 half-lives prior to screening, whichever is longer

In the event a prohibited medication is used, a conversation between the Investigator and the AstraZeneca study physician should take place to determine whether continuation on IP or discontinuation of IP is in the best interest of the patient.

6.5.1 Oral Corticosteroids and Tapering

The background medication OCS (prednisolone/prednisone) is not regarded as an IP but may be provided/reimbursed by AstraZeneca according to local regulations, in order to ensure access to this concomitant therapy:

- Patients already on prednisone/prednisolone at screening (Visit 1) can continue their current background prednisone/prednisolone (patients may be reimbursed according to local regulations), OR
- Patients not already taking prednisone/prednisolone at screening (Visit 1) (ie, patients taking another OCS for management of EGPA) must switch to an equivalent prednisone/prednisolone dose (may be provided by the study site/AstraZeneca or reimbursed according to local regulations) and remain on a stable dose for 4 weeks prior to baseline (Visit 2). Oral corticosteroids other than prednisolone or prednisone may be acceptable but must be discussed with the AstraZeneca study physician.

Protocol requirements specified in Section 5.1 and Section 5.3.1 must be adhered to, regardless of the source of prednisone/prednisolone (see Appendix K for Belgium).

Between baseline (Visit 2) and Week 4 (Visit 4), patients will be required to continue their stable OCS dose (if necessary, upward adjustments are permitted for clinical management of the patient). From Week 4 post-baseline (Visit 4) onwards if the patient's BVAS = 0 their oral prednisolone/prednisone dose should be tapered downwards according to standard of care practice. If the BVAS ≠ 0, the Investigator may taper the patient's OCS downwards at his/her clinical discretion. Use of daily or alternate-day dosing with prednisolone/prednisone is acceptable. For alternate-day dosing the daily dose will be considered to be equivalent to half the alternate-day dose (eg, 5 mg taken on alternate days is equivalent to a 2.5 mg/day daily dose). A recommended tapering schedule, as provided in Appendix H, enables a reduction in OCS every 2 weeks, with the intention of achieving a prednisolone/prednisone dose of 4 mg/day or less.

Once a patient has achieved a dose of 4 mg/day prednisolone/prednisone, the Investigator should continue tapering downwards, if clinically warranted at dose increments of 0.5 to 1.0 mg every 2 weeks. However, upward adjustment in the dose of OCS is permitted within the 0 to 4.0 mg range without necessarily being defined as a relapse. This approach recognises that some patients on long-term OCS are relatively resistant to complete discontinuation of therapy and are vulnerable to precipitation of Addisonian symptoms.

The possibility of acute adrenal insufficiency should be considered, according to the guidance in Appendix I, in any acutely unwell patient undergoing withdrawal of chronic systemic corticosteroid treatment. Assessment of hypothalamic-pituitary-adrenal axis integrity may be performed, according to standard of care, at the discretion of the Investigator.

The minimally effective dose of OCS in each patient will be defined as the dose of prednisolone/prednisone one step above the dose at which the first relapse occurs. Where the patient has achieved a dose of OCS of 0 to 3.5 mg, the minimally effective dose will be defined as 4.0 mg/day prednisolone/prednisone. The intention of defining the minimally effective OCS dose is to provide information to the Investigator for use during any subsequent

tapering. This will reduce the likelihood that a patient will experience a second relapse during the study, and therefore balances the efficacy objectives of the study with patient safety.

6.5.2 Other Concomitant Treatment

Use of immunosuppressive therapy (eg, methotrexate, azathioprine, mycophenolate mofetil) will be permitted during the study as long as the dosage remains stable from screening until the end of the DB period (if the patient does not enter the OLE), or from screening until completion of the first 6 months of the OLE period (if the patient continues into the OLE). Reduction in the dose for safety reasons, with a return to the original dose, where possible, is permitted. After completion of the first 6 months of the OLE, a decrease in dose or discontinuation of immunosuppressant is allowed at the Principal Investigator's discretion.

In the event immunosuppressive therapy for EGPA is initiated or the dose increased during the study, then study treatment should be discontinued and, where possible, the patient continue to be followed up as per protocol until the end of DB period as per Section 7.1.1.

Use of inhaled and topical steroids will be permitted throughout the study.

In case of acute illness, medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

It is recommended that patient should not receive allergen immunotherapy on the same day as the IP administration.

6.6 Dose modification

Modification of the dose (benralizumab or mepolizumab) is not permitted. Management of missed doses is covered in Section 6.4.

6.7 Treatment After the End of the Study

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

7 DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of Study Treatment

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 up to the study completion as described in Section 7.1.1. Patients may be discontinued from IP in the following situations:

1 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.
2 AE that in the opinion of the Investigator contraindicates further dosing
3 Severe non-compliance with the CSP
4 Risk to the patient as judged by the Investigator or AstraZeneca
5 IP unblinding
6 Development of any study specific criteria for discontinuation:
   – Anaphylactic reaction to the IP requiring administration of epinephrine
   – Development of helminth parasitic infestations requiring hospitalisation
   – A respiratory-related event requiring invasive mechanical ventilation
   – Increasing the dose of, or initiating, immunosuppressive therapy for EGPA
   – Patient experiences one organ-threatening or life-threatening EGPA relapse

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.

See the SoAs (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6) and Section 7.1.1 (IPD visit) for data to be collected at the time of IP discontinuation and for any further evaluations that need to be completed.

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

A patient that 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.

Discontinuation of IP will be registered in IRT/RTSM system.

See the SoA (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6) for data to be collected at the time of treatment discontinuation and for any further evaluations that need to be completed.

Note: The EOT visit is only used 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 period or OLE period) should return to the study site for an IPD visit within 4 weeks (± 7 days) after the last dose of IP for procedures described in Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6. The IPD visit replaces the nearest scheduled visit after IP discontinuation. Reasons for patients not electing to go into the OLE will be collected.

After the IPD visit, the prohibited medications in Section 6.5 will no longer apply.

IPD during double-blind treatment period

At the IPD visit, the patient will be offered the following options for further FU:

- Patients are encouraged to return for all scheduled site visits, but without IP administration. For patients who are willing to continue with scheduled visits, the next visit after IPD will be conducted as per SoA until the last DB period visit at Week 52 (Visit 17).
- If the patient is unwilling/unable to attend the scheduled clinic visits until end of the DB period, he/she will be offered monthly telephone contact instead and will be encouraged to attend the last DB period visit (Visit 17) at the study site, if feasible. During telephone contact, the Investigator will collect information about concomitant medications, including OCS use, EGPA relapse, and AE/SAEs (Section 8.3). During this time, all ePRO assessments will continue at home.

IPD during OLE period

- Patients who prematurely discontinue IP during the OLE period of the study will attend an IPD visit at 4 weeks (± 7 days) after last dose of IP, after which the patient exits the study. The ePRO device will be returned at the IPD visit.

7.1.1.2 Discontinuation of Treatment on Notification of Closure of Study

The following visit should be performed (Table 2, Table 3, Table 4, Table 5, and Table 6, dependent on when notification of study closure occurs) for all ongoing patients within 3 months of notification from AstraZeneca of closure of the study (Section 4.4):

- EOT visit: within 4 weeks (± 7 days) after the last dose of IP

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 the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from IP.

If the agreed decision is to discontinue IP, patients should be encouraged to complete an IPD visit (Section 7.1.1.1).

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

7.2 Lost to Follow-up

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

To prevent patients being lost to FU, it is recommended that the study sites maintain up-to-date patients' contact details, including next of kin or other emergency contacts (if allowed by national 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 clinic 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.
- Repeated attempts must be made to regain contact with the patient or next of kin by, eg, repeat telephone calls, emails, and certified letter. These contact attempts should be documented in the patient's medical record.

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

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

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

7.3 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 evaluate the patient fully 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 as much data as possible for the patient as per IPD visit described in SoA (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6). The withdrawal visit (IPD assessments) should take place as soon as the patient notifies the Investigator/delegate of intent to withdraw consent, without the need to wait until 4 weeks after the last dose. The patient will return all study supplied equipment including the ePRO device.

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 the retention of biological samples (blood, nasal, sputum, urine, etc.) for future exploratory use (eg, DNA, study of biomarkers of EGPA, identifying potential new drug targets for EGPA, or for assay development purposes), 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.

7.3.1 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.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6).

The Investigator will ensure that data are recorded on the eCRF. Medidata Rave web-based data capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, and completeness, of the eCRFs including: the legibility and timeliness of the data recorded and of the provision of answers to data queries according to the clinical study agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

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

Adherence to the study design requirements, including those specified in the SoA (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6), is essential and required for study conduct.

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

8.1 Efficacy Assessments

8.1.1 Clinical Outcome Assessments

Investigators will complete clinician-reported outcome assessments during site visits in accordance with the SoA (Table 1, Table 2, Table 3, Table 4, Table 5, and Table 6).

The following assessments will be completed by the Investigator: BVAS, EGPA relapse/remission, and VDI (Sections 8.1.1.1, 8.1.1.2, and 8.1.1.3, respectively).

Patient-reported outcome assessments (Sections 8.1.1.4 to 8.1.1.11) will be completed by the patients using a handheld ePRO device. The ePRO device will be given to patients at screening (Visit 1) and must be returned at the end of the first year of the OLE period (Visit 30) or at the patient's final study visit if it occurs before Visit 30.

Patients and sites will be trained on the use of the ePRO device. Sites should be aware of the guidelines for ePRO administration as provided to the sites in a separate manual. Sites and Investigators should be aware that the ePRO device is the only acceptable source of PRO data; paper questionnaires are not acceptable.

The site staff should check ePRO completion and compliance at each visit.

If compliance with the Corticosteroid Medication Usage ePRO assessment completion drops below 80%, or if the overall compliance with completion of any of the other ePRO assessments (ACQ-6, SSQ, SNOT-22, SF-36v2, PGIS, PGIC, or WPAI-GH) drops below 80%, it is highly recommended that the study site has a discussion with the patient to ask if they are having difficulties and to remind them of the importance of completing ePRO assessments.

8.1.1.1 Birmingham Vasculitis Activity Score

The BVAS is a validated, clinician-completed tool used for the comprehensive multisystem clinical assessment of disease activity in systemic vasculitis (Luqmani et al 1994, Luqmani et al 1997, Mukhtyar et al 2009b). A copy of the BVAS questionnaire will be provided to the site separately.

The Investigator will be required to complete the paper BVAS form and transfer data to eCRF BVAS module at screening (Visit 1), baseline (Visit 2) and Q4W until the end of the first year of the OLE (Visit 30), withdrawal from the study, or the EOT visit (Table 1 and Table 2).

During subsequent years of the OLE (if applicable), the Investigator is only required to complete BVAS at unscheduled visits (eg, in the event of a relapse) and at the IPD/EOT visit (Table 3, Table 4, and Table 5). The requirement for monthly BVAS assessment is replaced with a clinical assessment of relapse/remission based on the Investigators' overall clinical assessment. In case of clinically suspected relapse, an unscheduled visit should be performed. The BVAS form is divided into 9 organ-based systems, with each section including symptoms/signs that are typical of that particular organ involvement in systemic vasculitis. The form is designed to record features that are attributable to current vasculitis, after exclusion of other causes such as infection, hypertension etc. The scoring sheet records the presence or absence of each item. Each item is weighted, and a maximum total score applied to each system. The total score on all 9 organ systems gives an indication of the disease activity of each patient at the time of scoring and reflects the need for therapy.

An Outcomes Oversight Committee will be utilised for this study.

8.1.1.2 EGPA Remission and Relapse

Investigators will be required to assess patients for EGPA relapse and remission from baseline (Visit 2) until withdrawal from the study or the EOT visit (Table 1, Table 2, Table 3, Table 4, and Table 5).

EGPA Remission

Remission at any visit is defined as a BVAS score of 0 with OCS dose of prednisolone/prednisolone ≤ 4 mg/day (see Appendix K for Belgium). This is main definition of remission utilised in the primary endpoint derivation (Table 7).

In the event a patient has achieved remission and at any subsequent visit has a BVAS = 1 which does not require an increase in corticosteroid dose above 4 mg/day or 7.5 mg/day (in accordance with the relevant remission definition), or any other significant clinical intervention or investigation, the patient will be considered to be in continued remission.

EGPA Relapse

EGPA relapse will be defined as worsening or persistence of active disease since the last visit characterised by:

- Active vasculitis (BVAS > 0); **OR**
- Active asthma symptoms and/or signs with a corresponding worsening in Asthma Control Questionnaire (6-item version) (ACQ-6) score (compared to the most recent previous score); **OR**
- Active nasal and/or sinus disease, with a corresponding worsening in at least one of the sino-nasal symptom questions (compared to the most recent previous assessment);

warranting **any** of the following:

  - An increased dose of OCS therapy to > 4 mg/day prednisolone total daily dose; **OR**
  - An increased dose or addition of immunosuppressive therapy; **OR**
  - Hospitalisation related to EGPA worsening

In the event of a suspected EGPA relapse, the patient should attend an unscheduled visit (Table 1, Table 2, Table 3, Table 4, and Table 5). A BVAS evaluation will be conducted at the time of the relapse, or as soon as possible afterwards.

The time of onset of a relapse will be defined as:

- The time of increase in dose of OCS therapy, **and/or**
- Increase in dose or addition of immunosuppressive therapy, **and/or**
- Hospitalisation in association with the worsening in BVAS, asthma, or sino-nasal symptoms

Investigators will be required to record details pertaining to each relapse event in the eCRF from baseline (Visit 2) until withdrawal from the study or the EOT visit (Table 1, Table 2, Table 3, Table 4, and Table 5), eg, details regarding the BVAS item, asthma or nasal/sinus

disease resulting in the relapse with detail of the required intervention(s), eg, OCS dose increase, use or change in immunosuppressive therapy or requirement for hospitalisation. For consenting patients participating in the mechanistic sub-study, where possible (only during the DB period and first year of the OLE), a blood and sputum sample should be collected in the event of relapse. In addition, where possible, (ie, as part of standard of care management), a tissue (biopsy) sample should be collected.

Note: in the event a patient has achieved remission (ie, BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) and at a subsequent visit has a BVAS = 1, which does not require an increase in corticosteroid dose above 4 mg/day, or any other significant clinical intervention or investigation, this will not be considered a relapse.

A major relapse (a sub-set of the total relapse events) will be defined as: any organ or life-threatening EGPA event; **OR** BVAS ≥ 6 (involving at least two organ systems in addition to any general symptoms where present [myalgia, arthralgia/arthritis, fever > 38°C or weight loss > 2 kg]); **OR** an asthma relapse requiring hospitalisation; OR sino-nasal relapse requiring hospitalisation.

