Clinical Study Protocol	
Drug Substance	Benralizumab
Study Code	D3255C00001
Version	7.0
Date	01 April 2022

A Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab for Eosinophilic Esophagitis (MESSINA)

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifying Number(s):

EudraCT number: 2019-002871-32

NCT number: [04543409]

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.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 6 (CSP ver 7.0)	01-April-2022
Amendment 5 (CSP ver 6.0)	30-April-2021
Amendment 4 (CSP ver 5.0)	11-Feb-2021
Amendment 3 (CSP ver 4.0)	26-Aug-2020
Amendment 2 (CSP ver 3.0)	31-July-2020
Amendment 1 (CSP ver 2.0)	01-Nov-2019
Original protocol (Initial creation 1.0)	10-July-2019

Amendment 6 (CSP ver 7.0): 01 April 2022

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

Overall Rationale For the Amendment

The rationale for this amendment is to adjust the ordering of endpoints within the multiple testing procedure and update the analysis method for treatment failure intercurrent events for continuous endpoints. In addition, some minor clarifications were made to ensure 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 1.1 Schedule of Activities (SoA) Table 2, Table 3 Section 8.2.2 Pregnancy test Section 6.1.4.1 Optional Remote Visits for Patients doing At-Home or Remote-Location IP Administration	Updated urine pregnancy testing frequency after week 52. Removal of *'and urine dipsticks for pregnancy tests (for WOCBP)'*	For clarification and to reduce patient/site burden	Non-Substantial
Section 1.1 Schedule of Activities (SoA	Addition of a footnote and a separate row for 'Benralizumab administration' to confirm the start of open-label dosing	For clarification	Non-Substantial
Section 1.2 Synopsis, Table 5, Table 6 Section 3 Objective and Endpoints, Table 7, Table 8 Section 9.4.1.3Analysis methods for secondary efficacy variables Section 9.4.5 Methods for multiplicity control	Adjustment of endpoint prioritisation including promotion of secondary endpoints to key secondary endpoints, addition of key treatment responder endpoint and promotion of PEESS to a secondary (non-ranked) rather than exploratory endpoint	To ensure that clinically meaningful endpoints are multiplicity-protected and to reflect the importance of PEESS.	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 1.2 Synopsis Section 9.4.1.1 General principles Statistical analyses Section 9.4.1.2Primary analysis method	Updated imputation methods to handle treatment failure intercurrent events for continuous endpoints to use return-to-baseline multiple imputation rather than worst observation carried forwards.	As a result of health authority feedback, multiple imputation methods using the distribution of baseline scores from all patients will be used to handle treatment failure intercurrent events. This is an improved method quality of imputation than the previously proposed single imputation approach as it ensures uncertainty around the imputed values are included in the analysis.	Substantial
Section 2.2 Background	Text added regarding outcome measures and remission scores	To reflect recent literature	Non-Substantial
Section 5.1 Inclusion criteria	Removal of systemic steroids from IC7	As this is included in EC15	Non-Substantial
Section 6.1.1 Before IP administration	Text adjusted; endoscopy added.	To clarify that all procedures must be performed prior to IP administration.	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 6.1.5 IP administration re-scheduling Section 8.2.4 Vital signs	Simplification of on-site patient visit	For simplification	Non-Substantial
Section 6.3.2 Methods for ensuring blinding	Text added; *'Additional biopsies are not to be sent to local labs in parallel'* *'Week 24 follow-up biopsy results will not be reported back to the investigative sites due to potential risk of unblinding'*	For clarification	Non-Substantial
Section 7.1.1.3 Discontinuation of treatment in the OLE treatment period	Definition of an EOT visit versus an IPD visit during the OLE added	For clarification	Non-Substantial
Section 8.4.7 Management of IP-related toxicities Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management, F 1 Introduction	Text added regarding the analysis of serum tryptase	For clarification	Non-Substantial
Throughout	Minor editorial or administrative changes that do not substantially alter the document	For better consistency and clarity	Non-Substantial

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

This study comprises 3 distinct treatment periods: A 24-week double-blind (DB) treatment period, a 28-week open-label (OL) treatment period, and an open-label extension (OLE) period.

All patients who complete the 52-week treatment period (DB+OL treatment periods) on investigational product (IP) will be offered the opportunity to continue into an OLE period on benralizumab 30 mg every 4 weeks (Q4W). The OLE period is intended to allow each patient at least 1 year of treatment with OL benralizumab after completion of the 52-week DB+OL treatment periods. Patients who do not enroll in the OLE period will have a follow-up visit 12 weeks after their last dose of IP.

The primary database lock is targeted to occur when the required number of patients have been randomised for the primary analysis (170 patients including approximately 130 adults and 40 adolescents) and they have completed the 24-week DB treatment period, including those who have had the opportunity to complete at least 52 weeks of follow-up (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods). The primary analysis will evaluate the effect of benralizumab on histologic signs and symptoms of EoE at Week 24 in patients with symptomatic and histologically active EoE. An additional analysis may be performed after the last patient completes 52 weeks of follow up. The final analysis will occur after the last patient completes the OLE period and FU visit.

The schedule of activities (SoA) for the 52-week study period (DB+OL treatment periods) is provided in Table 1. The SoA for the first year of the OLE period is provided in Table 2, the SoA for the second year and beyond of the OLE period is provided in Table 3.

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
General procedures																			
Informed consent / assent	X																		Appx A 3
Demography / medical history	X																		
History of EoE and treatment	X																		
Height, weight	X							X							X		X		8.2.3.1
Inclusion / exclusion criteria	X	X																	5.1, 5.2
Efficacy assessments																			
PRO assessments																			
In-office:																			
Provide handheld device and instructions	X																		8.1.3
Record visit in the handheld device; Confirm that all PRO assessments have been completed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.1.3
Review compliance of at-home PRO assessments [f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.1.3

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
At-home [g]:																			
Daily: • Daily Diary (including DSQ, EoE-3D) Weekly: • EoE-QoL-A Every two weeks: • PGI-S Monthly: • PEESS [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		8.1.3.1, 8.1.3.2, 8.1.3.3, 8.1.3.4, 8.1.3.5
PGI-C		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		8.1.3.6
SF-36 (Version 2) and WPAI+CIQ		X			X			X			X				X		X		8.1.3.7, 8.1.3.8
Other assessments in office																			
Diet questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.11.2
Healthcare resource utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	8.10
[redacted]	[redacted]												[redacted]						[redacted]
Procedures																			

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Endoscopy • Esophageal biopsies • EREFS	X		X [j]		X [j]			X							X		X [k]		8.1.1, 8.1.2,
Endoscopy • EndoFLIP (sub-study [selected sites])	X							X							X		X [k]		8.1.4

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Safety assessments																			
AEs / SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication	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		X		8.2.3
Brief physical exam		X	X	X	X	X	X		X	X	X	X	X	X		X		X [l]	8.2.3
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.2.4
ECG		X																	8.2.5
Laboratory assessments																			
Hematology, WBC w/ differential	X		X [j]	X	X [j]	X		X			X				X		X	X [l, m]	8.2.1
Serum chemistry	X			X		X		X			X				X		X		8.2.1
Serology (hepatitis B and C) [n]	X																		8.2.1.1
HIV-1 and HIV-2	X																		8.2.1.1
Urinalysis	X					X		X			X				X		X		8.2.1
FSH [o]	X																		8.2.2
Serum pregnancy test in WOCBP	X																		8.2.2

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Urine pregnancy test in WOCBP [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	8.2.2
PK [q]		X	X [i]	X	X [i]	X		X			X				X		X	X [l]	8.5
ADA / nAb [q]		X		X		X		X			X				X		X	X [l]	8.9
[redacted]																			
[redacted]	[redacted]																		[redacted]
[redacted]	[redacted]							[redacted]							[redacted]				[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]							[redacted]				[redacted]
[redacted]	[redacted]		[redacted]		[redacted]			[redacted]							[redacted]		[redacted]		[redacted]
[redacted]		[redacted]																	[redacted]
Investigational product administration																			
Randomization		X																	6.3.1
Benralizumab or placebo administration [u]		X	X	X	X	X	X												6.1
Benralizumab administration								X	X	X	X	X	X	X	X [t]				6.1

Table 1 Schedule of Activities – Double-blind and Open-label Treatment Periods

Study Procedures	Run-in Period	DB Treatment Period							OL Treatment Period							Unsch Visit [d]	IPD [a]	FU	Details in CSP Section
Visit (V)	V1	V2	V3	V4	V5	V6	V7	V8 [b]	V9	V10	V11	V12	V13	V14	V15/ EOT [c]				
Week (Wk)	Wk -8 to -2	0	4	8	12	16	20	24	28	32	36	40	44	48	52		4 wks after final IP dose	12 wks after last IP dose	
Visit Window (Days) [e]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Telephone contact for patients who discontinue early from IP and unwilling/unable to continue with clinic visits																			
Telephone contact [v]			Telephone contact every 4 weeks from the date of last clinic visit, and to continue until the end of the DB + OL treatment period ⟷																7.1.1.1

[a] Details regarding procedures for patients who discontinue treatment but remain in the study are described in Section 7.1, for patients who discontinue from the study are described in Section 7.3, and for patients lost to follow up are described in Section 7.2.

[b] Visit 8 is the last visit of the DB period and the first visit of the OL period. During this visit the first dose of the OL treatment will be administered.

[c] For patients continuing in the OLE period, Visit 15 is the first treatment of the OLE period. If a patient chooses not to continue to the OLE period, then the patient will be considered to have completed the study; the site will perform an EOT visit at Week 52, and the patient will return for a FU visit 12 weeks (±7 days) after the last dose of IP, after which the patient exits the study.

[d] These are the minimum procedures that should be performed at an unscheduled visit. Other assessments may be performed at discretion of the Investigator.

[e] Visit windows are calculated from Visit 2.

[f] Compliance with the assessment schedule should be completed weekly.

[g] PROs will be administered at home on the handheld device according to the schedule in Table 4.

[h] The PEESS is only for patients aged 18 years and under at Visit 1.

[redacted]

[k] To be completed at the discretion of the Sponsor. Endoscopy at the IPD Visit should only be performed if ≥12 weeks have elapsed since the prior endoscopy. If a patient discontinues prior to Week 24, the patient should be asked to return for the endoscopy at Week 24 (rather than at the IPD visit).

[l] These assessments/procedures will only be performed on patients who attend the FU visit at the study site.

[m] Only WBC w/ differential will be measured at the FU visit.

[n] For patients that are HBsAg positive or anti-HBc positive at Visit 1, HBeAg, anti-HDV and HBV DNA testing will be performed. For these subjects that are HBsAg positive or anti-HBc positive, ALT and HBV DNA will be drawn to monitor for hepatitis B reactivation, see section 8.2.1.1

[o] FSH test done only to confirm postmenopausal status in women <50 years of age who have been amenorrheic for ≥12 months.

[p] A positive urine test (dipstick) result must be confirmed with a serum beta-HCG.

q All samples for PK and ADA/nAb must be taken prior to IP administration.

[redacted]

t IP will be administered at Visit 15 (Week 52) only for patients entering the OLE period.

u Patient training of self-administration of IP procedures may be offered at Visits 2 and 3.

v For patients using the phone follow-up option instead of attending the scheduled clinic visits, the handheld device will be returned at the IPD visit and no further PRO assessments will be collected.

ADA anti-drug antibody; AEs adverse events; ALT alanine aminotransferase; anti-HDV hepatitis D antibody; Appx Appendix; CSP Clinical Study Protocol; DB Double-blind; DNA deoxyribonucleic acid; DSQ Dysphagia Symptom Questionnaire; ECG electrocardiogram; EGD esophagogastroduodenoscopy; EoE eosinophilic esophagitis; EoE-3D Eosinophilic Esophagitis - Daily Dysphagia Diary; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EndoFLIP Endolumenal Functional Lumen Imaging Probe; EOT End of Treatment; EREFS Endoscopic Reference Score; FSH follicle stimulating hormone; FU follow up; HBc hepatitis B core; HBeAg hepatitis B e-antigen; HBsAg hepatitis B surface antigen; HBV hepatitis B-virus; HCG human chorionic gonadotropin; HIV-1/2 human immunodeficiency virus-1/2; IgE immunoglobulin E; IP investigational product; IPD investigational product discontinuation (visit); nAb neutralizing antibody; OL Open-label; OLE open-label extension; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; PRO Patient Reported Outcome; Q4W every 4 weeks; RNA ribonucleic acid; SAEs serious adverse events; SF36v2 Short Form-36 Version 2.0; Unsch Unscheduled; V visit; Wk week; WBC white blood cell (count); WOCBP women of childbearing potential; WPAI+CIQ Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions.

Table 2 Schedule of Activities after Week 52 – Open-label extension treatment period (Year 1)

Study Procedures	Treatment Period													Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V16[a]	V17[a]	V18	V19[a]	V20[a]	V21	V22[a]	V23[a]	V24	V25[a]	V26[a]	V27	V28				
													104		4 wks after final IP dose	12 wks after final IP dose	
Week (Wk)	56	60	64	68	72	76	80	84	88	92	96	100					
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
General procedures																	
Height, weight						X							X		X		8.2.3.1
Efficacy assessments																	
PRO assessments																	
In office:																	
Record visit in the handheld device; Confirm that all PRO assessments have been completed	X	X	X	X	X	X								X	X		8.1.3
Review compliance of at-home PRO assessments	X	X	X	X	X	X								X	X		8.1.3
At-home:																	
Daily: • Daily Diary (including DSQ, EoE-3D) Weekly: • EoE-QoL-A Monthly: • PEESS [e]	X	X	X	X	X	X											8.1.3.1, 8.1.3.2 8.1.3.3 8.1.3.4
PGI-S (by interview)						X							X		X		8.1.3.5

Table 2 Schedule of Activities after Week 52 – Open-label extension treatment period (Year 1)

Study Procedures	Treatment Period													Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V16[a]	V17[a]	V18	V19[a]	V20[a]	V21	V22[a]	V23[a]	V24	V25[a]	V26[a]	V27	V28				
Week (Wk)	56	60	64	68	72	76	80	84	88	92	96	100	104		4 wks after final IP dose	12 wks after final IP dose	
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Other assessments																	
Diet questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		8.11.2
Healthcare resource utilization	X	X	X	X	X	X	X	X	X	X	X	X	X		X		8.10
[redacted]						[redacted]											[redacted]

Table 2 Schedule of Activities after Week 52 – Open-label extension treatment period (Year 1)

Study Procedures	Treatment Period													Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V16[a]	V17[a]	V18	V19[a]	V20[a]	V21	V22[a]	V23[a]	V24	V25[a]	V26[a]	V27	V28				
Week (Wk)	56	60	64	68	72	76	80	84	88	92	96	100	104		4 wks after final IP dose	12 wks after final IP dose	
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Procedures																	
Endoscopy • biopsies • EREFS • EndoFLIP (sub-study [selected sites])													X		X[g]		8.1.1, 8.1.2 8.1.4
Safety assessments																	
AEs / SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete physical exam															X		8.2.3
Brief physical exam			X			X			X			X	X	X		X	8.2.3
Vital signs			X			X			X			X	X	X	X		8.2.4
Laboratory assessments																	
Hematology, WBC w/ differential [h]						X							X		X	X[i]	8.2.1
Serum chemistry						X							X		X		8.2.1
Urinalysis						X							X		X		8.2.1
Urine pregnancy test in WOCBP [j]			X			X			X			X	X		X	X	8.2.2

Table 2 Schedule of Activities after Week 52 – Open-label extension treatment period (Year 1)

Study Procedures	Treatment Period													Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V16[a]	V17[a]	V18	V19[a]	V20[a]	V21	V22[a]	V23[a]	V24	V25[a]	V26[a]	V27	V28				
Week (Wk)	56	60	64	68	72	76	80	84	88	92	96	100	104		4 wks after final IP dose	12 wks after final IP dose	
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
PK [k]						X							X		X	X	8.5
ADA / nAb [k]						X							X		X	X	8.9
[redacted]																	
[redacted]						[redacted]							[redacted]				[redacted]
Investigational product																	
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X				6.1

[a] These visits are designed to support self-administration at home/remotely but patients may opt to complete the visits at the study site.
[b] These are the minimum procedures that should be performed at an Unscheduled Visit. Other assessments may be performed at the discretion of the Investigator.
[c] The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after the decision to discontinue IP has been made, and at the latest 4 weeks ±3 days after the last dose of IP.
[d] Visit windows are calculated from Visit 2.
[e] The PEESS is only for patients age 18 years and under at Visit 1.
[redacted]
[g] Endoscopy at the IPD Visit should only be performed if ≥24 weeks have elapsed since the prior endoscopy. Endoscopy is not required at the IPD/EOT visit if it occurs after week 104.
[h] For patients that are HBsAg positive or anti-HBc positive at Visit 1, HBeAg, anti-HDV and HBV DNA testing will be performed. For these subjects that are HBsAg positive or anti-HBc positive, ALT and HBV DNA will be drawn to monitor for hepatitis B reactivation, see section 8.2.1.1 Other laboratory assessments
[i] Only WBC w/ differential will be measured at the FU visit
[j] A positive urine test (dipstick) result must be confirmed with a serum beta-HCG test.

[k] All samples for PK and ADA/nAB must be taken prior to IP administration.

ADA anti-drug antibody; AEs adverse events; ALT alanine aminotransferase; anti-HDV hepatitis D antibody; CSP Clinical Study Protocol; DNA deoxyribonucleic acid; DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; EoE-3D Eosinophilic Esophagitis - Daily Dysphagia Diary; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EOT End of Treatment (visit); EREFS Endoscopic Reference Score; FU Follow Up; HBc hepatitis B core; HBeAg hepatitis B e-antigen; HBsAg hepatitis B surface antigen; HBV hepatitis B-virus; HCG human chorionic gonadotropin; IP investigational product; IPD investigational product discontinuation (visit); nAb neutralizing antibody; OLE open-label extension; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; PRO Patient Reported Outcome; SAEs serious adverse events; V visit; WBC white blood cell; Wk week; WOCBP women of childbearing potential.