The minimally effective dose of OCS (prednisolone/prednisone) for each patient will be defined as the dose of OCS one step above the OCS dose at which the first relapse occurred. Where the patient has achieved a dose of OCS of 0 to 3.5 mg prednisolone/prednisone, the minimally effective dose will be defined as 4.0 mg/day. Upwards dose adjustments within the 0 to 4.0 mg range are permitted without being considered a relapse.

The management of patients who relapse will be according to standard of care and may involve increasing the dose of corticosteroids or adjustment in immunosuppressive therapy.

If the patient's first relapse is managed with the use of an increase in corticosteroid dose, tapering should be recommended as soon as the relapse has been appropriately controlled, as per standard of care practice. As stated above, the recommended tapering schedule is provided in Appendix H, although after the first relapse the Investigator may opt to use larger dose increments and shorter dose intervals than outlined in the schedule, if clinically indicated. Once a minimally effective dose of OCS is achieved, any down-tapering below this dose level will be at the discretion of the Investigator, based on the clinical condition of the patient. In the event of a second or subsequent relapse, any further OCS tapering, post-relapse, will be conducted at the discretion of the Investigator.

If a relapse is managed by increasing the dose of or initiating immunosuppressive therapy, the patient must be withdrawn from receiving further study treatment and where possible, continued to be followed up as per protocol.

If a patient experiences an organ threatening or a life-threatening relapse he/she will be withdrawn from receiving further study treatment and where possible, continue to be followed up as per protocol.

8.1.1.3 Vasculitis Damage Index

Vasculitis Damage Index (Exley et al 1998) will be used to document those features of vasculitis, which are due to persistent damage, where there is no current disease activity. Damage is defined as the presence of non-healing scars and does not give any indication of current disease activity. The VDI is divided into 11 organ systems and records items of damage, due to vasculitis, treatment or unrelated, that have occurred since the onset of vasculitis. Completion of the form provides a numerical score. A copy of the VDI questionnaire will be provided to the site separately.

The Investigator will be required to complete the paper VDI form and transfer data into the eCRF VDI module as specified in Table 1, Table 2, Table 3, Table 4, and Table 5.

8.1.1.4 Corticosteroid Medication Usage

The patient will be asked to report the daily dosage of OCS taken over the past 24 hours throughout the 52-week DB period. The daily OCS usage assessment will be completed by the patient each evening prior to going to sleep using an ePRO device as indicated in the SoA (Table 6). In the OLE period (after Visit 17), patients will complete the OCS usage assessment once weekly until Visit 30 (end of year 1 of the OLE; Table 6) using the ePRO device. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

The ePRO device will be returned at Visit 30 or at the patient's final study visit, if it occurs before Visit 30. After Visit 30, the Investigator will record the patient's prescribed corticosteroid usage in the eCRF at regularly scheduled monthly clinic visits or telephone contact visits (Table 3 Table 4, and Table 5).

Patient-reported corticosteroid use and dosage will be checked at each clinic visit/telephone contact visit. This check should include a review of ePRO compliance (Section 8.1.1) as well as compliance with the prescribed OCS dose between each visit and/or tapering of dose, as described in Section 6.5.1.

8.1.1.5 Asthma Control Questionnaire (6-Item Version)

The ACQ-6 was developed for self-administration by adults and adolescents by omitting the FEV1 % predicted question (Juniper et al 1999). Patients are asked to record their experience with 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and use of SABA over the previous week using a 7-point scale (0 = no impairment; 6 = maximum impairment). The ACQ-6 score is calculated by taking the mean of the 6 equally weighted items. The ACQ-6 score range is 0 (well controlled) to 6 (extremely

poorly controlled). Individual score change of at least 0.5 is meaningful and is used to support the responder definition (Juniper et al 2005, Juniper et al 2006). Mean ACQ scores ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and 1.5 indicate partly controlled asthma, and a score ≥ 1.5 indicates poorly controlled asthma (Juniper et al 2006).

The patient will complete the ACQ-6 on the ePRO device as described in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.6 Sino-nasal Symptom Questionnaire

The SSQ asks patients to report the severity of their symptoms over the previous week: "Considering your sinus and nasal symptoms over the last week, rate each symptom against the following categories: very severe, severe, moderate, mild, none." Symptoms include runny nose, post-nasal discharge (sensation of liquid in your throat), facial pain/pressure, loss or reduction in sense of taste/smell, and blockage/congestion of nose. Higher scores indicate greater severity (0 = none to 4 = very severe).

The patient will complete the SSQ on the ePRO device as specified in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.7 Sino-Nasal Outcome Test-22

The Sino-Nasal Outcome Test-22 (SNOT-22) is a condition-specific HRQoL assessment which captures patient-reported physical problems, functional limitations, and emotional consequences of sino-nasal conditions (Piccirillo et al 2002, Hopkins et al 2009). Patient-reported symptom severity and symptom impact over the past 2 weeks are captured via a 6-point scale (0 = no problem to 5 = problem as bad as it can be). The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes). A Minimal Clinical Importance Difference of 8.90 has been established for individual score change (Hopkins et al 2009).

The patient will complete the SNOT-22 on the ePRO device as specified in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.8 Short Form-36 Version 2 (Acute Recall)

The Short Form-36 version 2 (acute recall) (SF-36v2) is a 36-item, self-report survey of functional health and well-being, with a 1-week recall period (Lincoln 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 are computed from subscale scores to give a broader metric of physical and mental HRQoL.

The SF-36v2 threshold is suitable for interpreting change at the individual level and is referred to as the responder threshold (Table 14) or responder definition (Lincoln 2011).

Table 14 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 health component summary; MH, mental health; PCS, physical health component summary; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical health; SF, social functioning; SF-36v2, Short Form 36-Item Health Survey (version 2, acute recall); VT, vitality.

The patient will complete the SF-36v2 on the ePRO device as specified in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.9 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).

The patient will complete the PGIS on the ePRO device as described in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.10 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).

The patient will complete the PGIC on the ePRO device as described in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.11 Work Productivity and Activity Impairment questionnaire

The WPAI general health version 2.0 is a self-administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated

tool captures data from the past 7 days. WPAI outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity (Reilly Associates 2012).

The patient will complete the WPAI on the ePRO device as described in Table 6. Any within-window assessment that has not been completed prior to the site visit will be completed at the site prior to other study procedures.

8.1.1.12 Spirometry

General requirements

Lung function (FEV1 and forced vital capacity) will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorised delegate according to American Thoracic Society/European Respiratory Society guidelines (Miller et al 2005).

The vendor providing central spirometry will ensure that the spirometer meets American Thoracic Society/European Respiratory Society recommendations and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

- 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 site.
- Patients should withhold their usual maintenance therapies (if applicable) on the day(s) when lung function testing is being performed as below:
  - SABA and short-acting muscarinic antagonist should be withheld at least 6 hours prior to scheduled spirometry at site.
  - Twice daily LABA- or LAMA-containing therapies should be withheld for at least 12 hours prior to scheduled spirometry at site.
  - Once daily LABA- or LAMA-containing therapies should be withheld for at least 24 hours prior to scheduled spirometry at site.
  - Twice daily theophylline should be withheld for at least 12 hours prior to scheduled spirometry at site.
  - Once daily theophylline for at least 24 hours prior to scheduled spirometry at site.

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

Order of Administration for any Asthma Maintenance Medication (if Applicable) and IP Relative to the Scheduled Pre- and Post-bronchodilator Spirograms

For patients that are taking any asthma maintenance therapies, they should not take their morning maintenance therapy until after the pre- and post-BD spirograms are complete. The patient's usual asthma medications may be administered following completion of the pre/post-BD spirograms, and (if applicable) should be taken prior to IP dosing.

Investigational product dosing should also be withheld until pre- and post-BD spirometry is complete.

Time of Day for Scheduled Site Visit Spirometry

Spirometry testing should be done according to the SoA (Table 1) (Table 2), (Table 3), and (Table 4). Spirometry testing must be initiated in the morning between 0600 and 1100 at the baseline visit (Visit 2).

All post-randomisation spirometry assessments should be performed within ± 2 hours of the time of day that the baseline (Visit 2) spirometry is performed, if possible.

Spirometry Technique

Detailed procedures for performing spirometry will be described in a separate instruction manual. Details regarding assessment of the quality of spirometry and the best test review process will also be detailed in the manual.

Record Keeping

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

Spirometry References

The Global Lung Function Initiative equations will be used to determine the PNV and are pre-programmed into the spirometer.

Forced expiration volume in 1 second, expressed as percent of the PNV, will be calculated as follows:

$$FEV1\% \text{ of } PNV = (FEV1 \text{ measured}/FEV1_{PNV}) \times 100$$

Percent reversibility will be calculated as follows:

$$\text{Percent reversibility} = (\text{post-BD } FEV - \text{pre-BD } FEV1) \times 100\%/\text{pre-BD } FEV1$$

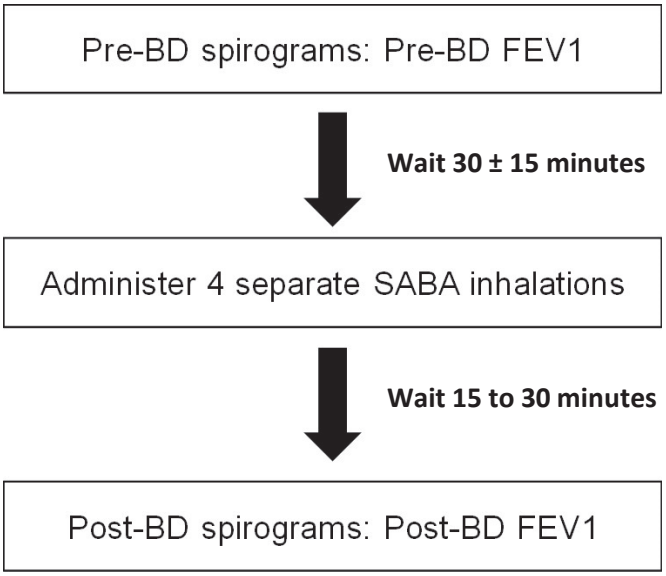
Reversibility Test and Post-Bronchodilator FEV1 Efficacy Assessment

The procedure described in this section refers to the reversibility test and post-BD spirometry that should be performed only at baseline (Visit 2).

Endpoint maximal bronchodilation will be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose), or levalbuterol (45 µg metered dose) 4 inhalations within 30 ± 15 minutes of the final pre-BD spirometry measurement. Post-BD spirometry should be performed 15 to 30 minutes after SABA dosing. It is highly recommended to use a spacer device for this procedure. A nebuliser should not be used.

The algorithm for reversibility testing is outlined in Figure 4.

Figure 4 Reversibility Testing Algorithm



BD, bronchodilator; FEV1, forced expiration volume in 1 second; SABA, short acting β_2 agonist.

8.1.2 Patient Qualitative Interview Sub-study

Up to 45 patients will be invited to participate in a set of concept elicitation interviews to characterise their experience during the DB portion of the study. Interviews will be non-interventional and will collect data on HRQoL and patients' experiences with the study treatment. Interviews will be performed by an AstraZeneca vendor via telephone contact on a one-to-one basis and interview duration will be approximately 60 minutes. Please refer to a separate Patient Qualitative Interview Manual describing interview processes.

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 provided in a separate Patient Qualitative Interview 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 provided in a separate Patient Qualitative Interview Manual.

Each participating patient will be interviewed twice. The first hour-long interview will take place at least 7 and up to 21 days after Visit 2. The second interview will take place at least 7 and up to 21 days after Visit 16 (or IPD within the DB portion of the study). With the patient's permission (ascertained via the consent form and confirmed verbally prior to the start of the interview), the interviews will be audio recorded.

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. Interview discussion guides are provided in a separate Patient Qualitative Interview 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 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 study patient or potential study patient reports or is noted to have experienced an AE involving study treatment, information about the AE will be reported to the AstraZeneca. AstraZeneca will follow standard procedures for handling AEs reporting involving these patients.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5).

8.2.1 Clinical Safety Laboratory Assessments

See Table 15 for the list of clinical safety laboratory tests to be performed and the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the separate laboratory manual and the SoA.

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

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

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.6.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry and haematology analyses will be performed at a central laboratory. Urinalysis will be performed at a central laboratory only at Visit 1; subsequent analyses will be performed locally using a dipstick provided centrally.

Erythrocyte sedimentation rate will be performed at a local laboratory.

As described in Section 6.3.2.1, from baseline (Visit 2) until Visit 18, the eosinophil, basophil, and monocyte counts will be redacted from central laboratory reports to prevent the site staff/AstraZeneca from possibly deducing the 'eosinophil + basophil + monocyte' contribution to the complete blood count.

Table 15 Laboratory Safety Variables

Haematology [a]	**Clinical chemistry**
Haemoglobin (Hb)	Creatinine
Leukocyte count (white blood cell [WBC] count)	Bilirubin, total
Leukocyte differential count (absolute count)	Bilirubin, direct
Platelet count	Bilirubin, indirect
Red cell count (red blood cell [RBC] count)	Alkaline phosphatise (ALP)
Reticulocytes	Aspartate aminotransferase (AST)
Mean Corpuscular Volume (MCV)	Alanine aminotransferase (ALT)
Mean Corpuscular Haemoglobin (MCH)	Albumin
Mean Corpuscular Haemoglobin Concentration (MCHC)	Potassium
Neutrophil (absolute and differential [%])	Calcium, total
Lymphocytes (absolute and differential [%])	Sodium
Monocytes (absolute and differential [%])	Creatine kinase (CK)
Eosinophils (absolute and differential [%])	Chloride

Table 15 Laboratory Safety Variables

Basophils (absolute and differential [%])	Phosphorous inorganic
	Glucose
Urinalysis	Protein, total
U-Hb/erythrocytes/blood	Urea nitrogen
U-Protein/albumin	Lactic dehydrogenase (LD)
U-Glucose	Cholesterol, total
U-Ketones	Gamma glutamyl transaminase (GGT)
Microscopic: WBC and RBC (screening [Visit 1] only)	Lipoproteins (fasting)
Urine human chorionic gonadotropin (HCG)	Troponin
	Other laboratory parameters
	Hepatitis B Surface Antigen
	Hepatitis C antibody
	anti-neutrophil cytoplasmic antibodies (ANCA) (myeloperoxidase [MPO] and PR3 [proteinase-3])
	Total immunoglobulin E (IgE), fluoroenzyme immunoassay (FEIA)
	C-reactive protein (CRP)
	human immunodeficiency virus (HIV)-1 and HIV-2
	erythrocyte sedimentation rate (ESR)
	follicle stimulating hormone (FSH)
	Serum pregnancy test

[a] Eosinophils, basophils, and monocytes counts and percentage will be redacted from central laboratory reports from Visit 2 (Week 0) to Visit 18 (Week 56) (Section 8.8.1).