Table 3 Schedule of Activities after Week 104 – Open-label extension treatment period (Year 2 +)

Study Procedures	Treatment Period												Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V29[a] /41[a]	V30[a] /42[a]	V31 /43	V32 [a] /44[a]	V33[a] /45[a]	V34 /46	V35[a] /47[a]	V36[a] /48[a]	V37 /49	V38[a] /50[a]	V39[a] /51[a]	V40 /52				
Week (Wk)	108/156	112/160	116/164	120/168	124/172	128/176	132/180	136/184	140/188	144/192	148/196	152 /200		4 wks after final IP dose	12 wks after final IP dose	
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
Diet questionnaire			X			X			X			X	X	X		8.11.2
Healthcare resource utilization			X			X			X			X		X		8.10
Safety assessments																
AEs / SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication			X			X			X			X	X	X	X	6.5
Complete physical exam														X		8.2.3
Brief physical exam			X			X			X			X	X		X	8.2.3
Vital signs			X			X			X			X	X	X		8.2.4
Laboratory assessments																
Hematology, WBC w/ differential [e]						X						X		X	X [f]	8.2.1
Serum chemistry						X						X		X		8.2.1
Urinalysis						X						X		X		8.2.1
Urine pregnancy test in WOCBP [g]			X			X			X			X		X	X	8.2.2
PK [h]						X						X		X	X	8.5
ADA / nAb [h]						X						X		X	X	8.9

Table 3 Schedule of Activities after Week 104 – Open-label extension treatment period (Year 2 +)

Study Procedures	Treatment Period												Unsch Visit [b]	IPD / EOT [c]	FU	Details in CSP Section
Visit (V)	V29[a] /41[a]	V30[a] /42[a]	V31 /43	V32 [a] /44[a]	V33[a] /45[a]	V34 /46	V35[a] /47[a]	V36[a] /48[a]	V37 /49	V38[a] /50[a]	V39[a] /51[a]	V40 /52				
Week (Wk)	108/156	112/160	116/164	120/168	124/172	128/176	132/180	136/184	140/188	144/192	148/196	152/200		4 wks after final IP dose	12 wks after final IP dose	
Visit Window (Days)[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		± 3	± 7	
[redacted]																
[redacted]						[redacted]						[redacted]				[redacted]
Investigational product																
Benralizumab administration	X	X	X	X	X	X	X	X	X	X	X	X				6.1

[a] These visits are designed to support self-administration at home/remotely but patients may opt to complete the visits at the study site.
[b] These are the minimum procedures that should be performed at an Unscheduled Visit. Other assessments may be performed at the discretion of the Investigator.
[c] The IPD/EOT visit replaces the nearest regular visit: IPD visit procedures should be performed as soon as possible after the decision to discontinue IP has been made, and at the latest 4 weeks ±3 days after the last dose of IP.
[d] Visit windows are calculated from Visit 2.
[e] For patients that are HBsAg positive or anti-HBc positive at Visit 1, HBeAg, anti-HDV and HBV DNA testing will be performed. For these subjects that are HBsAg positive or anti-HBc positive, ALT and HBV DNA will be drawn) to monitor for hepatitis B reactivation, see section 8.2.1.1 Other laboratory assessments
[f] Only WBC w/ differential will be measured at the FU visit
[g] A positive urine test (dipstick) result must be confirmed with a serum beta-HCG test.
[h] All samples for PK and ADA/nAB must be taken prior to IP administration.

ADA anti-drug antibody; AEs adverse events; ALT alanine aminotransferase; anti-HDV hepatitis D antibody; CSP Clinical Study Protocol; DNA deoxyribonucleic acid; EoE eosinophilic esophagitis; FU Follow Up; HBc hepatitis B core; HBeAg hepatitis B e-antigen; HBsAg hepatitis B surface antigen; HBV hepatitis B-virus; HCG human chorionic gonadotropin; IP investigational product; IPD investigational product discontinuation (visit); nAb neutralizing antibody; OLE open-label extension; PK pharmacokinetics; SAEs serious adverse events; V visit; WBC white blood cell; Wk week; WOCBP women of childbearing potential.

Please note;

For patients continuing in the study beyond visit 52 (week 200), continue the pattern that is outlined in Table 3, starting with visit 53 (week 204) which instructs the investigator to apply assessments under Visit 29/41 (Week 108/156).

Table 4 Schedule of PRO assessments

Instruments	Schedule
Daily Diary (including DSQ, EoE-3D, and other symptom questions)	Every evening (between 17:00 on Day *n* and 4:59 on Day *n*+1). First administration at home on the day of Visit 1. Assessments stop after Visit 21 is confirmed.
PEESS	Only for patients age 18 years and under at Visit 1. First administration at home on the day of Visit 1, then every 28±3 days thereafter. Assessments stop after Visit 21 is confirmed.
EoE-QoL-A	First administration at home on the day of Visit 1, then every 7±3 days thereafter until Visit 2 is confirmed. Then, administration will occur every 7±3 days thereafter. Assessments stop after Visit 21 is confirmed.
PGI-S	First administration on the device at home on the day of Visit 1, then every 14±3 days thereafter until Visit 2 is confirmed. Then, administration will occur on the device every 14±3 days from Visit 2 until Visit 15 is confirmed. Thereafter administration will occur by interview and entered into the eCRF at Visit 21 and Visit 28 (or at IPD/EOT if before Visit 28).
PGI-C	First administration at home 7±3 days after Visit 2, then every 7±3 days thereafter. Assessments stop after Visit 15 is confirmed.
SF-36 v2, WPAI+CIQ	First administration at home on the day of Visit 2, then every 84±3 days thereafter. Assessments stop after Visit 15 is confirmed.

DSQ Dysphagia Symptom Questionnaire; EoE eosinophilic esophagitis; EoE-3D Eosinophilic Esophagitis - Daily Dysphagia Diary; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PRO Patient Reported Outcome; SF36v2 Short Form-36 Version 2.0; WPAI+CIQ Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions

1.2 Synopsis

International Co-ordinating Investigator:

Protocol Title: A Multicenter, Randomized, Double-blind, Parallel-group, Placebo controlled Study to Investigate the Use of Benralizumab for Eosinophilic Esophagitis (MESSINA)

Short Title: A Study of Benralizumab in Patients with Eosinophilic Esophagitis

Rationale:

Benralizumab is a humanized, afucosylated, monoclonal antibody (mAb) that binds specifically to the human interleukin-5 (IL-5) receptor alpha subunit (IL-5Rα) on the target cell and directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity (ADCC). The direct eosinophil-depleting ability of benralizumab has been shown to be effective in eosinophilic asthma, and preliminary results suggest that benralizumab is effective in treating hypereosinophilic syndrome (HES), which shares clinical and histologic features with eosinophilic esophagitis (EoE). The prominent accumulation and activation of pro-inflammatory eosinophils in the esophagus of EoE patients and their pathogenic role in pre-clinical modelling suggests that a direct eosinophil-depleting approach may prove beneficial in depleting eosinophils from gastrointestinal (GI) tissue(s), improve the symptoms of dysphagia, and improve endoscopy scores as well as other markers of disease activity.

The aim of this Phase 3 study is to investigate the use of benralizumab as a treatment for patients with EoE. The effect of doses of benralizumab 30 mg every 4 weeks (Q4W) on EoE histologic signs and symptoms will be assessed over a 52-week treatment period (including a 24-week DB placebo-controlled treatment period and a 28-week OL treatment period). It is proposed that benralizumab will deplete eosinophils from GI tissue(s), improve the symptoms of dysphagia, and improve endoscopy scores as well as other markers of disease activity.

Table 5 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

The following objectives/endpoints are for the 52-week study period (DB+OL treatment periods):	
Primary Objective:	**Dual-primary Endpoints/Variables:**
To evaluate the effect of benralizumab 30 mg Q4W on histologic signs and symptoms of EoE in patients with symptomatic and histologically active EoE	• Proportion of patients with a histologic response at Week 24, defined as a peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 24
Secondary Objectives:	**Endpoints/Variables:**
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Key secondary endpoint: Percent change from baseline in tissue eosinophils at Week 24 • Key secondary endpoint: Change from baseline in EoE-HSS grade score at Week 24 • Key secondary endpoint: Change from baseline in EoE-HSS stage score at Week 24 • Key secondary endpoint: Changes from baseline in centrally-read EoE EREFS at Week 24 • Key secondary endpoint Treatment responder rate at Week 24, defined as a composite of histological response (≤ 6 eos/hpf) and clinically meaningful improvement from baseline in DSQ (30% improvement) • Centrally-read biopsies for additional histopathology including tissue eosinophil counts at Week 24 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 24 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 24 • Changes from baseline in PEESS at Week 24
To evaluate the effect of benralizumab 30 mg Q4W on patient reported QOL measures	• Changes from baseline in EoE-QoL-A at Week 24 • SF-36 v2 Health Survey at Week 24
To evaluate the effect of benralizumab 30 mg Q4W on healthcare resource utilization due to EoE	• Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study through Week 24
To evaluate the effect of benralizumab 30 mg Q4W on patient reported measures of disease severity and health status	• PGI-S at Week 24 • PGI-C at Week 24
To assess the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE	• Serum benralizumab concentration • ADA and nAb

Table 5 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

Other objectives	Endpoints/Variables:
To describe the longer-term effect of benralizumab 30 mg Q4W in patients with EoE	• Proportion of patients with a histologic response at Week 52, defined as a peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 52 • Changes from baseline in centrally-read EoE EREFS at Week 52 • Centrally-read biopsies for histopathology and tissue eosinophil counts at Week 52 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 52 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 52 • Changes from baseline in PEESS at Week 52 • Changes from baseline in EoE-QoL-A at Week 52 • SF-36 v2 Health Survey at Week 52 • Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study through Week 52 • PGI-S at Week 52 • PGI-C at Week 52
Safety Objective:	**Endpoints/Variables:**
To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE	Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory values Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height Assessments related to vital signs cover • Observed value • Absolute and percent change from baseline values over time

Table 5 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

Exploratory Objectives:	Endpoints/Variables:
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Changes from baseline in EndoFLIP (esophageal distensibility) assessment at Week 24 and at Week 52 (sub-study)
To evaluate the effect of benralizumab 30 mg Q4W on early histologic signs, clinical features, symptoms and [redacted] of EoE (sub-study)	• Replicate histology, EREFS and PRO endpoints at weeks 4 and 12 • [redacted]
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on the ability to work, attend classes, and perform regular daily activities	• WPAI+CIQ scores

ADA anti-drug antibody; AEs adverse events; DB Double-blind; DSQ Dysphagia Symptom Questionnaire; EndoFLIP Endolumenal Functional Lumen Imaging Probe; EoE eosinophilic esophagitis; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; eos Eosinophils; EoE-HSS Eosinophilic Esophagitis-Histology Scoring System; EREFS Endoscopic Reference Score; hpf high power field; nAb neutralizing antibody; OL Open-label; OLE Open-label Extension; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; PRO Patient Reported Outcome; Q4W every 4 weeks; QoL Quality of Life; SF-36v2 Short Form-36 Version 2.0.; WPAI+CIQ Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions.