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

8.2.1.1 Pregnancy Test

The following tests are applicable to female patients only and will be conducted in accordance with the schedules provided in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5).

- Serum beta-human HCG: To be performed for all females at screening (Visit 1) except for those who are NOT of child-bearing potential as defined in inclusion criterion 9 (Section 5.1). This test is to be sent to and analysed at the central laboratory;
- FSH: To be performed at screening (Visit 1) only, for female patients to confirm postmenopausal status in women < 50 years who have been amenorrhoeic for > 12 months;

- Urine HCG: To be performed at the study site for all WOCBP at each treatment visit before IP administration using a dipstick, defined in exclusion criterion 19. A positive urine test result must be confirmed with serum beta-HCG.

8.2.1.2 Serology

Hepatitis B surface antigen and hepatitis C antibody: To be performed at screening and Visit 16; test to be performed at central laboratory.

In case of positive result of HBsAg or hepatitis C virus antibody, additional testing (eg, hepatitis C RNA polymerase chain reaction test) may be performed to confirm eligibility, please see exclusion criterion #9 for full details (hepatitis status Section 5.2).

Human immunodeficiency virus-1 and HIV-2 antibodies (along with p24 antigen): To be performed at screening and Visit 16; test to be performed at central laboratory.

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

8.2.2 Physical Examinations

Physical examination will be performed at timelines as specified in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5). Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs (Section 8.3.6 for details).

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

8.2.2.1 Complete Physical Examination

A complete physical examination will be performed at visits indicated in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) and includes 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.

8.2.2.2 Brief Physical Examination

The brief physical examination will be performed at visits indicated in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) and includes an assessment of the general appearance, abdomen, cardiovascular and respiratory system.

8.2.3 Vital Signs

Pre-dose vital signs are to be obtained in accordance with the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5).

Vital signs are to be taken prior to IP administration, and if possible, before blood draw. Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed:

- Body temperature will be measured in Celsius before IP administration in accordance with local standards.
- Blood pressure and pulse measurements will be assessed while sitting and will be assessed utilising 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.
- 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.

8.2.4 Electrocardiograms

Triplicate 12-lead ECGs are to be performed at screening (Visit 1) to assess eligibility for this study, and then as indicated in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) during the treatment period using an ECG machine that automatically calculates the heart rate and measures PR, QRS complex, QT, and QTc intervals.

Each of the three 12-lead ECGs at each timepoint will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry, blood draw).

An independent reader at the central EGC vendor will provide overall interpretation as normal or abnormal. The Investigator will assess the clinical significance of any potential ECG findings. A reassessment ECG may support evaluation of clinical significance, when uncertain. Further details are provided in a separate ECG user manual.

8.2.5 Other Safety Assessments

8.2.5.1 Weight and Height and Body Mass Index

Weight and height will be measured in accordance with schedules provided in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5).

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

Body mass index will be automatically calculated in the eCRF.

8.3 Collection of Adverse Events

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

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs see Section 8.3.2.

8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

Adverse events will be collected from randomisation throughout the treatment period up to the end of OLE Year 3 and including the FU period last contact with patient.

Serious adverse events will be recorded from the time of signing of the ICF. During OLE Year 4 onwards, only SAEs or significant medical/adverse events that lead to an intervention should be captured and recorded in the eCRF.

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

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

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

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

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

Any AEs that are unresolved at the patient's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 Adverse Event Data Collection

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE description
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.4 Causality Collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the clinical study protocol.

8.3.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient *or care provider,* or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.6 Adverse Events Based on Examinations and Tests

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

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

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (Section 8.3.7).

8.3.7 Disease Under Study

Symptoms of the disease under study are those which might be expected to occur as a direct result of EGPA. Events which are unequivocally due to EGPA should not be reported as an AE during the study unless they meet the criteria below.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. EGPA symptoms or signs, such as wheeze, cough, dyspnoea, allergic rhinitis, abdominal pain, symptoms of vasculitis will be recorded as AEs only when:

- The sign or symptom is serious according to definitions, see Appendix B
- The patient discontinues the study due to the sign or symptom.

- The sign or symptom is new to the patient or not consistent with the patient's preexisting EGPA history (defined as within one year of Visit 1) as judged by the Investigator.

If an EGPA relapse fulfils any of the above criteria, the sign or symptom should also be recorded as an AE.

8.4 Safety Reporting and Medical Management

8.4.1 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca 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 FU is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any FU information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

8.4.2 Pregnancy

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

If the pregnancy is discovered before the study patient has received any study drug.

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

8.4.2.1 Maternal Exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for SAEs (Section 8.3.2) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy report form in the eCRF is used to report the pregnancy and the paper-based pregnancy outcome report is used to report the outcome of the pregnancy.

8.4.3 Overdose

8.4.3.1 Benralizumab Overdose

No clinical data regarding overdose are available. Single doses of up to 200 mg were administered SC in clinical trials to patients with eosinophilic disease without evidence of dose-related toxicities. For management of IP-related toxicities, see Section 8.4.7.

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

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

8.4.3.2 Mepolizumab Overdose

Single doses of up to 1500 mg have been administered IV to patients in a clinical trial with eosinophilic disease without evidence of dose-related toxicities. For management of IP-related toxicities, see Section 8.4.7.

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

8.4.4 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 F.

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.

8.4.4.1 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 medical device deficiencies is provided in Appendix F.

8.4.4.2 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.

8.4.4.3 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.
- Where an SAE has occurred in addition to the malfunction, the SAE will be recorded in the eCRF as detailed in Section 8.4.1.
- AstraZeneca will be the contact for the receipt of medical device deficiency reports.

8.4.4.4 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 F.

8.4.4.5 SADE Reporting

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

Any device constituent deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device constituent deficiency. The sponsor will review all device constituent deficiencies and determine and document in writing whether they could have led to an SAE. These device constituent deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

8.4.5 Medication Error, Drug Abuse, and Drug Misuse

8.4.5.1 Timelines

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow up fatal/life-threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error, drug abuse, or misuse (Section 8.3.1) and **within 30 days** for all other events.

8.4.5.2 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 that either causes harm to the patient or has the potential to cause harm to the patient.

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

8.4.5.3 Drug Abuse

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

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

8.4.5.4 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study patient) of IP for medicinal purposes outside of the authorised product information, or for unauthorised 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.

8.4.6 Reporting of Overdose

Refer to Section 8.4.3 for definition and treatment of overdose.

- An overdose with associated AEs should be 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 should be only reported on the overdose eCRF module.

If an overdose on an 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 (see Section 8.3.1) and **within 30 days** for all other overdoses.

8.4.7 Management of IP-related Toxicities

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 E.

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

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

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix E 2.

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.

Pharmacokinetic analysis will only be done on samples from patients who received benralizumab.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the AstraZeneca and site study files, but will not constitute a protocol amendment. The IRB/IEC

will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

For the PK analysis, it is important that the date and time 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 serum samples, except for samples collected at Week 1 and Week 25, will be collected pre-dose according to the schedule of study procedures (Table 1, Table 2, Table 3, Table 4, and Table 5).

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

8.5.1 Determination of Drug Concentration

Samples for determination of benralizumab concentration in serum will be analysed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The result from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

8.5.2 Storage and Destruction of Pharmacokinetic Samples

The PK samples will be retained for a period of 6 months from bioanalytical report finalisation.

8.6 Pharmacodynamics

Relevant information for blood eosinophils and other biomarkers including serum, RNA, nasal secretions, sputum, tissue biopsy (optional) and whole blood for cell phenotyping and PBMC isolation are described in Section 8.8.

8.7 Genetics

8.7.1 Optional Exploratory Genetic Sample

The blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study. Samples can be collected at any time after the genetic consent form is signed. See Appendix D for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the separate laboratory manual provided to the sites.

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

8.7.2 Storage and Destruction of Genetic Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA. For further details, see Appendix D.

8.8 Biomarkers

Biomarkers that may be analysed in both mandatory and mechanistic sub-study sample collections include, but are not limited to, sputum differential leukocyte counts; whole blood gene expression; blood and tissue leukocyte phenotypic markers; serum/sputum/nasal secretion proteins including, but not limited to, eosinophil granule proteins, cytokines, chemokines, and inflammatory mediators associated with EGPA; eosinophil activation; immunological function; and the pharmacology of benralizumab and mepolizumab.

8.8.1 Blood Eosinophils

Table 1Table 2, Table 3, Table 4, and Table 5).Note that the eosinophil, basophil and monocyte counts will be redacted from the haematology report sent to the investigative site in order to maintain the study blinding from baseline (Visit 2) until Week 56 (Visit 18).

8.8.2 Mandatory Biomarker Samples

Mandatory collection of samples for exploratory biomarker research is part of this study. The following samples for exploratory biomarker research are required and will be collected pre-dose from all patients in this study, as specified in the SoA:

- Blood (serum, whole blood PAXgene RNA tube)

Serum samples will be collected according to the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5), and whole blood PAXgene RNA tube samples will be collected according to the SoA (Table 1), in order to evaluate the effect of benralizumab compared to mepolizumab on biomarkers of eosinophil recruitment, activation, and survival (eg, IL-5, eosinophil-derived neurotoxin, and eotaxin), inflammation and immunological mechanisms related to EGPA, as well as to identify baseline biomarkers predicting response to benralizumab or mepolizumab.

Additional samples will be collected and analysed as part of the mechanistic sub-study (Section 8.8.4).

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

8.8.3 Nasal Secretions (Mandatory at Selected Sites)

Collection of nasal secretions for exploratory biomarker research is required only for those sites with the necessary equipment to process the samples. The Investigator or study staff will collect samples from all study patients at that site.

Samples will be collected pre-dose according to the SoA (Table 1). For biomarkers to be evaluated, see Section 8.8.2.

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

8.8.4 Mechanistic Sub-study Sampling (Induced Sputum, Tissue Biopsy, and Whole Blood Cells)

Additional exploratory biomarker research will be performed at sites participating in the mechanistic sub-study. The purpose of the sub-study is to more extensively evaluate the effect of benralizumab compared to mepolizumab on biomarkers of eosinophil recruitment, activation, and survival (eg, IL-5, eosinophil derived neurotoxin, and eotaxin); inflammation and immunological mechanisms related to EGPA; as well as to identify baseline biomarkers predicting response to benralizumab or mepolizumab. The following additional samples will be collected pre-dose at the time points shown in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) only from patients who have consented to participate in this sub-study:

- Induced sputum (for inflammatory cell counts, protein biomarkers, and transcriptomics)
- Tissue biopsy (for histology, immunohistochemistry, and transcriptomics)
- Whole blood for cell phenotyping and PBMC isolation

Sputum will be induced, collected, and processed using a modification of a previously published method (McCormick et al 2007, Pizzichini et al 1998). The sputum, tissue biopsies and whole blood will be collected and processed locally at the clinical sites according to the process detailed in separate laboratory manuals provided to the sites. Spirometry will be performed as part of the sputum induction procedure as described in the separate laboratory manual. All planned sample analyses will be performed at a central laboratory.

Tissue biopsies from the nose should be collected from patients with chronic rhinosinusitis with or without nasal polyps. Biopsies from other sites may be taken as per clinical judgment (unscheduled visit); these biopsies must remain blinded. Instructions for the collection and processing of the tissue biopsies are described in a separate laboratory manual.

Sampling of whole blood for cell phenotyping and PBMC isolation will occur only for patients participating at North American mechanistic sub-study sites.

8.8.5 Storage, Reuse, and Destruction of Biomarker Samples

AstraZeneca or a designee will retain biomarker samples for a maximum of 15 years following the Last Patient's Last Visit, after which they will be destroyed.

8.8.6 Reporting of Biomarker Research

The results of the biomarker research will be reported separately from the DB CSR in separate scientific reports or publications as appropriate. The results of the biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Immunogenicity

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

Anti-drug antibodies/nAb analysis will only be done on samples from patients who received benralizumab.

The immunogenicity samples will be retained at AstraZeneca or designee for a maximum of 5 years following the final CSR or publication associated with the study in order to properly address potential questions from regulatory authorities.

A summary of the analysis will be presented in the primary analysis CSR, and subsequent analyses in addendum to the primary analysis CSR and/or a separate OLE period CSR. Details of the analytical method used will be described in a bioanalytical report.

8.9.1 Anti-drug Antibodies

Serum samples for analysis of ADA will be collected pre-dose at selected visits according to the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5).

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

8.9.2 Benralizumab Neutralising Antibodies

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

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

8.10 Medical Resource Utilisation and Health Economics

At visits when health care use is being collected, as specified in the SoA (Table 1, Table 2, Table 3, Table 4, and Table 5) the Investigator should ask the patient if they have had any need to seek medical treatment for EGPA or an EGPA-related episode since the previous scheduled visit.

Details of all healthcare resource utilisation related to treatment for EGPA or an EGPA-related episode will be recorded by the Investigator on paper or designee in the eCRF.

8.11 Other Assessments and Procedures

8.11.1 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.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

9.1.1 Primary Endpoint Hypothesis

The primary efficacy endpoint is the proportion of patients who achieve remission at both Week 36 and Week 48. EGPA remission is defined as having a BVAS = 0 and OCS dose ≤ 4.0 mg/day. The primary analysis is to demonstrate NI of benralizumab versus mepolizumab based on the primary endpoint of remission.

The null hypothesis is that the proportion of patients achieving remission on benralizumab is inferior to that of patients on mepolizumab by a NI margin of -25%. The alternative hypothesis is that benralizumab is not inferior to mepolizumab.

For the null hypothesis to be rejected, the lower 95% confidence limit for the absolute difference between benralizumab and mepolizumab remission rates needs to be above the NI margin of -25%. The primary endpoint will be tested at the 0.025 one-sided level. The primary endpoint will be evaluated using logistic regression, as outlined in Section 9.4.1.2 below. If NI is demonstrated for the primary endpoint, the same logistic regression model used to evaluate NI will be used to test superiority of benralizumab compared to mepolizumab at the one-sided 0.025 level. In this case, the null hypothesis is that the benralizumab remission rate is not higher than the mepolizumab remission rate, and the alternative hypothesis is that the remission rare is greater on benralizumab compared to mepolizumab.