Table 6 Study Objectives for the OLE Period

The following objectives/endpoints are for the OLE period of the study:	
Safety Objective:	**Endpoints/Variables:**
To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory values Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height Assessments related to vital signs cover • Observed value • Absolute and percent change from baseline values over time
Other Objectives:	**Endpoints/Variables:**
To describe the longer-term effect of benralizumab 30 mg Q4W in patients with EoE	• Changes from baseline in DSQ; frequency of dysphagia episodes (EoE-3D), dysphagia-free days (DSQ), and associated pain, discomfort, overall severity; abdominal pain and nausea (daily diary); EoE-QoL-A up to Week 76 • Changes from baseline in PEESS up to Week 76 • Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study • Centrally-read biopsies for histopathology and tissue eosinophil counts at Week 104 • Changes from baseline in centrally-read EoE EREFS at Week 104 • PGI-S at Week 104
To describe the effect of benralizumab on the use of background EoE medications and related therapies and diet restrictions	• Changes in concomitant medications and diet regimens • Changes in patient experience as reported by PROs
To describe the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE	• Serum benralizumab concentration • ADA and nAb

Table 6 Study Objectives for the OLE Period

Exploratory Objectives:	Endpoints/Variables:
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Changes from baseline in EndoFLIP (esophageal distensibility) assessment at Week at Week 104 (sub-study)
[redacted]	[redacted]

ADA anti-drug antibody; AEs adverse events; DSQ Dysphagia Symptom Questionnaire; EndoFLIP Endolumenal Functional Lumen Imaging Probe; EoE eosinophilic esophagitis; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EREFS Endoscopic Reference Score; nAb neutralizing antibody; OLE Open-label Extension; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; Q4W every 4 weeks; PRO Patient Reported Outcome

Overall design:

This is a randomized, placebo-controlled, DB, parallel-group, multicenter, Phase 3 study to compare the efficacy and safety of repeat dosing of benralizumab versus placebo in male and female patients 12 to 65 years of age with symptomatic and histologically active EoE.

The clinical study consists of 4 periods:

- a 2- to 8-week run-in period
- a 24-week placebo-controlled, DB, parallel-group treatment period (DB period)
- a 28-week OL benralizumab treatment period (OL period)
- an additional OLE treatment period (OLE period)

Following informed consent (or assent, if applicable), all patients will enter a run-in period of 2 to 8 weeks during which inclusion/exclusion criteria are assessed, medical history taken, endoscopy with biopsies performed, and patient reported outcomes (PROs), clinical laboratories, and diet questionnaires administered. Patients may be on background medication for EoE and related treatments during the study as long as the background medications have been stable for at least 4 weeks (8 weeks for PPI) prior to screening, and there is an agreement not to change type of background medication or dosage during the run-in period and for the first 52 weeks of the study unless a change is medically indicated. If a medication for EoE (including swallowed steroids, systemic steroids and PPI) is discontinued prior to screening, there should be a washout period of a least 8 weeks. The justification and rationale for

changes to the background medication for EoE and related treatments should be documented in the eCRF. Additionally, patients should remain on a stabilized diet for treatment of their EoE for at least 6 weeks prior to the run-in period throughout the run-in period and the first 52 weeks of the study unless medically indicated. Diet will be tracked and assessed by the diet questionnaire.

Eligible patients with symptomatic and histologically active EoE before randomization will be randomized in a 1:1 ratio to receive either 30 mg of benralizumab or placebo at 4-week intervals for a 24-week treatment period (DB period). The randomization for adults will be stratified by region (North America vs Rest of World [ROW]) and use of swallowed steroids at baseline (categorical, Yes/No). Adolescents will be randomized in a separate stratum with no other factors included.

Patients who complete the DB, placebo-controlled treatment period on investigational product (IP) will continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period).

All patients who complete the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) on IP will be offered the opportunity to continue into an OLE period on benralizumab 30 mg Q4W (OLE). The OLE period is intended to allow each patient at least 1 year of treatment with OL benralizumab after completion of the 52-week DB+OL treatment periods. The Sponsor may choose to extend the OLE period beyond one year and reserves the right of terminating the OLE early (eg, if development in this indication is terminated or marketing authorisation is obtained). Patients who do not enroll in the OLE period will have a follow-up visit 12 weeks after their last dose of IP.

The primary database lock is targeted to occur when the required number of patients have been randomised for the primary analysis (170 patients including approximately 130 adults and 40 adolescents) and they have completed the 24-week DB treatment period, including those who have had the opportunity to complete at least 52 weeks of follow-up (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods). The primary analysis will evaluate the effect of benralizumab on histologic signs and symptoms of EoE at Week 24 in patients with symptomatic and histologically active EoE. An additional analysis may be performed after the last patient completes 52 weeks of follow up. The final analysis will occur after the last patient completes the OLE period.

Study Period:

First patient enrolled: [redacted]

Estimated date of last patient completed: [redacted]

Number of Patients:

Approximately 170 eligible patients are planned to be randomized. Recruitment of adolescent patients is targeted to be broadly in line with expected prevalence rates of adolescents in the overall patient population. Approximately 20 adolescent patients (12 to 17 years of age) per arm are targeted for inclusion in the study.

Treatments and treatment duration:

Following the run-in period, patients confirmed to be eligible will be randomized in a 1:1 ratio to receive 30 mg of benralizumab or placebo at 4-week intervals for a 24-week treatment period (DB period). Patients who complete the DB, placebo-controlled treatment period on IP will continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period). All patients who complete the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) on IP will be offered the opportunity to continue into an OLE period on benralizumab 30 mg Q4W (OLE period). The OLE period is intended to allow each patient at least 1 year of treatment with OL benralizumab after completion of the 52-week DB+OL treatment periods.

The IP will be administered subcutaneously (SC) as a single injection via an accessorized prefilled syringe (APFS). All doses of IP during the 52-week treatment period will be administered at the study site by the investigator/authorised delegate. After week 52, IP will be administered as scheduled in the SoA, either at the site during the visit by a healthcare professional or at home/remotely by the patient or caregiver, see section 6.1.4. No dose changes are allowed. If a patient presents with a condition that contraindicates dosing, administration of IP will be withheld and resumed as soon as the condition resolves. If a patient misses 2 or more doses (consecutively or non-consecutively) of IP within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take place to review the patient's adherence to treatment and decide on the patient's further disposition (see Section 7.1 for details). All patients, regardless of whether they remain on IP treatment or not, will be encouraged to remain in the study and be followed to study completion (see Section 7.1).

Data Monitoring Committee:

An independent data monitoring committee (IDMC) will be utilized for this study. Section A 5 provides more details on the rationale for and the remit of the committee.

Statistical methods

Approximately 170 patients will be randomized in a 1:1 ratio to benralizumab or matching placebo. This will provide >95% power for the first primary endpoint of proportion of patients achieving histological response to demonstrate an increase from 20% or less on placebo to 50% on benralizumab at the 2-sided 5% significance level. The power calculation

for the second primary endpoint of the change from baseline in Dysphagia Symptom Questionnaire (DSQ) score at Week 24 is based on detecting similar effect sizes (mean difference in change from baseline of the PRO / standard deviation) as seen in previous studies. Assuming an effect size of 0.6, which equates to a 7.2-point difference in change in the DSQ, 85 patients per arm will allow >95% power for statistical significance at the 5% 2-sided level. The high level of power for the primary endpoints will ensure stronger statistical evidence can be demonstrated in this single Phase 3 study.

Efficacy analyses will be performed using the full analysis set (FAS), which will include all patients randomized who receive at least 1 dose of IP. The treatment arms will be compared on the basis of randomized treatment, regardless of treatment actually received.