The external validity of the study will be assessed using an approach which compares the observed benralizumab rate in this study with the historical placebo remission rate of 2 of 68 patients (2.9%) observed within the MIRRA study (Wechsler et al 2017). The null

hypothesis is that of patients achieving remission on benralizumab is equal to placebo. The alternative hypothesis is that patients achieving remission on benralizumab is greater than placebo. Superiority of the remission rate of benralizumab within this trial over the historical placebo remission rate observed in the mepolizumab trial will be evaluated with a two-sample test for binomial proportions and one-sided, 0.025 level test.

9.2 Sample Size Determination

Assuming that benralizumab and mepolizumab each have a remission rate of 32%, 140 patients will provide approximately 90% power to demonstrate NI with a NI margin of -25% at the 2.5% one-sided significance level. For the study to be positive, the lower 95% confidence limit for the difference between benralizumab and mepolizumab needs to be above the NI margin of -25%. The external validity of the study will be assessed using an indirect comparison to placebo. Assuming rates of 32% for benralizumab and 2 of 68 (2.9%) for historic placebo and sample sizes of 70 and 68, respectively, it is expected there will be > 90% power to demonstrate benralizumab has an improved remission rate over historical placebo with a one-sided alpha of 0.025. Power at the 2.5% one-sided significance level for comparison of benralizumab to historic placebo was evaluated with a two-sample test for binomial proportions using a placebo rate of 3%. This method accounts for the uncertainty in the historical placebo estimate as well as uncertainty in the current trial.

Patients will be randomised in a 1:1 ratio to benralizumab or mepolizumab treatment.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined in Table 16.

Table 16 Description of Populations for Analyses

Population	Description
Enrolled	All patients who sign the ICF
Randomly assigned to study treatment	All patients who sign the ICF and are randomised to an investigation product regardless of whether they receive a dose of an IP or exit prior to receiving the first dose.
Full analysis set	All patients randomised and receiving at least 1 dose of IP will be included in the full analysis set, 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 ITT 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.

Table 16 Description of Populations for Analyses

Population	Description
Safety analysis set	The safety analysis set consists of all patients who have received at least one dose of IP. Erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who has received active IP (benralizumab) on one or several occasions is classified as active (benralizumab).
Pharmacokinetic analysis set	All patients who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

ICF, informed consent form; IP, investigational product; ITT, intent to treat; PK, pharmacokinetics.

9.4 Statistical Analyses

All personnel involved with the analysis of the study will remain blinded until the primary database lock, which is after CSP deviations identified for the primary analysis.

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

9.4.1 Efficacy Analyses

Efficacy analyses will be performed using the full analysis set.

All analyses described below apply to the full analysis of all patients, through to the end of the DB period (Week 52) unless otherwise stated. Primary database lock will occur when the last patient completes 52 weeks of DB treatment. Unblinding and data analysis will occur after primary database lock.

9.4.1.1 Calculation or Derivation of Variables for Efficacy Analyses

Remission

Eosinophilic granulomatosis with polyangiitis remission is defined as having a BVAS = 0 and OCS dose ≤ 4.0 mg/day and is calculated at each time point every 4 weeks. The primary efficacy endpoint is the proportion of patients who achieve remission at both Week 36 and Week 48. For a supportive analysis, remission will also be defined as having a BVAS = 0 and OCS dose ≤ 7.5 mg/day and is calculated at each time point every 4 weeks.

Total Accrued Duration of Remission

Total accrued duration of remission (defined as a BVAS = 0 and OCS dose ≤ 4.0 mg/day) will be evaluated over the 52-week treatment period. The accrued duration will be assigned with the following categories: 0 weeks, > 0 to < 12 weeks, 12 to < 24 weeks, 24 to < 36 weeks, and ≥ 36 weeks. For a supportive analysis, remission will also be defined as having a BVAS = 0 and OCS dose ≤ 7.5 mg/day.

Time to First EGPA Relapse

Time from randomisation to first relapse will be evaluated over the 52-week treatment period. Eosinophilic granulomatosis with polyangiitis relapse will be defined as worsening or persistence of active disease since the last visit as specified in Section 8.1.1.2. For patients who have not experienced a relapse by Week 52, their time to relapse will be right-censored at the last available assessment time.

Average Daily Prednisolone/Prednisone Dose During the Last 4 Weeks of the Double-Blind Treatment Period

Average daily prednisolone/prednisone dose during Weeks 48 through 52 will be calculated (see Appendix K for Belgium). The average daily dose will be assigned with the following categories:

- 0 mg/day, > 0 to ≤ 4 mg/day, > 4 to ≤ 7.5 mg/day, and > 7.5 mg/day
- ≤ 4 mg/day

The percent reduction of average daily prednisolone/prednisone dose from baseline at Weeks 48 through 52 will be calculated with categories:

- No reduction or premature discontinuation from treatment before Week 48, < 25% reduction, 25 to < 50% reduction, 50 to < 75% reduction, 75 to < 100% reduction, and 100% reduction.
- ≥ 50% reduction from baseline.
- 100% reduction from baseline.

For the endpoints of ≥ 50% and 100% reduction from baseline, patients who prematurely discontinue from treatment before Week 48 will be considered non-responders.

Clinical Benefit

Any clinical benefit is a composite endpoint that is defined as any of the following 3 component endpoints (Steinfeld et al 2019):

- Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the DB treatment period.

- ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52.
- EGPA relapse free during the DB treatment period.

The patients who prematurely discontinue from treatment before Week 48 will be considered non-responder for the percentage reduction in average daily prednisolone/prednisone dose component of the clinical benefit.

Complete response is a composite endpoint and patients meet complete response if all of the 3 components above are met.

The analyses on any clinical benefit and complete response will be repeated for the supportive remission definition.

Remission within 24 Weeks and Remained in Remission for Remainder of the Double-Blind Treatment Period

Remission (defined as a BVAS = 0 and OCS dose ≤ 4.0 mg/day) over the first 24 weeks and remained in remission for remainder of the DB treatment period will be evaluated over the 52-week treatment period. The proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of 52-week treatment period will be calculated. For a supportive analysis, remission will also be defined as having a BVAS = 0 and OCS dose ≤ 7.5 mg/day.

Asthma Control Questionnaire (6-Item Version)

The ACQ-6 is an assessment of 5 asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and short-acting beta-agonist use.

Sino-nasal Questionnaire

The SSQ captures the severity of 5 sinus and nasal symptoms.

Sino-nasal Outcome Test-22

The SNOT-22 is a condition-specific HRQoL assessment, which captures 22 items on patient-reported physical problems, functional limitations, and emotional consequences of sino-nasal conditions (Hopkins et al 2009, Piccirillo et al 2002).

Short Form 36-item Health Survey, Version 2

The SF-36v2 is a 36-item, self-report survey of functional health and well-being, with a one-week recall period (Lincoln 2011). 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 are computed from subscale scores.

Patient Global Impression of Severity

The PGIS is a single item designed to capture the patient's perception of overall symptom severity.

Patient Global Impression of Change

The PGIC is a single item designed to capture the patient's overall evaluation of response to treatment.

9.4.1.2 Methods for Efficacy Analyses

Analyses of the Primary Endpoint

The primary analysis is to demonstrate NI of benralizumab versus mepolizumab based on the primary endpoint of remission. For NI of benralizumab compared to mepolizumab to be demonstrated for the primary endpoint, the lower 95% confidence limit for the absolute difference in remission between benralizumab and mepolizumab needs to be above the NI margin of -25%. The primary endpoint of the proportion of patients who achieve remission at both Week 36 and Week 48 will be analysed using a logistic regression model. The model will include covariates of treatment arm, baseline dose of prednisone, baseline BVAS, and region. From this model, the absolute difference in remission rates (benralizumab-mepolizumab) will be estimated, with the associated two-sided 95% CI. Results will be presented in terms of adjusted response rates and difference in response rates with 95% CIs and p-values. If this analysis demonstrates NI, a formal test of superiority between benralizumab and mepolizumab will be assessed.

To assess external validity of the study a direct comparison of benralizumab to historic placebo will be evaluated using remission rate. An unadjusted rate for benralizumab from this study will be compared to a historic rate of 2 of 68 (~2.9%) for placebo. Superiority of benralizumab over historical placebo will be evaluated with a two-sample test for binomial proportions using a one-sided test of benralizumab having an improved rate over placebo with a 2.5% significance level. This method accounts for the uncertainty assuming the sample size of 68 from the historical placebo estimate and a sample size of 70 for the benralizumab arm in the current trial. A normal approximation will be used for this comparison of benralizumab to historic placebo.

Analysis of Secondary Endpoints

Time to first EGPA relapse will be analysed using a Cox-proportional hazards model. Cox-proportional hazards model results will be presented in terms of adjusted hazard ratios with 95% CIs. Treatment arm, baseline dose of prednisone, baseline BVAS, and region will be included as covariates in the model.

Annualised relapse rate, defined as the number of relapses per year, will be evaluated using a negative binomial model. Treatment arm, baseline dose of prednisone, baseline BVAS, and region will be included as covariates in the model. The logarithm of the follow-up time will be used as an offset in the model.

The secondary endpoints of accrued duration of remission, the average of daily prednisolone/prednisone dose during Weeks 48 through 52 (with categories 0 mg/day, > 0 to ≤ 4 mg/day, > 4 to ≤ 7.5 mg/day, and > 7.5 mg/day), and percentage reduction from baseline in average prednisolone/prednisone dose at Weeks 48 through 52 (with categories no reduction or premature discontinuation from treatment before Week 48, < 25% reduction, 25 to < 50% reduction, 50 to < 75% reduction, 75 to < 100% reduction, and 100% reduction) will be analysed using a proportional odds model, with categories for the dependent variable as outlined in Section 9.4.1.1. Treatment arm, baseline dose of prednisone, baseline BVAS, and region will be included as covariates in the model. Results from the proportional odds model will be presented in terms of adjusted odds ratios with 95% CIs.

The following secondary endpoints will be analysed using a logistic regression model:

- Proportion of patients who achieved remission within the 24 weeks and remained in remission for remainder of the DB treatment period.
- Proportion of patients with ≥ 50% reduction in daily prednisolone/prednisone dose from baseline during Weeks 48 through 52.
- Proportion of patients with 100% reduction in daily prednisolone/prednisone dose from baseline during Weeks 48 through 52.
- Proportion of patients with average daily prednisolone/prednisone dose of ≤ 4 mg/day during Weeks 48 through 52.
- Proportion of patients who achieved any clinical benefit during DB treatment period.
- Proportion of patients who achieved complete response during DB treatment period.

Treatment arm, baseline dose of prednisone, baseline BVAS, and region will be included as covariates in all the models.

The supportive remission endpoint will also be defined as a BVAS = 0 and prednisolone/prednisone dose ≤ 7.5 mg/day. The following variables will be evaluated under this supportive remission definition and analysed as above: proportion of patients who achieve remission at both Week 36 and Week 48, total accrued duration of remission, any clinical benefit, complete response, and proportion of patients who have achieved remission within the first 24 weeks and remained in remission for remainder of treatment period.

BVAS, VDI, ACQ-6, pulmonary function testing, SNOT-22, SF-36v2 (acute; PCS, MCS, and domain scores), and blood eosinophil counts will be assessed as change from baseline over the 52-week treatment period. The change from baseline in the secondary endpoints will be

analysed using a MMRM analysis with treatment arm, baseline dose of prednisone, baseline BVAS, visit, endpoint's baseline, visit by treatment, and region 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 52 time point. The estimate of the treatment effect at Week 52 will be based on a contrast from this MMRM model.

Descriptive statistics will be provided for WPAI observed and change from baseline values over time by treatment group. Descriptive statistics will be provided for PGIS responses over time and PGIC responses between Visits 2 and 4.

The proportion of patients with an ACQ-6 response (defined as a decrease in score from baseline of 0.5) at end of the 52-week DB period will be evaluated. The ACQ-6 responder analysis will be performed using a logistic regression model adjusted for treatment group, baseline ACQ-6 score, baseline dose of prednisone, baseline BVAS score, and region.

Sensitivity Analysis

Sensitivity analyses may be conducted using an on-treatment analysis where patients are assumed to not be in remission if they discontinue IP and also using a per-protocol population where patients are excluded based on important protocol deviations related to efficacy. These sensitivity analyses will be carried out depending on the extent of treatment discontinuations and important protocol deviations related to efficacy. Full details of the sensitivity analyses will be prespecified in the SAP.

Subgroup Analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses will include, but may not be limited to the following factors: eosinophils (< 150, ≥ 150 cells/μL), OCS use at baseline (< 12, ≥ 12 mg/day), gender, age (≥ 18 to 65 and > 65 years), BMI (≤ 30, > 30), geographic region, time since EGPA diagnosis (≤ 4, > 4 years), immunosuppressive therapy usage at baseline (yes/no), baseline VDI score (< 5, ≥ 5), race, and ANCA-positive status. These analyses are to be considered as exploratory and will be performed on the full analysis set.

9.4.2 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 at AstraZeneca/designee.

Safety data will be presented using descriptive statistics unless otherwise specified. Adverse events 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 taking into consideration relationship as assessed by the Investigator, intensity, seriousness, death, and events leading to discontinuation of IP. An additional table will present the number and percentage of patients with most common AEs. In accordance with the requirements of the FDA, 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 first dose of IP
- Worsening of preexisting events on or after first dose of IP

9.4.3 Other Analyses

Pharmacokinetics, PD, and biomarker exploratory analyses will be described in the SAP finalised before the primary database lock. The population PK analysis and PD analyses will be presented separately from the CSR for the DB period.

9.4.4 Interim Analyses

No interim analyses are planned for this study.

9.4.5 OLE Period Analyses

For the OLE period, descriptive statistics will be presented for safety, ADA, PK, remission, relapse, and OCS use. Additional analyses may be performed after the primary database lock to analyse the data that were not available in the primary analysis. The final database lock will occur after the last patient has completed at least one year in the OLE and when the end of the study has been declared. A summary of data from the OLE period will be presented in an addendum to the primary analysis CSR, and/or a separate OLE period CSR.

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 (CIOMS) International Ethical Guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

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

Any 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, 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 the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- 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 utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - 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 the sponsor will review and then file it along with the Investigator's Brochure 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 Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency 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 one year after completion of the study.

A 3 INFORMED CONSENT PROCESS

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be reconsented 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.

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

The ICF will contain a separate section that briefly addresses the qualitative patient interview sub-study. The Investigator or authorised designee will explain the objectives of the 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. If patients in the countries participating in the qualitative patient interview sub-study indicate that they are interested in participating in the sub-study, the patient will then complete a separate sub-study ICF addendum.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for 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, 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 procedures. The Investigator or authorised 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.

A 4 DATA PROTECTION

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

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

The patient must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

The participant must be informed that in some cases their data may be pseudonymised. The General data Protection Regultaion (GDPR) defines pseudonymisation as the processing of

personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

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

- In compliance with applicable laws, the Data Controller[4] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.

- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

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

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.

- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and

- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).

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

- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.

- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.

- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.

- If a personal data breach involving an AstraZeneca's representative device (i.e Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.

- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 DISSEMINATION OF CLINICAL STUDY DATA

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

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

A 6 DATA QUALITY ASSURANCE

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

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

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s).

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(s).

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, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 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 7 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 CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Monitoring Plan.

A 8 STUDY AND SITE START AND CLOSURE

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

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

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

A 9 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 EVENT DEFINITIONS AND ADDITIONAL SAFETY INFORMATION

B 1 DEFINITION OF ADVERSE EVENTS

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

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

B 2 DEFINITIONS OF SERIOUS ADVERSE EVENT

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 abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above

AEs for malignant tumours reported during a study should generally be assessed as **serious** AEs. If no other seriousness criteria apply, the ‘important medical event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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 emergency room is not in itself a 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 emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale

1 Mild (awareness of sign or symptom, but easily tolerated)

2 Moderate (discomfort sufficient to cause interference with normal activities)

3 Severe (incapacitating, with inability to perform normal activities).

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

B 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?
- Dechallenge 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.
- Rechallenge experience: Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- 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 disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 MEDICATION ERROR, DRUG ABUSE, AND DRUG MISUSE

Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for an 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 error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognising 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, for example, 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 IRT/RTSM errors)
- Wrong drug administered to the patient (excluding IRT/RTSM errors)

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

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

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 IP 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 IP for medicinal purposes outside of the authorised product information, or for unauthorised IPs, 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 OF BIOLOGICAL SAMPLES

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

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

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

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

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

C 2 WITHDRAWAL OF INFORMED CONSENT FOR DONATED BIOLOGICAL SAMPLES

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

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

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

C 3 INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION 6.2 GUIDANCE DOCUMENT

Labelling and shipment of biohazard samples

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

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

Appendix D 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. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

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

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

Genetic research may consist of the analysis of the structure of the patient's DNA, 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.

The samples will be retained while research on benralizumab continues, but no longer than 15 years or other period as per local requirements.

D 2 GENETIC RESEARCH PLAN AND PROCEDURES

Selection of Genetic Research Population

Study selection record

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

Inclusion Criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

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

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

Withdrawal of Consent for Genetic Research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.3 of the main CSP and Appendix C 2.

Collection of Samples for Genetic Research

The blood sample for genetic research will be obtained from the patients at baseline (Visit 2), 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, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at baseline (Visit 2), 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's 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 either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

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

Ethical and Regulatory Requirements

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

Informed Consent

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

Patient Data Protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

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

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP may be prepared where appropriate.

Appendix E ANAPHYLAXIS: DEFINITION, SIGNS, SYMPTOMS AND MANAGEMENT

E 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 non-immunologic (Johansson et al 2004). The clinical criteria for defining anaphylaxis for this study are listed in Section E 2 of this Appendix. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section E 3 of this Appendix. Appropriate drugs, such as 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 as soon as possible after the event, at 90 ± 30 minutes after the event, and at discharge; analysis for serum tryptase will be performed at a local laboratory. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

E 2 CLINICAL CRITERIA FOR DEFINING ANAPHYLAXIS 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) **and at least one of the following:**
   (a) Respiratory compromise (eg, dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that 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 PEF, hypoxemia).

(c) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).

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

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours). For adults, this corresponds to a systolic blood pressure of less than 90 mm Hg or a 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.

E 3 SIGNS AND SYMPTOMS AND MANAGEMENT OF ACUTE ANAPHYLAXIS

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

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

E 4 MANAGEMENT OF ACUTE ANAPHYLAXIS

E 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.

E 4.2 POSSIBLY APPROPRIATE, SUBSEQUENT MEASURES DEPENDING ON RESPONSE TO EPINEPHRINE

(a) Place patient in recumbent position and elevate lower extremities

(b) Establish and maintain airway

(c) Administer oxygen

(d) Establish venous access

(e) Normal saline IV for fluid replacement

E 4.3 SPECIFIC MEASURES TO CONSIDER AFTER EPINEPHRINE INJECTIONS, WHERE APPROPRIATE

(a) Consider epinephrine infusion

(b) Consider H1 and H2 antihistamines

(c) Consider nebulised β2 agonist (eg, albuterol [salbutamol]) for bronchospasm resistant to epinephrine

(d) Consider systemic corticosteroids

(e) Consider vasopressor (eg, dopamine)

(f) Consider glucagon for patient taking β-blocker

(g) Consider atropine for symptomatic bradycardia

(h) Consider transportation to an emergency department or an intensive care facility

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary

Adapted from Kemp et al 2008.

Appendix F 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 medical devices/combination products provided for use in the study. See Section 6.1.2 for the list of sponsors combination products.

F 1 DEFINITION OF MEDICAL DEVICE AE AND ADE

Medical Device AE and ADE Definition

- A medical device AE is any untoward medical occurrence in a clinical study 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.
- Adverse Device Effect 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.

F 2 DEFINITION OF MEDICAL DEVICE SAE, SADE AND USADE

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 pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Chronic disease (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.

USADE Definition

- A USADE (also identified as UADE in 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 (see Section 2.3).

F 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. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

F 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 sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all patient identifiers, except for the patient number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any protocol revision 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 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 and/or Product Information for marketed products in their assessment.
- For each AE/SAE/medical device deficiency, the investigator must document in the medical notes that they have reviewed the AE/SAE/medical device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor. However, it is very important that

the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor.

- The investigator may change their 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 5 different levels of causality. AstraZeneca and the investigators will use the following definitions to assess the relationship of the SAE to the investigational device[5] or procedures.

1 Not related: Relationship to the device or procedures can be excluded when:

(a) The event has no temporal relationship with the use of the investigational device or the procedures;

(b) 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;

(c) 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;

(d) The event involves a body-site or an organ not expected to be affected by the device or procedure;

(e) 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);

(f) 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 concurrent illness/clinical condition or/and an effect of another medical device, drug, or

[5] Investigational device: Any device object of the clinical investigation, including the comparators.

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:

(a) The event is a known side effect of the product category the investigational device belongs to or of similar devices and procedures;

(b) The event has a temporal relationship with investigational device use/application or procedures;

(c) The event involves a body-site or organ that

(d) the investigational device or procedures are applied to;

(e) the investigational device or procedures influence;

(f) The serious event follows a known response pattern to the investigational device (if the response pattern is previously known);

(g) 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 the serious event (when clinically feasible);

(h) 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;

(i) Harm to the patient is due to error in use;

(j) The event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order 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 sposnor 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 healthcare professionals.
- If a patient dies during participation in the study or during a recognised follow-up period, the investigator will provide sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the original form used to report the deficiency.

- The investigator will submit any updated SAE data to sponsor **within 24 hours** of receipt of the information.

F 5 REPORTING OF MEDICAL DEVICE SAES AND SADES

- All medical device SAEs will be reported in accordance with Section 8.4.1.

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 8.4.1, the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form will be used to capture details of the device and related deficiency.
- Email transmission of the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form is the preferred method to transmit this information to the Study Clinical Lead/SAE coordinator.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the AstraZeneca Clinical Study Medical Device/Device Constituent Report Form within the designated reporting time frames.
- AstraZeneca will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.

Appendix G 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 notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AZ Study Physician. If patient testing is performed as a result of the public health crisis, results may be documented for this study.

G 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 and should be obtained prior to performing the procedures described in Sections F2 to F5. Local and regional regulations and/or guidelines regarding consent/reconsent 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 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 consent/reconsent should be avoided.

G 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 SoA (Table 1) the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another

opportunity to re-screen a patient in addition to that detailed in Section 5.5.1 (Rescreening**).** The procedures detailed in Section 5.3 (Criteria to be Confirmed/Reconfirmed at Baseline) must be undertaken to confirm eligibility using the same screening/ enrolment number as for the patient.

G 3 HOME OR REMOTE VISIT TO REPLACE ON-SITE VISIT (WHERE APPLICABLE)

A qualified HCP from the study site or TPV service will visit the patients home / or other remote location as per local Standard Operating Procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP).

G 4 TELEMEDICINE VISIT TO REPLACE ON-SITE VISIT (WHERE APPLICABLE)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow assessments such as adverse events, concomitant medications, BVAS/VDI, OCS usage to be reported and documented.

G 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 regulations/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures patient 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.

G 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.

G 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.

G 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, or by the patient themselves.

Appendix H RECOMMENDED PREDNISOLONE/PREDNISONE TAPERING SCHEDULE FROM WEEK 4 (VISIT 4)

Baseline prednisolone/prednisone dose

Taper week	45-50 mg	40-44 mg	35-39 mg	30-34 mg	25-29 mg	20-24 mg	17.5-19.5 mg	15-17 mg	12.5-14.5 mg	10-12 mg	9.0-9.5 mg	8.0-8.5 mg	7.5 mg
1	40	35	30	25	20	17.5	15	12.5	10	8	8	6	6
2	40	35	30	25	20	17.5	15	12.5	10	8	8	6	6
3	30	30	20	20	17.5	15	12.5	10	8	6	6	5	5
4	30	30	20	20	17.5	15	12.5	10	8	6	6	5	5
5	20	20	17.5	17.5	15	12.5	10	8	6	5	5	4	4
6	20	20	17.5	17.5	15	12.5	10	8	6	5	5	4	4
7	17.5	17.5	15	15	12.5	10	8	6	5	4	4		
8	17.5	17.5	15	15	12.5	10	8	6	5	4	4		
9	15	15	12.5	12.5	10	8	6	5	4				
10	15	15	12.5	12.5	10	8	6	5	4				
11	12.5	12.5	10	10	8	6	5	4					
12	12.5	12.5	10	10	8	6	5	4					
13	10	10	8	8	6	5	4						
14	10	10	8	8	6	5	4						
15	8	8	6	6	5	4							
16	8	8	6	6	5	4							
17	6	6	5	5	4								
18	6	6	5	5	4								
19	5	5	4	4									
20	5	5	4	4									
21	4	4											
22	4	4											

Once a subject has achieved a dose of 4 mg/day OCS, the investigator should continue tapering downwards, if clinically warranted, at dose increments of 0.5-1.0 mg every 2 weeks

Appendix I ADRENAL CRISIS GUIDELINES

Management of Acute Adrenal Insufficiency Secondary to Glucocorticoid Withdrawal

National or local guidelines for the management of acute adrenal insufficiency (adrenal crisis), where they exist, should be followed. The following guidelines have been adapted from the guidelines of the Society for Endocrinology[6]. They are intended for guidance subject to clinical judgement only.

The possibility of acute adrenal insufficiency should be considered in any acutely unwell patient undergoing withdrawal of chronic systemic corticosteroid treatment.

Recognition

- Clinical signs and symptoms:
  - Fatigue, lack of energy, weight loss
  - Low blood pressure, postural dizziness and hypotension (≥ 20 mmHg drop in systolic blood pressure from supine to standing position), dizziness, collapse, and in severe cases hypovolaemic shock
  - Abdominal pain, tenderness and guarding, nausea, vomiting
  - Fever
  - Confusion, somnolence, in severe cases delirium or coma
  - Back and leg cramps/spasms may be reported
- Lab findings:
  - Hyponatraemia
  - Pre-renal failure (increased serum creatinine due to hypovolaemia)
  - Normochromic anaemia, sometimes also lymphocytosis and eosinophilia
  - Hypoglycaemia

Management

- **Hydrocortisone** (immediate bolus injection of 100 mg hydrocortisone IV or IM followed by continuous IV infusion of 200 mg of hydrocortisone per 24 hours (alternatively 50 mg of hydrocortisone per IV or IM injection every 6 hours)
- **Rehydrate** with IV 0.9% sodium chloride in hypotensive patients. The rate and total volume of infusate must be decided on an individual patient basis with continuous

[6] Arlt W. Society for Endocrinology Clinical Committee. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect 2016;(5):G1-G3

monitoring for fluid overload. Correction of hyponatremia must be according to relevant local guidelines

- Consider any other potential precipitating factors (in addition to corticosteroid withdrawal), eg, infection; investigate and treat as appropriate.

Contact an endocrinologist at an early stage to advise on ongoing management.

Appendix J ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire (6-item version)
ADA	Anti-drug antibodies
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANCA(s)	Anti-neutrophil cytoplasmic antibody (ies)
APFS	Accessorised prefilled syringe
AST	Aspartate aminotransferase
BD	Bronchodilator
BMI	Body mass index
BVAS	Birmingham Vasculitis Activity Score
CI	Confidence interval
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTIS	Clinical Trial Information System
CYC	Cyclophosphamide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EGPA	Eosinophilic granulomatosis with polyangiitis
EOT	End of treatment
ePRO	Electronic patient-reported outcome
EU	European Union
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FEV1	Forced expiration volume in 1 second
FSH	Follicle stimulating hormone
FU	Follow-up
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCG	Human Chorionic Gonadotropin
HCP	Health Care Professional
HES	Hypereosinophilic syndrome

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
International Coordinating Investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally
Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG1	Immunoglobulin G, subclass 1
IgG1κ	Immunoglobulin G1, kappa isotype
IL	Interleukin
IL-5Rα	Interleukin-5 receptor alpha
IM	Intramuscular
IP	Investigational product
IPD	Investigational product discontinuation
IRB	Institutional review board
IV	Intravenous(ly)
IRT	Interactive response technology
LABA	Long-acting β_2 agonist
LAMA	Long-acting muscarinic antagonist
mAb	Monoclonal antibody
MCS	Psychometrically-based mental health component summary score (in SF-36v2 questionnaire)
MMRM	Mixed-effect model for repeated measures
MoA	Mechanism of action
MPO	Myeloperoxidase
nAb	Neutralising antibodies
NI	Non-inferiority
NYHA	New York Heart Association
OCS	Oral corticosteroids
OLE	Open-label extension
PBMC(s)	Peripheral blood mononuclear cell(s)
PCS	Psychometrically-based physical health component summary score (in SF-36v2 questionnaire)

Abbreviation or special term	Explanation
PD	Pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PNV	Predicted normal value
PK	Pharmacokinetic(s)
PR3	Proteinase 3
PRO(s)	Patient-reported outcome(s)
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QTc	QT interval corrected
QTcF	QT interval corrected by Fredericia's
RNA	Ribonucleic acid
RoW	Rest of World
RTSM	Randomisation and trial supply system management
SABA	Short acting β_2 agonist
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SADE	Serious adverse device effect
SC	Subcutaneous(ly)
SF-36v2	Short Form 36-Item Health Survey (version 2)
SNOT-22	Sino-Nasal Outcomes Test 22
SoA	Schedule of assessments
SOP	Standard Operating Procedure
SSQ	Sino-nasal Symptoms Questionnaire
SUSAR	Suspected unexpected serious adverse reactions
TPV	Third Party Vendor
ULN	Upper limit of normal
US	United States
VDI	Vasculitis Damage Index
WBC	White blood cells
WOCBP	Women of child-bearing potential
WPAI	Work Productivity and Activity Impairment Questionnaire
WPAI-GH	Work Productivity and Activity Impairment Questionnaire - General Health

Appendix K COUNTRY-SPECIFIC REQUIREMENTS

K 1 FRANCE (VERSION 1.0, 29 JULY 2019)

Reason for Addendum:

A local EGPA cohort was initiated in France meeting the definition of "interventional clinical study" without any administration of investigational product.