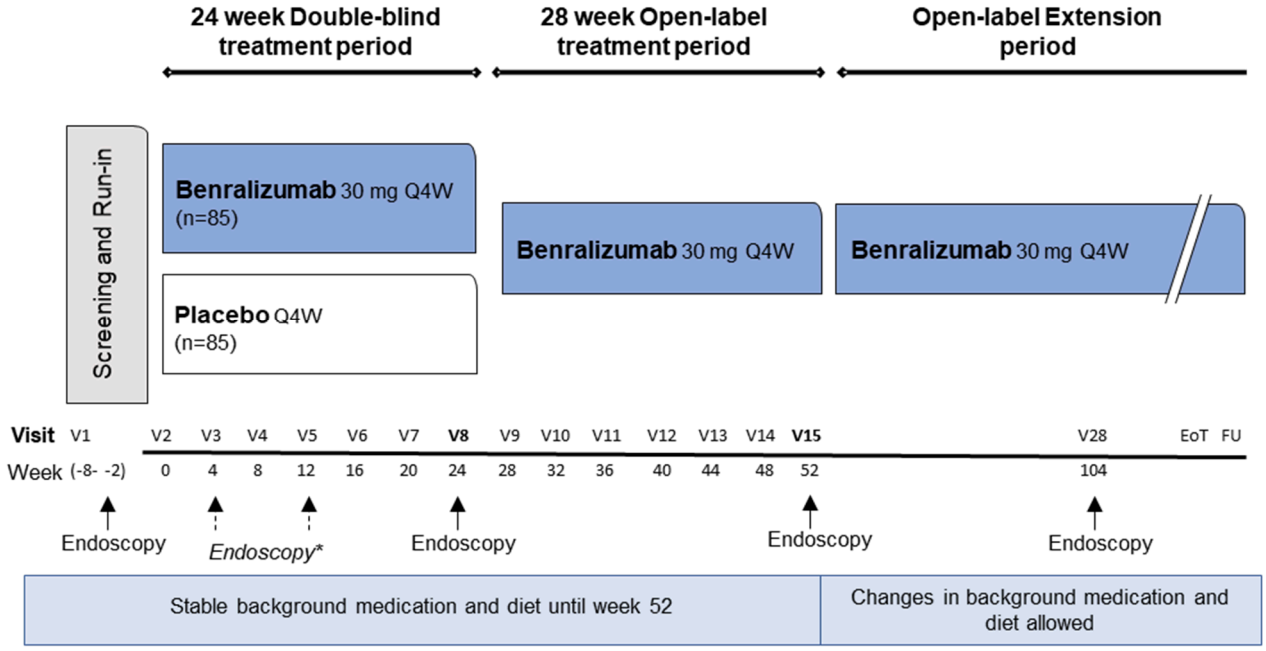
The primary efficacy analyses will be based on the DB placebo-controlled first 24 weeks of the study (DB period). A composite estimand strategy will be used for the primary analyses, whereby any patients with intercurrent events of randomized therapy discontinuation, an increase of background therapy or addition of a new therapy to treat their EoE, or having dilation procedures prior to week 24 will be considered as treatment failures at week 24. For the first dual primary endpoint of proportion of patients achieving a histological response at Week 24, defined as a peak esophageal intraepithelial eosinophil count ≤6 eos/hpf on centrally-read esophagogastroduodenoscopy (EGD) biopsies, any patient experiencing these intercurrent events will be considered non-responders at week 24. The endpoint will be compared between benralizumab and placebo using a Cochran-Maentel-Haenszel (CMH) test stratified by region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline. For the second dual-primary endpoint of change from baseline in DSQ score at Week 24, any patient experiencing the described intercurrent events will have their week 24 value imputed using a return to baseline multiple imputation method. The change at week 24 will then be analysed for each imputation dataset by analysis of covariance (ANCOVA) including covariates for treatment, region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline. Results will be combined across the datasets using Rubin's rule (Rubin et al 1986, Rubin et al 1987). Hypothesis testing for the primary analyses will be performed at the 2-sided 5% significance level.

Descriptive summary statistics and graphical data displays will be used for Week 52 efficacy data and all analyses of data in the OLE period; no formal statistical analyses will be performed.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



Q4W every 4 weeks; V Visit; EoT End of Treatment; FU Follow up, *Only for patients in the the Early Time Point Sub-study (see Section 8.1.5)

2 INTRODUCTION

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the IL-5Rα on the target cell and directly depletes eosinophils through ADCC. The mechanism of action of benralizumab makes it a potential treatment option for the high unmet need in patients with symptomatic and histologically active EoE.

Benralizumab has been or is being investigated in patients with asthma, chronic obstructive pulmonary disease (COPD), HES, nasal polyposis, eosinophilic granulomatosis with polyangiitis (EGPA), eosinophilic chronic rhinosinusitis, and eosinophilic gastritis/gastroenteritis. The present study (D3255C00001 [MESSINA]) represents the first clinical study dedicated to the assessment of benralizumab in patients with EoE.

2.1 Study rationale

[redacted]

2.2 Background

Eosinophilic esophagitis is a chronic allergic inflammatory disorder of the esophagus, defined histologically by esophageal inflammation of ≥15 eosinophils per high power field (eos/hpf) as obtained from 2 to 4 biopsies from either the proximal, mid, and/or distal esophagus and exclusion of secondary causes of esophageal eosinophilia. In addition, a response to treatment (selective dietary elimination; swallowed topical corticosteroids; proton pump inhibitor [PPI] therapy) supports, but is not required for, diagnosis (Dellon et al 2013). Typical symptoms include dysphagia and food impaction in adolescents and adults (Dellon et al 2017).

There is a clinical unmet need for new therapies for use in patients with EoE. There are no products indicated for the treatment of the disease in the US. Jorveza® (orodispersible budesonide tablet) was approved in the EU for the treatment of EoE in adults in 2018, and there are no approved products for the treatment of EoE in the paediatric population. Additionally, most current treatment approaches are either burdened with compliance problems, and/or limited efficacy, or reserved for the treatment of complications.

Current treatment approaches include swallowed topical corticosteroids (asthma preparations that are swallowed rather than inhaled so that the medication coats the lining of the esophagus [fluticasone or budesonide]), though these are suboptimal for use in EoE (Dellon et al 2013a, Dellon et al 2014). There is evidence that PPIs can also be used to treat EoE when response is measured by histological improvement; however, clinical responses have been less frequently

studied and it is difficult to draw conclusions about symptom benefit. In addition, only a portion of patients with EoE are PPI responders (Dellon et al 2018). Dietary elimination of all food allergens can be effective, but the evidence for this is shorter term and can present challenges with longer term compliance and effectiveness over time. In addition, esophageal dilation, approached conservatively, may be used as an effective therapy in symptomatic patients with strictures that persist despite medical or dietary therapy. Because EoE is chronic and symptoms recur when treatments are discontinued, maintenance therapy should be considered in all patients (Dellon et al 2013). The limitations of currently available therapeutic approaches have led to the search for alternate potential therapies.

Because eosinophilic inflammation is a central finding in EoE, safe and effective therapies that target eosinophils will likely be beneficial for treatment of EoE. The mechanism of action of benralizumab suggests it may potentially be effective in EoE and eosinophilic-driven gastrointestinal diseases. In the aforementioned clinical study in patients with platelet-derived growth factor receptor alpha (PDGFRA) negative- HES by Kuang et al (described in Section 2.1), a subset of patients with symptoms of dysphagia or a diagnosis of EoE was identified (n=5). Four of the patients in Kuang et al had elevated eosinophil counts in the proximal, mid, and/or distal esophagus at baseline. The remaining patient did not have a formal diagnosis of EoE but had a history of dysphagia.

Following 24 weeks of treatment with benralizumab 30 mg Q4W, near complete depletion of eosinophils in the proximal/mid esophagus and the distal esophagus were observed for all 4 patients with elevated esophageal eosinophil concentrations at baseline. Among all 5 patients with EoE or dysphagia symptoms, eosinophils were also depleted in all other GI tissues at Week 24. Improvement in GI symptoms was observed in all 5 patients.

A core set of outcome measures for clinical trials in EoE has been developed through a multidisciplinary collaboration (The COREOS Collaborators 2022). Comprehensive literature reviews, patient surveys and experienced clinicians in this field contributed to build a framework of outcome domains. Several of the recommendations are relevant to the MESSINA study, including the concept of histologic remission. There was consensus that the proportion of patients with <15 eos/hpf in all esophageal locations should be considered for histologic remission, while there was no consensus on using a more stringent threshold of ≤6 eos/hpf. The MESSINA study will apply this more stringent FDA EoE Guidance cut-off of ≤ 6 eos/hpf (FDA 2020). Use of the EoEHSS was encouraged, specifically with both the grade and stage of each component item reported, with EoEHSS remission score of ≤ 3 for grade AND ≤ 3 for stage. Recommendations for endoscopic EREFS outcome was also provided and defined as an EREFS score ≤ 2. Endoscopic inflammatory EREFS-based remission should be defined as the inflammation-associated components (exudate, edema, furrows) score ≤ 2, while endoscopic fibrotic EREFS-based remission should be defined as absence of strictures, moderate and severe rings. Applying this outcome terminology will support the analyses of

data in the context of an evolving understanding of the disease.

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

2.3 Benefit/risk assessment

In order to evaluate the clinical benefit/risk balance for benralizumab, preclinical and clinical data have been taken into consideration. The key goals of treatment in EoE are to decrease the signs and symptoms of EoE, ideally with histologic improvement in esophageal eosinophilia, and improve patient quality of life. By depleting eosinophils, one of the presumed key effector cells in the pathogenesis of EoE, benralizumab is likely to improve outcomes in patients with EoE. Expected benefits of benralizumab over placebo include clinically significant improvements in symptoms of dysphagia, histologic response, and endoscopy scores, as well as other markers of disease activity.

Benralizumab has been well tolerated with the most frequently observed adverse events (AEs) from the asthma and COPD Phase 3 controlled studies being generally reflective of each study's respective patient population. Potential risks of benralizumab are as follows:

- Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.
- Malignancies have been reported at a low incidence in the completed and ongoing studies of benralizumab. Eosinophils have been found in association with solid tumors, especially tumors of epithelial origin (breast and colon) and may play an active role in tumor defense by modulating host defenses, or may be a bystander effect. However, the cause and consequences (i.e. pro-tumorigenic versus anti-tumorigenic) of eosinophil recruitment and accumulation into tumors are unclear (Jacobsen et al 2012).
- Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes observation of the patient at the study site following IP administration for the appearance of any acute drug reactions in line with clinical practice. For patients who select to do the optional/remote location IP administration during the OLE, the first dose of IP during the OLE should be given on-site. In the instructions for remote/at-home administration of IP, the patient will be informed about what symptoms to watch for and to seek medical care in the event of such symptoms. When IP is administered at the patient's home/remotely, it is strongly recommended that the patient is contacted by the Investigator or qualified designee after the dose is administered in line with clinical practice (see Section 6.1.4 for details).

- Development of anti-drug antibodies (ADA) to benralizumab has been documented. Theoretical risks of developing ADA may include decreased effective drug concentrations and hypersensitivity reactions (e.g. anaphylaxis or immune complex disease). There was no impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in asthma.
- 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 tumors. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites or negatively impact the natural history of certain malignant tumors. Risk minimization measures include exclusion of patients with untreated parasitic infection and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities.

Risk of study participation may also include those associated with protocol-mandated study procedures and essential components of the diagnosis and follow-up assessments for patients with EoE. This study of EoE involves baseline and follow-up endoscopies with biopsies. Potential AEs associated with this procedure include bleeding complications, infection, and tears of the GI tract. Patients will be informed of the risks associated with endoscopy and EGD before entering the study.

The benefit/risk assessment for benralizumab in patients with EoE based on previous clinical experience in other indications appears favorable. Risk minimization measures include the exclusion of patients with allergy or reaction to any component of the IP formulation, untreated helminth parasitic infection, and active or recent malignancy, in conjunction with the performance of routine pharmacovigilance activities. An IDMC will be used for this study who will have the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. See Section 9.6 and Appendix A 5 for information regarding the IDMC.

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

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the 52-week study period (DB+OL treatment periods) are presented in Table 7; the objectives and endpoints for the OLE period of the study are provided in Table 8.

Table 7 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

The following objectives/endpoints are for the 52-week study period (DB+OL treatment periods):	
Primary Objective:	**Dual-primary Endpoints/Variables:**
To evaluate the effect of benralizumab 30 mg Q4W on histologic signs and symptoms of EoE in patients with symptomatic and histologically active EoE	• Proportion of patients with a histologic response at Week 24, defined as a peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 24
Secondary Objectives:	**Endpoints/Variables:**
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Key secondary endpoint: Percent change from baseline in tissue eosinophils at Week 24 • Key secondary endpoint: Change from baseline in EoE-HSS grade score at Week 24 • Key secondary endpoint: Change from baseline in EoE-HSS stage score at Week 24 • Key secondary endpoint: Changes from baseline in centrally-read EoE EREFS at Week 24 • Key secondary endpoint Treatment responder rate at Week 24, defined as a composite of histological response (≤ 6 eos/hpf) and clinically meaningful improvement from baseline in DSQ (30% improvement) • Centrally-read biopsies for additional histopathology including tissue eosinophil counts at Week 24 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 24 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 24 • Changes from baseline in PEESS at Week 24
To evaluate the effect of benralizumab 30 mg Q4W on patient reported QOL measures	• Changes from baseline in EoE-QoL-A at Week 24 • SF-36 v2 Health Survey at Week 24
To evaluate the effect of benralizumab 30 mg Q4W on healthcare resource utilization due to EoE	• Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study through Week 24

Table 7 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

Secondary Objectives:	Endpoints/Variables:
To evaluate the effect of benralizumab 30 mg Q4W on patient reported measures of disease severity and health status	• PGI-S at Week 24 • PGI-C at Week 24
To assess the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE	• Serum benralizumab concentration ADA and nAb
Other objectives:	**Endpoints/Variables:**
To describe the longer-term effect of benralizumab 30 mg Q4W in patients with EoE	• Proportion of patients with a histologic response at Week 52, defined as a peak esophageal intraepithelial eosinophil count ≤ 6 eos/hpf • Changes from baseline in DSQ score at Week 52 • Changes from baseline in centrally-read EoE EREFS at Week 52 • Centrally-read biopsies for histopathology and tissue eosinophil counts at Week 52 • Dysphagia-free days as captured by the DSQ • Frequency of dysphagia episodes as captured by the EoE-3D • Changes from baseline in dysphagia associated pain, discomfort, and overall severity as captured by the EoE-3D at Week 52 • Changes from baseline in abdominal pain and nausea as captured by the daily diary at Week 52 • Changes from baseline in PEESS at Week 52 • Changes from baseline in EoE-QoL-A at Week 52 • SF-36 v2 Health Survey at Week 52 • Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study through Week 52 • PGI-S at Week 52 • PGI-C at Week 52

Table 7 Study Objectives for the 52-week Study Period (DB+OL Treatment Periods)

Safety Objective:	Endpoints/Variables:
To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE	Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory values Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height Assessments related to vital signs cover • Observed value • Absolute and percent change from baseline values over time
Exploratory Objectives:	**Endpoints/Variables:**
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity (sub-study)	• Changes from baseline in EndoFLIP (esophageal distensibility) assessment at Week 24 and at Week 52 (sub-study)
To evaluate the effect of benralizumab 30 mg Q4W on early histologic signs, clinical features, symptoms and [redacted] of EoE (sub-study)	• Replicate histology, EREFS and PRO endpoints at weeks 4 and 12 • [redacted]
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on the ability to work, attend classes, and perform regular daily activities	• WPAI+CIQ scores

ADA anti-drug antibody; AEs adverse events; DB Double-blind; DSQ Dysphagia Symptom Questionnaire; EndoFLIP Endolumenal Functional Lumen Imaging Probe; EoE eosinophilic esophagitis; EoE-HSS Eosinophilic Esophagitis- Histology Scoring system; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; eos eosinophils; EREFS Endoscopic Reference Score; hpf high-power field; IP investigational product; nAb neutralizing antibody; OL Open-label; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-C Patient Global Impression of Change; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; Q4W every

4 weeks; QOL Quality of Life; SF-36v2 Short Form-36 Version 2.0; WPAI+CIQ Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions.

Table 8 Study Objectives for the OLE Period

The following objectives/endpoints are for the OLE period of the study:	
Safety Objective:	**Endpoints/Variables:**
1 To assess the safety and tolerability of benralizumab 30 mg Q4W in patients with EoE	Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory values Assessments related to AEs cover • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height Assessments related to vital signs cover • Observed value • Absolute and percent change from baseline values over time
Other Objectives:	**Endpoints/Variables:**
To describe the longer-term effect of benralizumab 30 mg Q4W in patients with EoE	• Changes from baseline in DSQ; frequency of dysphagia episodes (EoE-3D), dysphagia-free days (DSQ), and associated pain, discomfort, overall severity; abdominal pain and nausea (daily diary); EoE-QoL-A up to Week 76 • Changes from baseline in PEESS up to Week 76 • Percent of patients with relevant concomitant procedures and healthcare resource utilization during the study • Centrally-read biopsies for histopathology and tissue eosinophil counts at Week 104 • Changes from baseline in centrally-read EoE EREFS at Week 104 • PGI-S at Week 104
To describe the effect of benralizumab on the use of background EoE medications and related therapies and diet restrictions	• Changes in concomitant medications and diet regimens • Changes in patient experience as reported by PRO
To describe the PK and immunogenicity of benralizumab 30 mg Q4W in patients with EoE	• Serum benralizumab concentration • ADA and nAb

Table 8 Study Objectives for the OLE Period

Exploratory Objectives:	Endpoints/Variables:
[redacted]	[redacted]
To evaluate the effect of benralizumab 30 mg Q4W on clinical features of EoE and disease activity	• Changes from baseline in EndoFLIP (esophageal distensibility) assessment at Week at Week 104 (sub-study)
[redacted]	[redacted]

ADA anti-drug antibody; AEs adverse events; DSQ Dysphagia Symptom Questionnaire; EndoFLIP Endolumenal Functional Lumen Imaging Probe; EoE eosinophilic esophagitis; EoE-QoL-A Adult Eosinophilic Esophagitis Quality of Life Questionnaire; EREFS Endoscopic Reference Score; nAb neutralizing antibody; OLE Open-label Extension; PEESS Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2.0, Children and Teens Report; PGI-S Patient Global Impression of Severity; PK pharmacokinetics; Q4W every 4 weeks; PRO patient reported outcome.

4 STUDY DESIGN

4.1 Overall design

This is a randomized, placebo-controlled, DB, parallel-group, multicenter, Phase 3 study to compare the efficacy and safety of repeat dosing of benralizumab versus placebo in male and female patients 12 to 65 years of age with symptomatic and histologically active EoE.

The clinical study consists of 4 periods:

- a 2- to 8-week run-in period
- a 24-week placebo-controlled, DB, parallel group treatment period (DB period)
- a 28-week OL benralizumab treatment period (OL period)
- an additional OLE treatment period (OLE period)

Approximately 170 eligible patients are planned to be randomized. Recruitment of adolescent patients is targeted to be broadly in line with expected prevalence rates of adolescents in the overall patient population. Approximately 20 adolescent patients (12 to 17 years of age) per arm will be targeted for inclusion in the study.

Following informed consent or assent (if applicable), all patients will enter a run-in period of 2 to 8 weeks during which inclusion/exclusion criteria are assessed, medical history taken, endoscopy with biopsies performed, and PROs, clinical laboratories, and a diet questionnaire are administered. Patients may be on background medications for EoE and related treatments

as long as the background medications have been stable for at least 4 weeks (8 weeks for PPI) prior to screening and there is an agreement not to change type of background medication or dosage during the run-in period and for the first 52 weeks of the study unless a change is medically indicated. If a medication for EoE (including swallowed steroids, systemic steroids and PPI) is discontinued prior to screening, there should be a washout period of a least 8 weeks. The justification and rationale for changes to the background medication for EoE and related treatments should be documented in the eCRF. Additionally, patients should remain on a stabilized diet for treatment of their EoE for at least 6 weeks prior to the run-in period throughout the run-in period and the first 52 weeks of the study unless a change is medically indicated. Diet will be tracked and assessed by the diet questionnaire.