In order to give a chance to patient participating to this cohort to be included in D3253C00001 clinical trial, an exception needs to be added to the current exclusion criterion #18.

Centres Affected by the Addendum

All French sites

Change text is indicated in bold italic underlined where applicable.

Section of Protocol Affected

Section 5.2 - Exclusion Criterion #18

Previous Text:

18. Patient is currently participating in any other interventional clinical study.

Revised Text:

18. Patient is currently participating in any other interventional clinical study ***(with the exception of "registry"/ "cohort" trials which may include periodic biological sampling and/or patient questionnaires but in which no other un-licenced investigational product is administered).***

K 2 BELGIUM (VERSION 1.0, 31 OCTOBER 2019)

Centres Affected by the CSP Country Addendum:

This Local Addendum affects all Centres in Belgium.

Reason for Use of CSP Country Addendum:

The global CSP requires that the background standard of care corticosteroid treatment consists of either prednisone or prednisolone for all patients. In addition, the OCS doses should be tapered as described in the CSP and the study protocol provides a tapering scheme for guidance of tapering steps.

The primary endpoint as described in the global study protocol is the proportion of patients with relapsing or refractory EGPA, achieving remission, defined as BVAS=0 and OCS dose ≤ 4 mg/day (Main Remission definition) at both weeks 36 and 48.

Prednisone and prednisolone are not commercially available in Belgium (unless in magistral preparation) and are therefore not usually used in Belgium as OCS treatment in EGPA patients. Therefore, the use of methylprednisolone as background OCS treatment will be allowed for Belgian sites. Methylprednisolone is the standard of care used in Belgium to treat EGPA patients who require OCS.

The conversion factor for prednisone/prednisolone to methylprednisolone is 0.8 (Source: The online conversion calculator https://clincalc.com/corticosteroids/ for conversion of other OCS doses or other OCS products):

Estimated OCS Dose Therapy Equivalence:

Oral Corticosteroid	**Approximate equivalence dose**
Prednisone	10 mg
Prednisolone	10 mg
Methylprednisolone	8 mg

Conversion table based on above-mentioned 'Estimated OCS Dose Therapy Equivalence':

Prednisone/Prednisolone	**Approximate equivalence dose methylprednisolone**
50 mg	40 mg
45 mg	36 mg
40 mg	32 mg
35 mg	28 mg
30 mg	24 mg
25 mg	20 mg
20 mg	16 mg
17.5 mg	14 mg
15 mg	12 mg
12.5 mg	10 mg
10 mg	8 mg
8 mg	6.4 mg
5 mg	4 mg
4 mg	3.2 mg
2.5 mg	2 mg
2 mg	1.6 mg
1 mg	0.8 mg
0.5 mg	0.4 mg

As per the Clinical Study Protocol (section 6.5.1), patients will be required to continue their stable OCS dose (if necessary, upward adjustments are permitted for clinical management of the patient) between baseline (Visit 2) and Week 4 (Visit 4). Week 4 post-baseline (Visit 4) onwards if the patient's BVAS=0 their OCS dose should be tapered downwards according to standard of care practice. If the BVAS ≠ 0, the Investigator may taper the patient's OCS downwards at his/her clinical discretion. A recommended tapering schedule is provided in Appendix H. The tapering schedule provided in Appendix H has reductions of:

- 10 mg prednisone/prednisolone (equivalence dose of 8 mg methylprednisolone)
- 5 mg prednisone/prednisolone (equivalence dose of 4 mg methylprednisolone)
- 2.5 mg prednisone/prednisolone (equivalence dose of 2 mg methylprednisolone)
- 2 mg prednisone/prednisolone (equivalence dose of 1.6 mg methylprednisolone)
- 1 mg prednisone/prednisolone (equivalence dose of 0.8 mg methylprednisolone)
- 0.5 mg prednisone/prednisolone (equivalence dose of 0.4 mg methylprednisolone)

Current presentations in Belgium include methylprednisolone 32 mg, 16 mg & 4 mg tablets. The 2 mg, 0.8 mg, and 0.4 mg tablets methylprednisolone are not available. The 4 mg tablet methylprednisolone can be divided in four equal pieces. Local practice and guidelines will be used for the lower doses of methylprednisolone.

In all sections of the CSP please replace the previous text by the revised text below:

Previous text:

Prednisone/prednisolone
0.5 mg / 1 mg / 2 mg / 2.5 mg / 4 mg / 5 mg / 8 mg / 10 mg / 12.5 mg / 15 mg / 17.5 mg / 20 mg / 25 mg / 30 mg / 35 mg / 40 mg / 45 mg / 50 mg

Revised text:

Methylprednisolone
0.4 mg / 0.8 mg / 1.6 mg / 2 mg / 3.2 mg / 4 mg / 6.4 mg / 8 mg / 10 mg /12 mg / 14 mg / 16 mg / 20 mg / 24 mg / 28 mg / 32 mg / 36 mg / 40 mg

Appendix L PROTOCOL VERSION HISTORY

The Summary of Changes Table for the current version is located directly before the Table of Contents.

L 1 AMENDMENT 4 (VERSION 5.0): 11 APRIL 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, because it may affect the safety or physical/mental integrity of patients or the scientific value of the study.

Overall Rationale for the Amendment

The primary rationale for this protocol amendment is to extend the intended duration of the open-label extension (OLE), to add an additional objective of clinical benefit rate, consistent with that reported in Steinfeld et al 2019 to the objectives table, and to add additional steroid reduction endpoints to the existing oral corticosteroid objective. Furthermore, the protocol has been amended to comply with the requirements/legislation due to changes in EU Clinical Trial Regulation, regulatory requirements, inspection outcomes, and protocol template and to incorporate changes due to local requirements. Minor editorial changes have also been made throughout the protocol.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
1.1 Schedule of Assessments (Table 2)	Reduced frequency of assessments for weight and urine pregnancy test (dipstick) and removed brief physical examination from all visits except from unscheduled visits.	To reduce patient/site burden.	Non-substantial
1.1 Schedule of Assessments (Table 3) and (Table 4)	Increased visits that can be done remotely, reduced frequency of assessments for vital signs, serum chemistry, and urine pregnancy test (dipstick), removed assessments for weight from all visits except unscheduled and IPD/EOT visits, removed assessments for health resource use and complete physical examination from all visits except IPD/EOT visit, and removed assessments for spirometry, brief physical examination, ESR, and	To reduce patient/site burden. Spirometry, health resource use, ESR, and CRP are not part of the OLE Year 2 and 3 objectives.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	CRP from all visits except unscheduled visits.		
1.1 Schedule of Assessments (Table 5)	Added a new Schedule of Assessments presenting the assessments to be performed during Year 4 onwards in the OLE.	To ensure continuity of treatment for patients who would end Year 3 of the OLE before all patients have been allowed at least one year of treatment with open-label benralizumab.	Substantial
1.2 Synopsis (Table 7) and Statistical Methods 3 Objectives and Endpoints (Table 9) 9.4.1 Efficacy Analyses	Changed one secondary objective and clarified one corresponding secondary endpoint and added corresponding secondary endpoints: Changed objective: To assess the effect of benralizumab on ~~average daily dose of~~ corticosteroid dose required during Weeks 48 through 52 ~~in patients receiving benralizumab~~ compared to mepolizumab Clarified and added new endpoints: Based on the average daily prednisolone/prednisone dose during Weeks 48 through 52: Proportion of patients in each category ~~of average daily prednisolone/prednisone dose during Weeks 48 through 52 using the following categories~~: 0 mg; > 0 to ≤ 4 mg; > 4 to ≤ 7.5 mg, and > 7.5 mg (clarified). Proportion of patients in each category of percent reduction from baseline: no reduction or withdrawal from treatment; < 25% reduction; 25 to < 50% reduction; 50 to < 75% reduction; 75 to < 100% reduction; 100% reduction (new). Proportion of patients with ≥ 50% reduction from baseline (new).	To assess the steroid sparing effect of treatment.	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	Proportion of patients with 100% reduction from baseline (new). Proportion of patients with ≤ 4 mg in average daily dose (new).		
1.2 Synopsis (Table 7) and Statistical Methods 3 Objectives and Endpoints (Table 9)	Added a secondary objective: To assess the clinical benefit of benralizumab compared to mepolizumab. AND Added corresponding endpoints: Proportion of patients who have achieved any clinical benefit when meeting any of the criteria below. Proportion of patients who have achieved complete response when meeting all of the criteria below. Remission (defined as BVAS = 0 and prednisolone/prednisone dose ≤ 4 mg/day) at any time during the double-blind treatment period ≥ 50% reduction in average daily prednisolone/prednisone dose during Weeks 48 through 52 EGPA relapse free during the double-blind treatment period. Analysis will be repeated for the supportive remission definition.	To combine current endpoints to assess clinical benefit in a clinically relevant way (Steinfeld et al 2019).	Substantial
1.1 Schedule of Assessments (Table 2) 1.2 Synopsis (Table 8) and Statistical Methods 3 Objectives and Endpoints (Table 10) 8.8.2 Mandatory Biomarker Samples 8.8.3 Nasal Secretions (Mandatory at Selected Sites)	Removed 'nasal secretions' from the SoA Year 1 of OLE. Removed whole blood for PAXgene RNA, nasal secretions, and tissue biopsies and sputum (mechanistic sub-study only) from the exploratory biomarker endpoints in the OLE. Updated the sections which describes the collection of these samples.	These biomarkes are only collected during the double-blind period.	Non-substantial
1.2 Synopsis, Study Period	Updated the estimated date of last patient completed from first quarter 2024 to third quarter of 2024.	This is the current estimate of when the last randomised patient will	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
4.4 End of Study Definition		complete one year of treatment with open-label benralizumab in the OLE.	
1.2 Synopsis, Statistical Methods 4.1 Overall Design	Clarified which data will be included in the primary analysis and updated definition of final database lock.	Clarifications.	Non-substantial
4.4 End of Study Definition	Clarified definition of the end of study according to EU and FDA requirements.	To comply with regulatory requirement(s) (eg, EU CTR) and global company requirement.	Non-substantial
5.2 Exclusion Criteria	Added an exception to exclusion criterion #18 per local CSP addendum in France.	To consolidate local protocol addendum with global study protocol.	Non-substantial.
6.1.2 Medical Devices Including Combination Products with a Device Constituent 8.4.4 Medical Device Deficiencies Appendix F Medical Device AEs, ADEs, SAEs, SADEs, USADEs, and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added section regarding device constituents. Updated current section regarding device deficiencies. Added a new Appendix describing the processes to follow if device deficiencies fulfill definition of an AE/SAE.	To comply with regulatory requirement(s) (eg, EU CTR) and global company requirement.	Non-substantial
6.2.1 Preparation and Handling of IP 8.2.1.1 Pregnancy Test	Clarified that no urine pregnancy test (dipstick) will be performed during those visits in the OLE which can be done remotely.	To reduce patient/site burden.	Non-substantial
6.2.4 Conditions Requiring Investigational Product Administration Rescheduling	The requirement regarding patient being febrile within 72 hours prior to the IP administration has been deleted.	This is not a requirement anymore and has been removed from the Sponsor's Project Specific Safety Requirements	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
6.5 Concomitant Therapy (Table 12)	Removed the words 'or investigational' from the last row.	Investigational products are prohibited without exeptions, according to Exclusion criterion 18.	Non-substantial
8.3.1 Method of Detecting Adverse Events and Serious Adverse Events	Removed the section.	Section 8.3.1 is redundant as the process for collecting adverse events in AstraZeneca clinical studies is described in Section 8.3.5 Adverse Events Based on Signs and Symptoms	Non-substantial
8.4.3 Overdose	Moved text regarding reporting of overdose to Section 8.4.6.	To align with current Transcelerate unified protocol template.	Non-substantial
8.4.5 Medication Error, Drug Abuse, and Drug Misuse Appendix B4 Medication Error, Drug Abuse, and Drug Misuse	Added subheadings covering timelines and definitions of medication error, drug abuse, and drug misuse.	To comply with CT-3 Regulation and corporate safety CAPA.	Non-substantial
8.5.2 Storage and Destruction of Pharmacokinetic Samples	Updated the retention of PK samples to a period of 6 months from bioanalytical report finalisation.	To comply with regulatory requirement(s) (eg, EU CTR) and global company requirement.	Non-substantial
9.4.1.1 Calculation or Derivation of Variables for Efficacy Analyses	Added derivation of the new endpoints.	To present how the new endpoints will be derived.	Substantial
9.4.1.2 Methods for Efficacy Analyses	Added the new endpoints to the secondary endpoint statistical analyses.	To present how the new endpoints will be analysed.	Substantial
9.4.1.2 Methods for Efficacy Analyses	Added two factors (ie, BMI and ANCA-positive status) to the exploratory subgroup analyses.	These factors have been specified in the SAP.	Non-substantial
Appendix A1 Regulatory and Ethical Considerations	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches".	To comply with regulatory requirement(s) (eg, EU CTR) and global company requirement.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
Appendix A6 Data Quality Assurance	Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations.	To comply with regulatory requirement(s) (eg, EU CTR) and global company requirement.	Non-substantial
Appendix K Country-specific Requirements	Added a new appendix to present changes as per local CSP addendums in France and Belgium and added references to the appendix where applicable in the protocol.	To consolidate local protocol addendums with global study protocol.	Non-substantial
Appendix L Protocol Version History	Moved previous amendment details to a new protocol version history appendix.	To align with current Transcelerate unified protocol template.	Non-substantial
Throughout	Minor editorial changes	To clarify text, improve consistency and organization, and align with current Transcelerate unified protocol template and Sponsor style conventions.	Non-substantial

AE, adverse event; ANCA, anti-neutrophil cytoplasmic antibody; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; CAPA, corrective and preventive action; CRP, C-reactive protein; CSP, clinical study protocol; CTR, Clinical Trial Regulation; EGPA, eosinophilic granulomatosis with polyangiitis; EOT, end of treatment; ESR, erythrocyte sedimentation rate; EU, European Union; FDA, Food and Drug Administration; IP, investigational product; IPD, IP discontinuation; OCS, oral corticosteroids; OLE, open-label extension; PK, pharmacokinetics; RNA, ribonucleic acid; SAE, serious adverse event; SoA, Schedule of Assessments; SAP, statistical analysis plan.