Eligible patients with symptomatic and histologically active EoE before randomization will be randomized in a 1:1 ratio to receive either 30 mg of benralizumab or placebo at 4-week intervals for a 24-week treatment period (DB period). The randomization for adults will be stratified by region (North America vs ROW) and use of swallowed steroids at baseline (categorical, Yes/No). Adolescents will be randomized in a separate stratum with no other factors included.

Adult patients at participating sites will also be offered the opportunity to participate in an Early Time Point Sub-study (section 8.1.5). Approximately 20 patients are targeted to participate in this sub-study aiming to generate early time point evidence and demonstrate the impact of eosinophil depletion in tissue and to understand its relationship with endoscopic findings and symptom response.

Patients who complete the DB, placebo-controlled treatment period on investigational product (IP) will continue into an OL treatment period with benralizumab 30 mg Q4W until Week 52 (OL period).

Patients who prematurely discontinue from IP during the first 52 weeks of the study for any reason should return to the study site for the investigational product discontinuation (IPD) visit. It is recommended that the IPD visit is performed within 4 weeks (±3 days) after the last dose of IP, and the Follow-up (FU) visit 12 weeks (±7 days) after the last dose of IP. Patients are encouraged to return for all scheduled site visits, but without IP administration, following the IPD visit, and to continue with data collection according to the study protocol.

All patients who complete the 52-week treatment period (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) on IP will be offered the opportunity to continue into an OLE period on benralizumab 30 mg Q4W (OLE). The OLE period is intended to allow each patient at least 1 year of treatment with OL benralizumab after completion of the 52-week DB+OL treatment periods. The Sponsor may choose to extend the OLE period beyond one year and reserves the right of terminating the OLE early (eg, if development in this indication is terminated or marketing authorisation is obtained). For

patients who enter the OLE period, background medications and diet for treatment of EoE may be adjusted. Patients who do not enroll in the OLE period will have a follow-up visit 12 weeks after their last dose of IP.

All patients recruited up to and including the date when the required number of patients have been achieved for the primary analysis (minimum of 170 patients including approximately 40 adolescents and 130 adults) will contribute to the primary analysis. If at this time sufficient patients have not been recruited to the Early Time Point Sub-study, recruitment may be extended for sub-study patients only. Sub-study patients recruited after recruitment to the primary analysis population is completed will not be included in the primary efficacy analyses, and will be reported in a later analysis. The primary database lock is targeted to occur when all patients randomised for the primary analysis have completed the 24-week DB treatment period, including those who have had the opportunity to complete at least 52 weeks of follow-up (the 24-week DB treatment period and the 28-week OL treatment period; DB+OL treatment periods) Additional analyses may be performed after the last patient completes 52 weeks of follow up and/or when sufficient patient numbers and follow up in the Early Time Point Sub-study are achieved, if this was not available in the primary analysis.

The final database lock will occur after the last patient completes the OLE period and FU visit. Data reported at this analysis will be presented in an addendum to the primary analysis Clinical Study Report (CSR).

For an overview of the study design see Figure 1 Study design, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

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

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

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

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

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

- Obtaining consent/reconsent /assent/reassent for the mitigation procedures (note, in the case of verbal consent/reconsent/assent/reassent , the Informed Consent Form (ICF) or Assent Form(if applicable) 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 Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

[redacted]

[redacted]

[redacted]

4.3 Justification for dose

The pharmacokinetics (PK) of benralizumab are well-characterized (Wang et al 2017), and it is expected to demonstrate consistent PK across different disease populations. In adult and adolescent patients with severe asthma (SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]) treated with benralizumab 30 mg every 8 weeks (Q8W) or Q4W, near complete blood eosinophil depletions were observed for both dosing regimens. In a study of benralizumab in HES, where patients have higher blood eosinophils and significant organ manifestations of eosinophilic inflammation, a dosing regimen of 30 mg Q4W was effective in reducing blood and tissue eosinophilia (including GI tissue) in patients with varied clinical subtypes of HES (Kuang et al 2019). For the planned clinical study of patients with EoE, which is similar to HES in that the disease is characterized by significant eosinophilic inflammation of tissues that are thicker and less vascular than lung tissue, the Sponsor is proposing a dosing regimen of 30 mg Q4W as it is believed that a higher PK concentration is necessary to generate meaningful eosinophil reduction in the tissues of the esophagus and resolution of associated clinical symptoms.

In the CALIMA/SIROCCO studies, the PK/pharmacodynamic profiles of benralizumab (30 mg Q4W and 30 mg Q8W) were consistent between adolescents and adults, and the safety profile of benralizumab was similar to that of placebo in both adolescents and adults. Among adolescent patients who received benralizumab 30 mg Q4W, the incidence of treatment-emergent adverse events (TEAEs) and the most commonly reported preferred terms were similar to the Q8W group.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study. A patient is considered to have completed the study when he/she has completed his/her last scheduled visit/telephone contact.

As patients will be offered the opportunity to participate in an OLE period of at least 1 year after completing the first 52 weeks of the study (DB+OL treatment periods) on IP, the end of study is planned to be when the last randomized patient completes 1 year in the OLE period. However, AstraZeneca may choose to extend the OLE period (Section 4.1), this decision will

determine when the end of the study is declared. Notification of closure of the study will be communicated to sites at least 3 months in advance of the end of study, unless faster termination is warranted (eg, emergence of a safety concern).

After the end of the study, patients should be given standard-of-care therapy, which may include on label benralizumab, at the discretion of their treating physician, per local practice.

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

5 STUDY POPULATION

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

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

In this protocol, "enrolled" patients are defined as those who sign informed consent or assent (if applicable). "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

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:

Informed consent or assent (if applicable)

1 Provision of signed and dated, written informed consent form or assent form (if applicable) prior to any mandatory study specific procedures, sampling, and analyses.

2 Provision of signed and dated written Genetic informed consent prior to collection of 2 sample for genetic analysis for adult patients.

The Informed Consent Form (ICF)/assent form process is described in Appendix A 3.

Age

3 Patients 12 to 65 years of age, inclusive, at the time of signing the informed consent or assent (if applicable) form.

Type of patient and disease characteristics

4 Documented previous diagnosis of EoE by endoscopy (documented diagnosis defined as an esophageal count of ≥15 eos/hpf on at least 1 esophageal level) and confirmed diagnosis by a centrally-read esophageal biopsy for the purposes of this study (confirmed diagnosis defined as an esophageal count of ≥15 eos/hpf at 2 or more esophageal levels). Two to 4 biopsies should be obtained from both the proximal and distal esophagus. Biopsies can be taken from the mid-esophagus for additional evaluation.

5 Must be symptomatic at Visit 1 (screening) and Visit 2 (randomization):

(a) A patient reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to Visit 1

(a) AND

(b) An average of at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) between Visit 1 and Visit 2, and at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) in each of the 2 weeks immediately prior to randomization

6 Must be adherent to daily diary assessments:

(a) Must complete 70% of daily DSQ diaries between Visit 1 and Visit 2;

(b) AND

(b) Must have completed at least 8 of 14 daily DSQ diaries in the 14 days prior to randomization

7 May be on background medications for EoE and related treatments during the study as long as the background medications have been stable for at least 4 weeks (8 weeks for PPI) prior to screening and there is agreement not to change type of background medication or dosage during the run-in period and for the first 52 weeks of the study unless a change is medically indicated. If a medication for EoE (including swallowed steroids and PPI) is discontinued prior to screening, there should be a washout period of at least 8 weeks. See Section 6.5.1 for details regarding background medications.

Reproduction

8 Negative serum pregnancy test for women of childbearing potential (WOCBP) at Visit 1.

3

9 WOCBP must agree to use a highly effective form of birth control (confirmed by the Investigator) from randomization throughout the study duration and for at least 12 week after last dose of IP. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include:

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

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

(c) Intrauterine device (IUD)

(d) Intrauterine hormone-releasing system (IUS)

(e) Bilateral tubal occlusion

(f) Sexual abstinence, i.e. refraining from heterosexual intercourse (The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.)

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

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

– Women <50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (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 amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

5.2 Exclusion criteria

Medical conditions

1 As judged by the Investigator, any evidence of a medical illness which in the Investigator's opinion makes it undesirable for the patient to participate in the study.

2 Other GI disorders such as active *Helicobacter pylori* infection, history of achalasia, esophageal varices, Crohn's disease, ulcerative colitis, inflammatory bowel disease, or celiac disease.

3 Any clinical significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during 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.

4 Esophageal stricture that prevents the easy passage of a standard endoscope or any critical esophageal stricture that requires dilation during the run-in period.

5 Esophageal dilation performed within 8 weeks prior to screening and prior esophageal surgery that would impact the assessments for EoE.

6 Use of a feeding tube, or having a pattern of not eating solid food daily during the run-in period.

7 Hypereosinophilic syndrome, defined by multiple organ involvement and persistent blood eosinophil count >1500 eos/μL.

8 EGPA vasculitis.

9 Eosinophilic gastritis, gastroenteritis, enteritis, or colitis documented by biopsy.

10 Current malignancy, or history of malignancy, except for:

(a) Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable was obtained.

(b) 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, and assent when applicable, was obtained.

11 History of anaphylaxis to any biologic therapy or vaccine.

12 Current active liver disease, please note:

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

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

13 Helminth parasitic infection diagnosed within 24 weeks prior to screening that has not been treated with or has failed to respond to standard of care therapy.

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

Prior/concomitant therapy

15 Use of immunosuppressive medication (including but not limited to: methotrexate, cyclosporine, azathioprine, and systemic corticosteroids) within 8 weeks prior to screening.