L 2 AMENDMENT 3 (VERSION 4.0): 24 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 patients 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 during the OLE of the study.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
1.1 Schedule of Assessments (Table 2, Table 3, and Table 4) 6.1.1 Investigational Products 8.2.1.1 Pregnancy Test 6.2.1 Preparation and Handling of IP 6.2.3 Optional At-home or Remote-location Investigational Product Administration	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: V24, V25, V27, V28, V31, V32, V34, V35, V37, V38, V40, V41, V44, V45, V47, V48, V50, V51, V53, V54). Frequency of some on-site 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 administration revised to accommodate the option of IP self-administration.	To reduce patient burden and allow flexibility during the OLE.	Non-substantial
1.1 Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4) 1.3 Schema 4.1 Overall Design 6.5.2 Other Concomitant Treatment 7.1 Discontinuation of Study Treatment (including all subsections) 7.1.1.2 Discontinuation of Treatment on Notification of Closure of Study 7.3 Withdrawal From the Study	Removed the FU visit 8 weeks after last dose of IP.	To decrease patient burden by removing the additional FU visit; patients will have a follow-up visit 4 weeks after last dose of IP (IPD visit) and will be followed until the end of the DB period regardless of whether they continue IP	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
1.1 Schedule of Assessments – Double-blind Treatment Period (Table 1)	Added visit window of ± 3 days to Visit 2, Visit 9, and Visit 10.	Visit windows had mistakenly been deleted/omitted.	Non-substantial
	Added footnote that at Visit 17, IP will only be administered to patients who are entering the OLE.	To clarify.	Non-substantial
	Footnote stating that "Spirometry is required as part of the sputum induction procedure as described in the separate laboratory manual" moved from the induced sputum assessment at V15 to the induced sputum row header.	Correction as footnote applies to all induced sputum assessments.	Non-substantial
	Added row “Administer open-label benralizumab at the site (first dose of OLE)” with X at V17. Renamed “IP administration row” to “Administer blinded IP at the site” and removed X at V17.	To clarify that the IP dose on V17 is only for patients entering the OLE.	Non-substantial
	Added spirometry assessment to IPD visit.	To ensure spirometry is performed if patient discontinues IP.	Non-substantial
	Removed troponin assessment from unscheduled visit.	Troponin had been mistakenly been added to the unscheduled visit during the DB period.	Non-substantial
	Revised footnote regarding ePRO at Visit 2 to “Visit 2 must be confirmed on the handheld device by a trained site personnel prior to baseline ePRO questionnaires completion by the patient. Sites should ensure patients complete all baseline ePRO assessments. For subsequent visits, the site should confirm the visit either on the web portal Study Works or on the device.”	For clarification.	Non-substantial
1.1 Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4)	Brief physical examination, vital signs, and ePRO assessments changed to only be mandatory if the unscheduled visit is to assess a potential EGPA relapse.	To reduce patient burden; these assessments may not be required if the unscheduled visit is not to assess a relapse.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
1.1 Schedule of Assessments (Table 1, Table 6)	Added "and confirm compliance" to the row "Administer/(re)train /review ePRO assessments" to Table 1. Added a footnote to this assessment at Visit 2 stating that "It should be ensured at Visit 2 that the visit is confirmed in the handheld device and that baseline ePRO questionnaires are filled out by the patient" to Table 1. Deleted row "Return ePRO device" to Table 1. Deleted footnote "Only if the patient discontinues use of ePRO device at the IPD visit" from Table 3.	To ensure ePRO compliance is confirmed and encourage continued ePRO assessements throughout the study.	Non-substantial
1.1 Schedule of Assessments (Table 2)	Removed mandatory assessments of serum for biomarkers, nasal secretions, tissue sample, induced sputum from unscheduled visits	To reduce patient burden.	Non-substantial
	Added haematology assessments to Visits 19 and 21.	To better characterise PD parameters in the beginning of the OLE period.	Non-substantial
	Removed CRP assessments from Visits 20 and 22.	To reduce patient burden by reducing the number of blood draws needed.	Non-substantial
	Deleted row "Return ePRO device".	Redundant.	Non-substantial
1.1 Schedule of Assessments (Table 3 [formerly Table 14 in Appendix H], Table 4 [formerly Table 15 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
1.2 Synopsis Section 4.4 End of Study Definition	Revised estimated date or last patient completed to first quarter 2024.	To update the estimated date following delays in patient enrolment due to the Covid-19 pandemic.	Non-substantial
1.2 Synopsis (Table 8) 3 Objectives and Endpoints (Table 10)	Added footnote to the variable "Remission, relapse (as defined in Table 6/8), OCS use" stating that the definition in Table 6/8 is only applicable during the first year of the OLE. From the second	To clarify the definitions of remission and relapse during the OLE.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	year, the definitions of remission and relapse will be based on the Investigator's overall clinical assessment.		
4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Added clarification that at-home IP administration would only be applicable during the OLE period.	At-home IP administration not be possible during the DB period.	Non-substantial
5.2 Exclusion Criteria	Removed the text "A positive urine test result must be confirmed with a serum pregnancy test, before proceeding with further IP dosing. If serum test is positive, the patient should be excluded."	Redundant; covered in inclusion criterion 8 and in instructions for pre-IP administration pregnancy tests in Section 6 and Section 8.	Non-substantial
5.3.3 Criteria to be Confirmed Prior to Commencing OLE at Visit 17	Revised "Patients that enter the OLE must not have been randomised into the trial in error" to "If a patient had been randomised in error but the Investigator considers participation in the OLE to be safe and in the best interests of the patient, the Investigator should discuss the potential entry of the patient into the OLE with the AstraZeneca study physician".	To introduce the possibility of patients randomised in error to enter the OLE when considered safe and in the best interests of the patient.	Non-substantial
6.2.2.5 After Investigational Product Administration 8.4.6 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
6.3.1 Patient Enrolment and Randomisation - Double-blind Period	Added to the Visit 2 subsection to confirm Visit 2 on the handheld device prior to ePRO questionnaire completion by the	To ensure that the baseline ePRO questionnaires are filled out.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	patient and to ensure patients complete all baseline ePRO assessments.		
6.5 Concomitant Therapy	Blood products and marketed or investigational biologic products redefined from prohibited to restricted medications.	To make it possible for patients who have to use such therapies to treat co-morbidities (if medically indicated with no alternative treatment available) to continue on IP in some specific cases.	Non-substantial
	Revised the instructions regarding the use of prohibited medications to state that "In the event a prohibited medication is used, a conversation between the Investigator and the AstraZeneca study physician should take place to determine whether continuation on IP or discontinuation of IP is in the best interest of the patient."	To remove the requirement that IP must be withdrawn if a prohibited medication is used for cases when continuing IP may be in the best interest of the patient.	Non-substantial
7.1 Discontinuation of Study Treatment	Revised "Patients will be discontinued from IP in the following situations" to "Patients may be discontinued from IP in the following situations". Revised "Increasing the dose of, or initiating, immunosuppressive therapy" to "Increasing the dose of, or initiating, immunosuppressive therapy for EGPA". Deleted "Use of prohibited concurrent medication (ie, as noted in Section 6.5) including CYC" as a study-specific criterion for discontinuation.	To alignment with the changes made to Section 6.5.	Non-substantial
7.1.1.1 Early Discontinuation of Study Treatment	Removed the following text from the information on patients who are willing to continue with scheduled visits after IPD during the DB period: "Ideally, during this time, all ePRO assessments should continue at home, otherwise, return ePRO device at the IPD visit"	To ensure ePRO assessments are continued even if IP has been discontinued and are not considered optional.	Non-substantial
	Added the following text from the information on patients who are unwilling/unable to continue with scheduled visits after IPD during the DB		

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	period: "During this time, all ePRO assessments should continue at home."		
8.1.1 Clinical Outcome Measures 8.1.1.4 Corticosteroid Medication Usage	Revised both sections to state that the ePRO device must be returned at the end of the first year of the OLE period or the patient's final study visit if it occurs before Visit 30 (rather than "at an earlier IPD visit"). Added text to Section 8.1.1: "The site staff should check ePRO completion and compliance at each visit. If compliance with the Corticosteroid Medication Usage ePRO assessment completion drops below 80%, or if the overall compliance with completion of any of the other ePRO assessments (ACQ-6, SSQ, SNOT-22, SF-36v2, PGIS, PGIC, or WPAI-GH) drops below 80%, it is highly recommended that the study site has a discussion with the patient to ask if they are having difficulties and to remind them of the importance of completing ePRO assessments."	To ensure the ePRO device is not returned to the site too early and to provide instructions to help ensure ePRO assessment compliance.	Non-substantial
8.1.1.1 Birmingham Vasculitis Activity Score Section 8.1.1.2 EGPA Remission and Relapse	Removed IPD visit and added "withdrawal from the study" in the description of until when these assessments should be made.	To ensure these assessments are only stopped early if a patient withdraws from the study and not if the patient merely discontinues IP, since patients are encouraged to continue attending study visits even if IP has been discontinued.	Non-substantial
8.1.2 Patient Qualitative Interview Sub-study	Revised description of interview transcripts 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

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
8.2.2 Physical Examinations 8.2.2.2 Brief Physical Examination	Added sentence "For the physical examination, only information on whether the assessment was performed or not is to be recorded in the eCRF" to Section 8.2.2 and removed sentence "For the brief physical examination only information on whether the assessment was performed or not is to be recorded" from Section 8.2.2.2.	To clarify how physical examinations (both brief and full) should be recorded in the eCRF.	Non-substantial
9.4.1.2 Methods for Efficacy Analyses – Analyses of Secondary Endpoints	Revised "The primary analysis will fit a MMRM model using the data collected up to and including the Week 52/IPD 52 time point" to "The primary analysis will fit a MMRM model using the data collected up to and including the Week 52 time point."	Typo; corrected for clarity and consistency with the rest of the CSP and SAP.	Non-substantial
Throughout	"IVRS/IWRS" revised to "IWRS"	IVRS not used in this study.	Non-substantial
Throughout	Minor editorial changes	To clarify text, improve consistency and organization, and align with current templates and style conventions.	Non-substantial

L 3 AMENDMENT 2 (VERSION 3.0): 04 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 to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to the study integrity. The protocol has also been amended to modify spirometry frequency, revise recommendations on investigational product rescheduling, align with current sponsor safety recommendations in studies with benralizumab, clarify exclusion criteria, and revise, add, or remove minor text as needed to increase clarity or correct interpretation of the protocol.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
Section 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 mitigations 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 minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.	Substantial
Section 1.1 Schedule of Assessments (Table 1 and Table 2); Appendix H (Table 14 and Table 15)	Reduced the frequency of spirometry assessments to 12 week intervals (visit 2, 6, 9, 13, 16, 17) in the double blind treatment period. Spirometry is not required at IPD/EOT visit.	To decrease patient and HCP exposure to potential pathogens given COVID-19 pandemic.	Substantial
Section 1.1 Schedule of Assessments in OLE (Table 2); Appendix H (Table 14 and Table 15)	Additional Chemistry assessments added: V21, V26, V31, V33, V39, V44, V46, V52	Chemistry frequency adjusted to monitor disease under study (EGPA).	Non-substantial
Section 1.1 Schedule of Assessments in OLE (Table 2); Appendix H (Table 14 and Table 15)	Align OLE years two and three with OLE year one by removing required troponin assessments at unscheduled visits.	Troponin assessments changed for consistency within the CSP.	Non-substantial
Section 1.1 Schedule of Assessments (Table 1 and Table 2); Appendix	Efficacy assessment: “Record ~~prescribed~~ OCS dose and check compliance “	Modified to match the activity description in the CSP.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
H (Table 14 and Table 15) and corresponding footnote			
Section 5.2 (Exclusion criteria # 14 & 22), Table 13	Added a bullet to #14: "- *Receipt of any other marketed or investigational biologic products within 4 months or 5 half-lives prior to screening, whichever is longer*" Modified #22: "Other investigational *non-biologic* product: receipt of any investigational *non-biologic product* ~~drug~~ within 30 days or 5 half-lives prior to screening (Visit 1) whichever is longer. " Modified bullets beneath Table 10 to align with changes to exclusion criteria #14 & #22.	These changes were implemented to align with updated safety recommendations based on accumulated safety data.	Substantial
Section 5.5.1 Rescreening	"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, etc), patients may potentially be rescreened. These cases must be discussed with the AstraZeneca study physician prior to ~~randomisation~~ *rescreening* and documented in the Investigator study file."	Timing updated to ensure eligibility discussions occur prior to re-screening	Non-substantial
Section 6.2.6 (Conditions Requiring Investigational Product Administration Rescheduling) and Section 6.4 (Treatment Compliance)	In cases of IP re-scheduling, guidance modified to postpone, where possible, rather then than skip IP	Guidance revised to try to prevent missed doses of IP and align with other studies with benralizumab conducted by the sponsor.	Non-substantial
Section 1.2 (Statistical Methods) and Section 9.4.1.2 (Analysis of Secondary Endpoints)	Removed MMRM analysis for PGIS and WPAI to evaluate change from baseline.	The MMRM analysis was erroneously included in the original CSP, and the revised descriptive analysis aligns the	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	Added descriptive statistics for PGIS and WPAI to evaluate change from baseline	analysis approach with other benralizumab studies using these instruments	
Section 8.2.1.2 Serology	Text added: Hepatitis B surface antigen and hepatitis C antibody: To be performed ~~only~~ at screening and Visit 16 Human immunodeficiency virus-1 and HIV-2 antibodies (along with p24 antigen): To be performed ~~only~~ at screening and Visit 16	Text revised to clarify that, as per SoA, HBsAg, hepatitis C antibody and HIV-1 and HIV-2 antibody testing should also occur at Visit 16.	Non-substantial
Section 8.4.2.1 (Maternal Exposure); Section 7.1 (Discontinuation of Study Treatment)	Section 8.4.2.1: Modified text, "If a patient becomes pregnant during the course of the study, IP should be ~~discontinued immediately~~ *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" Section 7.1 Patients will be discontinued from IP in the following situations: Removed bullet "Pregnancy"	These changes were implemented to follow current sponsor safety recommendations in studies with benralizumab	Substantial
Section 8.4.3.1 Benralizumab Overdose	Sentence added: "*For this study, any dose of benralizumab greater than 200 mg will be considered an overdose. "*	Sentence was added to follow current sponsor safety recommendations in studies with benralizumab.	Non-substantial
Section 8.4.4 Devie Constituent Deficiencies	Text revised for: changed title and section contents from "Malfunctions of APFS " to "Device Constituent Deficiencies' Sub-section 8.4.4.1 about SADE reporting added	To ensure compliance with new regulatory guidance.	Non-substantial
Section 8.8.4 Mechanistic Sub-study Sampling	Sentence added: "*Spirometry will be performed as part of the sputum*	Sentence was added to clarify that separate spirometry is part of the	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
	induction procedure as described in the separate laboratory manual."	sputum collection procedure in the sub-study.	
Section 8.11 (Other Assessments and Procedures); Section 8.11.1 (Patient Testing Due to Public Health Crisis)	Section included if patient testing is performed due to public health crisis, the results may be documented for this study.	Section added for test results secondary to public health crisis to be collected allowing for an evaluation of the public health crosis on the study,	Non-substantial
Section 9.4.1.1 Calculation or Deriviation of Variables for Efficacy Analyses	Deleted Baseline section	Detailed definitions of baseline for efficacy and safety endpoints are specified in SAP Section 3.1.2	Non-substantial
Appendix A1 Regulatory and Ethical Considerations	Regulatory and Ethical Considerations text was updated for Regulatory Reporting Requirements for SAEs'	Provision of appropriate statements that describe Regulatory Reporting Requirements for SAEs in AZ studies. Correction to align with CSP template 5.0	Non-substantial
Appendix A5 Dissemination of Clinical Study Data	Text revision: A description of this clinical study will be available on http:// ~~astrazenecaclinicaltrials~~astrazenecagrouptrials.pharmacm.com	Section updated with correct weblink	Non-substantial
Appendix F	Appendix F "Medical device incidents: definition and procedures for recording, evaluating, follow-up and reporting" was removed.	Appendix was not applicable as Benralizumab is not considered a medical device. It is considered a drug device combination and subject to different reporting guidelines	Non-substantial
Appendix F	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigations 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	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial / Non-substantial**
		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 minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.	

Change to the Clinical Study Protocol- Amendment 1: 27 March 2020. Added change which was not documented in the summary of changes with CSP Amendment 1			
Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Table 8	Match placebo text modified from solutions for injections 2mL or 3mL syringes (3 syringes will be used on each dosing occasion) to Matching Placebo: solutions in 1 mL polypropylene syringes (3 syringes will be used on each dosing occasion). Injection volume per syringe is 1 mL. and 3x100 mg vials of powder for solution for injection reconstituted into 3 separate 2mL or 3mL syringes for administration on each dosing occasion. Into 3 × 100 mg vials of powder for solution for injection reconstituted into 3 separate 1 mL polypropylene syringes for administration on each dosing occasion.	Injection volume per syringe is 1 mL to correct inconsistencies in the CSP and mepolizumab leaflet	Non-substantial

L 4 AMENDMENT 1 (VERSION 2.0): 27 MARCH 2020

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 patients nor the scientific value of the study.

Overall Rationale for the Amendment

This protocol (study D3253C00001) has been amended to correct and/or clarify inclusion/exclusion criteria, clarify that nasal secretions will be collected from selected sites, correct text on capping, correct typos, and revise, add, or remove minor text as needed to increase clarity or correct interpretation of the protocol.

Summary of Changes to the Clinical Study Protocol

Section # and Name	Description of Change	Brief Rationale
General (throughout)	• Minor editorial and document formatting revisions • Corrected typos and spelling • Defined, fixed, removed, and added abbreviations as needed • Added or fixed hyperlinks as needed • Added footnotes to several tables to clarify information related to the study protocol • Added numeric scales for patients' scores as needed	• Minor; therefore, these have not been summarised.
Protocol amendment Summary of changes	• Summary of changes in CSP (amendment #1) added in a new section and table	• New section added to summarise amendment #1.
Section 1.1 Schedule of assessments (Table 1, Table 2, and Table 3)	• Updated the SoA for the OLE period, including wording clarifications	• Revisions were made to clarify type of visit and visit location.
Section 1.2 Synopsis (Table 7); Section 3 Objective and endpoints (Table 9); Section 8.1.1.2 EGPA remission and relapse	• Formatted bullets for EGPA relapse: "warranting **any** of the following: ° An increased dose of OCS …; OR ° An increased dose …; OR ° Hospitalisation related …"	• Formatting was corrected to align with EGPA relapse definition in Section 8.1.1.1 and the rest of the CSP.
Section 4.1 Overall design Section 5.5.2 Withdrawal from	• Text revision: "The number of patients with ANCA-positive status or an eosinophil count < 150 cells/µL will be restricted to approximately	• Anti-neutrophil cytoplasmic antibodies status and eosinophil capping should be 10% and 40 %, respectively, of total study

Summary of Changes to the Clinical Study Protocol		
Section # and Name	**Description of Change**	**Brief Rationale**
study due to recruitment cap	10% and 40%, respectively, of the total number of randomised patients."	population instead of per-treatment arm.
Section 5.1 Inclusion criteria	Text revisions: • #4, #4 Japan-only: Added "Investigator-initiated" • #5: Added "Stable doses of OCS other than prednisolone or prednisone may be acceptable, but must be discussed with the AstraZeneca study physician." • #6: Additional text moved here from exclusion criterion #14 • #9 Text added: "WOCBP must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration and ~~within 16~~ for at least 12 weeks after last dose of IP. Highly effective forms of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:	• #4, #4 Japan-only: An orally reported temporary increase of the OCS dose by a patient due to feeling worse is not a "confirmed" relapse. To be confirmed, the relapse must require an increase of the physician-initiated OCS dose (or require initiation/increased dose of immunosuppressive therapy or hospitalisation). • #5: Text was added for particular cases not involving prednisolone or prednisone to clarify that the AstraZeneca study physician should be contacted in all such cases. • #6: Text clarifies requirements for immunosuppressive therapy prior to baseline. • #9: These changes were implemented to follow current sponsor safety recommendations in studies with benralizumab and to ensure compliance with the Clinical Trial Facilitation Group guidance.
Section 5.2 Exclusion criteria	Text revisions: • #2, #3, and #6: revised to "within 3 months prior to screening (Visit 1) and through randomisation (Visit 2) • #8: Parasitic infection: revised to "within 6 months prior to screening (Visit 1) and through randomisation (Visit 2) • #9: Remove information related to Japanese requirements • #14: Abbreviation NB was changed to "Note" and bullet moved to inclusion criterion #6	• #2, #3, #6, and #8: Time window for life or organ-threatening relapse, angina, and parasitic infection prior to study was revised to clarify that this window also includes the time from screening to randomisation. • #9: Change made to apply world-wide consistent criteria • #14: Bullet clarifies requirements for immunosuppressive therapy prior to baseline, which applies to inclusion criterion #6.
Section 5.3.1 Inclusion criteria to be confirmed/reconfirmed at baseline (Visit 2)	• Text in bullet "Liver Function Tests" revised to "obtained at screening (Visit 1) or on repeat testing prior to Visit 2 if applicable"	• Adding "or on repeat testing prior to V2" is for cases where the screening's LFTs were abnormal and retesting was done (this is allowed [see exclusion criterion #24]); if LFTs were

Summary of Changes to the Clinical Study Protocol		
Section # and Name	**Description of Change**	**Brief Rationale**
		retested then the "on repeat testing prior to V2" is applicable.
Section 5.4 Lifestyle restrictions	Text revisions: • Women of child-bearing potential must use a highly effective contraceptive …for at least ~~16~~ 12 weeks ~~(5 half-lives)~~ after last administration of the IP… • Patients must abstain from donating blood, … for ~~16~~ 12 weeks ~~(5 half-lives)~~ after last dose of IP.	• Both changes were implemented to follow current sponsor safety recommendations in studies with benralizumab.
Section 6.3.2.3 Maintaining the blind to the patient's induced sputum cell count analysis - double blind period	• Removed sentence "~~The sample at Visit 1 will only be assessed for quality.~~"	• Sputum will be quantitatively analysed as per analysis plan.
Section 6.5 Concomitant therapy (Table 12)	• Text revision for live attenuated vaccines: "Not allowed from 30 days prior to screening (V 1), during the treatment period, and for 12 weeks after the last dose of IP."	• Text was added to clarify time period when patients taking an IP/benralizumab (OLE) cannot be administered live vaccines.
Section 6.5 Concomitant therapy (Table 13)	• Text revision for Rituximab: "…the patient must have shown recovery of peripheral B-cell count to above the lower level for the normal reference limit or above pre-rituximab [first treatment] level)."	• Patients may have lower B-cell levels due to their autoimmune disease or previous treatment.
Section 6.5.1 Oral corticosteroids and tapering	• Text added: "Oral corticosteroids other than prednisolone or prednisone may be acceptable but must be discussed with the AstraZeneca study physician."	• Patients in countries where prednisolone/prednisone is not available may be allowed to be treated with other glucocorticoids.
Section 6.5.2 Other concomitant treatment	• Text revision: "Use of immunosuppressive therapy …or from screening until completion of the first 6 months of the OLE period." • Text added: "... After completion of the first 6 months of the OLE, a decrease in dose or discontinuation of immunosuppressant is allowed at the Principal Investigator's discretion."	• Text was revised to clarify time when stable doses of immunosuppressive therapy will be permitted during the study. • Text was revised to 6 months; patients will have had ample time on open-label benralizumab before decreases in background immunosuppressant are allowed.
Section 7.1.2 Procedures for handling incorrectly	• Text revision: "… patients should be encouraged to ~~remain in the study and continue to be followed up~~ complete IPD and FU visits, ie, follow-up for	• A patient that has been incorrectly enrolled or randomised should not be encouraged to remain in study

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enrolled or randomised patients	8 weeks after last IP dose (if received) (Section 7.1.1.1)."	but rather to complete the IPD and FU visits.
Section 8.1.1.1 Birmingham Vasculitis Activity Score	• Text revision: "The requirement for monthly BVAS~~/VDI~~ assessment is replaced with…"	• Vasculitis Damage Index was deleted because this is not done monthly.
Section 8.1.1.8 SF-36v2 (acute recall) and Table 14	Text revisions: • "…asks patients to rate how their current state of health compared to their state of health ~~1 year ago~~ one week ago" • "~~Two types of thresholds have been developed for interpretation of~~ The SF-36v2 threshold ~~scores. The first type is suitable for comparing group mean scores and is generally referred to as the MCID. The second type~~ is suitable for interpreting change at the individual level and is referred to as the responder threshold (Table 11) or responder definition (Lincoln 2011)." Table 11 row "Group difference" was removed	• The text should say 1 week ago instead of 1 year ago. • We will be using only individual level threshold for SF-36v2 responder analysis as described further in the SAP.
Section 8.1.1.12 Spirometry (Time of day for scheduled site visit spirometry)	• Text revision: "Spirometry testing must be initiated in the morning between ~~6:00 AM and 11:00 AM~~ 0600 and 1100 ~~during the screening or re-screening period and~~ at the baseline visit (Visit 2)" • Text added: "Post-BD spirometry should be performed 15 to 30 minutes after SABA dosing."	• Spirometry is not planned at the screening period. • Text added for clarification and consistency within the CSP.
8.2.1 Clinical safety laboratory assessments	• Text added: "Urinalysis will be performed at a central laboratory only at Visit 1; subsequent analyses will be performed locally using a dipstick provided centrally."	• Text was revised to clarify that, as per SoAs, urinalysis should be performed centrally only at V1 and then locally using a dipstick.
8.2.1 Clinical safety laboratory assessments (Table 15)	• Text removed: Urinary sediment from urinalysis safety variables removed from list	• Urinary sediment is not a required assessment.
Section 8.8.2 Mandatory biomarker samples	• Text revisions: Deleted nasal secretions from mandatory samples and added new subsection: "8.8.3 Nasal secretions (mandatory at selected sites)"	• Only sites with the required equipment will collect nasal secretion samples.
8.8.3 Nasal secretions	• Text added: Describe how and when nasal secretions will be collected	• New section added to describe the mandatory nasal secretions at selected sites, collection

Summary of Changes to the Clinical Study Protocol		
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		times, and reference to laboratory manual.
Section 8.8.4 Mechanistic sub-study sampling (induced sputum, tissue biopsy, and whole blood cells)	• Text revisions: Add additional information regarding assessments to be performed on collected samples (induced sputum, tissue biopsy, and whole blood) and to add further detail on the collection of the tissue biopsies"	• Text revisions added to provide information on the purpose of the sub-study sample collections and to be consistent with the sub-study laboratory manual.
Section 9.4.1.2 Methods for efficacy analyses (ACQ-6 response analysis)	• Text added: New paragraph for the ACQ-6 responder analysis	• This was missing from the CSP, and it is part of the planned analysis.
Section 9.4.1.2 Methods for efficacy analyses (Analysis of secondary endpoints)	• Text added: Visit, endpoint's baseline, and visit by treatment were added as covariates • Text revision: "The proportion of patients with an ACQ-6 response (defined as a decrease in score from baseline of 0.5) ~~during Weeks 48 through 52~~ at end of 52-week double-blind period will be evaluated.	• To understand the relationship between change from baseline and treatment we need to adjust for the endpoints' baseline value. • Text was revised as per ACQ-6 responder definition in the SAP.
Appendix A	• A1: Subsection added: "Regulatory reporting requirement for SAEs" • A3: Text revision: "If patients <u>in the countries participating in the qualitative patient interview sub-study</u> indicate <u>that</u> they are interested in participating in the sub-study, the patient …" • A3: Text revision: If a patient's partner becomes pregnant during or within ~~16~~ 12 weeks after the ~~study~~ <u>last dose of IP</u>, the partner … • New A8: Sub-appendix added: "Study and site start and closure"	• A1: The language for regulatory requirements for SAEs was missing in the CSP. • A3: To clarify that an ICF addendum will be provided to patients joining the sub-study in participating countries only. • A3: Change implemented to follow current sponsor safety recommendations in studies with benralizumab. • New A8: text added as it is a requirement to address these study aspects in the CSP as per the International Conference on Harmonisation Good Clinical Practice.
Appendix E (E1 Introduction)	• Text revision: "a blood sample for serum tryptase should be collected as soon as possible after the event, at ~~60 minutes~~ <u>90 ±</u> 30 minutes"	• Change made because an interval of 60 minutes is too short to observe changes in tryptase.

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