16 Receipt of immunoglobulin or blood products within 30 days prior to screening.

17 Receipt of live attenuated vaccines 30 days prior to randomization..

18 Receipt of inactivated/killed vaccinations (e.g., inactive influenza) within 1 week prior to randomisation

19 Receipt of any marketed or investigational biologic (monoclonal or polyclonal antibody) within 4 months or 5 half-lives prior to screening, whichever is longer.

20 Receipt of oral and/or sublingual allergen immunotherapy within 8 weeks prior to screening.

21 Initiation or change of a food-elimination diet regimen or re-introduction of a previously eliminated food group in the 6 weeks prior to start of and during the run-in period.

Prior/concurrent clinical study experience

22 Previous participation in a benralizumab clinical study.

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

24 Receipt of any investigational drug within 30 days or 5 half-lives prior to screening, whichever is longer.

Other exclusions

25 Currently pregnant, breastfeeding, or lactating women.

26 A serum pregnancy test will be done for WOCBP at screening, and a urine pregnancy test must be performed for WOCBP at randomisation prior to IP administration. A positive urine test result must be confirmed with a serum pregnancy test. If the serum test is positive, the patient should be excluded.

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

4

5.3 Lifestyle restrictions

Women of childbearing potential must use highly effective contraceptive methods throughout the study and at least for 12 weeks (5 half-lives) after last administration of the IP, as stated in Section 5.1, inclusion criterion 9.

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent or assent (if applicable) and for 12 weeks (5 half-lives) after last dose of IP.

5.3.1 Meals and dietary restrictions

Patients should remain on stabilized diet for treatment of their EoE during the run-in and during first 52 weeks of the study, unless a change is clinically indicated. Stable diet is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups.

5.4 Screen failures

Screen failures are defined as patients who signed the informed consent or assent (if applicable) form to participate in the clinical study but are not subsequently randomly assigned to IP/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet criteria for participation in this study (screen failure) may be re-screened after careful consideration by the Investigator and in agreement with the AZ study physician (e.g. if a patient needs a long-term follow up to rule out an exclusory condition). Patients cannot be re-screened more than one time. Re-screened patients should sign new ICF form. In case of re-screening, all medical events that have occurred since the first enrollment will be recorded as part of medical history. All study procedures scheduled for Visit 1 (Table 1) should be repeated at the re-screening visit, with the exception of the EGD and biopsy, which should be completed at the discretion of the Investigator. Re-screened patients should be assigned the same patient number as for the initial screening. Re-screening will be documented so that its effect on study results, if any, can be assessed.

Re-screening a patient after failing the following inclusion/exclusion criteria is not allowed:

- Confirming histologically active disease by centrally-read esophageal biopsy for the purpose of the study, defined as an esophageal count of ≥15 eos/hpf at 2 or more esophageal levels (inclusion criterion #4).
- Biopsy in order to exclude eosinophilic gastritis, gastroenteritis, enteritis, or colitis (exclusion criterion #9)

- Screening in order to confirm a patient-reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to visit 1, or to confirm an average of at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) between Visit 1 and Visit 2, and at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) in each of the 2 weeks immediately prior to randomization (inclusion criterion #5).

Patients may be considered for re-screening in order to meet all other inclusion/exclusion criteria.

6 STUDY TREATMENTS

Study treatment is defined as any IPs (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 or placebo.

6.1 Treatments administered

Descriptions of the IPs are provided in Table 9. Benralizumab and placebo administered in the study will be a clear to opalescent, colourless to yellow solution. Benralizumab and placebo are formulated in 20 mM histidine/histidine hydrochloride monohydrate, 0.25 M trehalose dihydrate, and 0.006% (w/v) polysorbate 20, pH 6.0.

Table 9 Study Treatments

	Treatment 1	Treatment 2
Study treatment name:	Benralizumab	Placebo
Dosage formulation:	30 mg/mL solution for injection in accessorized prefilled syringe (APFS), 1 mL fill volume	Matching placebo solution for injection in APFS, 1 mL fill volume
Dosage level	30 mg every 4 weeks	Matching placebo every 4 weeks
Route of administration:	SC	SC
Dosing instructions:	Benralizumab active solution will be administered SC to patients by healthcare professionals in this clinical study using an APFS. Refer to Section 6.2.	Placebo solution will be administered SC to patients by healthcare professionals in this clinical study using an APFS. Refer to Section 6.2.
Packaging and labelling:	Study treatment will be provided in APFS. Each syringe will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. The labels will be translated into local	Study treatment will be provided in APFS. Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. The labels will be translated into local languages where applicable and required by local regulations.

Table 9 Study Treatments

	Treatment 1	Treatment 2
	languages where applicable and required by local regulations.	
Provider:	AstraZeneca	AstraZeneca

Patients will receive IP (i.e., benralizumab or matching placebo) Q4W. All doses of IP during the 52-week treatment period (DB+OL treatment periods) and the first dose of open-label extension (Visit 15) will be administered at the study site. After Visit 15, IP will be administered as scheduled in the SoA (Section 1.1, Table 2 and Table 3), either at the site during the visit by a healthcare professional or at home/remotely by the patient or caregiver, provided that the Investigator has assessed and trained the patient and/or caregiver for at-home/remote-location administration (Section 6.1.4). The acceptable visit windows are specified in the schedules in Section 1.1, and reasons and procedures for rescheduling investigational product administration are detailed in Section 6.1.5

6.1.1 Before IP administration

All applicable visit procedures, including endoscopy, [redacted] PK, and ADA samples and on-site PRO assessments, must be completed prior to IP administration. No procedures should be performed after the dosing of IP.

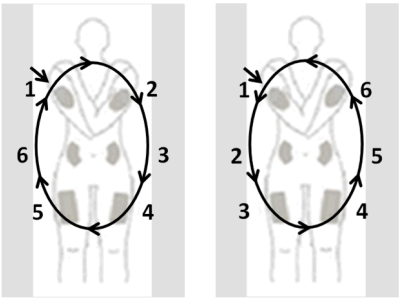
Prior to each IP administration:

- For WOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative (see Section 8.2.2).
- Investigator/authorized delegate will evaluate the patient's condition for potential contraindications for dosing (see Section 6.1.5).
- Investigator/authorized delegate will assess the injection site as per standards of medical care.

6.1.2 IP administration at the study Site

The IP will be administered subcutaneously as a single injection via the APFS by the Investigator/authorized delegate. It is advised that the site of injection of IP is rotated such that the patient receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (see Figure 2). The injection site must be documented in the source at each treatment visit and recorded in the electronic Case Report Form (eCRF). If rotation of the injection site is not possible, the reason should be included in the source.

Figure 2 Injection sites and examples of rotation scheme



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

After IP administration

After IP administration at the study site, the patient should be observed for any acute drug reactions in line with clinical practice (Section 8.4.7). If the patient reports an injection site reaction or other AEs, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

6.1.3 Self-administration of IP as Mitigation to Study Disruption

At Visits 2 and 3, appropriate patients and/or their caregiver may be trained in IP administration by the investigator or designee. If not possible at Visits 2 and 3 this may occur at later visits. This training will be provided to have patients prepared in case remote visits may be required secondary to study disruptions as described in Section 4.1.1. Patients may still participate in the study if they do not consent/assent to this training.

6.1.4 Optional At-home or Remote-Location IP Administration

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

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

Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

Refer to the Study Instructions for At-home or Remote Location Administration of Investigational Product by the Patient and/or His/Her Caregiver for step-by-step guidance, including Investigator assessment/training of patient and/or caregiver, drug accountability, and reconciliation requirements.

The option of at-home or remote-location administration of IP will only be available in countries where allowed according to local regulations.

6.1.4.1 Optional Remote Visits for Patients doing At-Home or Remote-Location IP Administration

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

During the OLE period mandatory on-site visits will occur at approximately 3-month intervals. At these visits the site will dispense up to 3 IP kits at a time. WOCBP should be asked if they are pregnant during the telephone visit.

6.1.5 IP administration re-scheduling

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

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

<u>IP should not be administered, and the dosing is to be re-scheduled in the presence of the following conditions:</u>

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

It is recommended that the AZ study physician/delegate be contacted in case of any questions.

If IP cannot be administered at a scheduled treatment visit (e.g. due to conditions listed above), it can be postponed as necessary and administered as soon as possible.

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

Re-scheduled IP dose can be then administered at an unscheduled visit along with the pregnancy test. Brief physical exam and vital signs assessment 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 (e.g. 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 2 weeks interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the postponed dose will be skipped, and the next dose of IP given at the regularly scheduled visit. The visit schedule will be always calculated from randomization visit date.

If 2 or more doses (consecutive or non-consecutive) of IP are missed[1] within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take place to review the patient's adherence to treatment and decide on the patient's further disposition. During the DB+OL treatment periods, all patients, regardless of whether they remain on IP or not, will be encouraged to remain in the study through the end of the DB+OL treatment periods. Discontinuation procedures are described in Section 7.1.

6.2 Preparation/handling/storage/accountability

Investigational product will be supplied to the site in a kit with an APFS of either benralizumab or placebo. Each kit will have a unique ID that is printed on all labels within the kit (i.e. the outer carton label and the label of each container within the carton).

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

Only patients enrolled in the study may receive IP, and only authorized site staff may supply or administer IP, except when self-administration or administration by patient’s caregiver is an

[1] A ‘missed’ dose is a dose not administered until the next treatment visit window.

option (Section 6.1.3 and 6.1.4). All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container. The IP must be kept under conditions specified on the label (between 2 to 8°C [36 to 46°F], protected from light), with access limited to the Investigator and authorized site staff. The temperature should be monitored on a daily basis and documented in the temperature monitoring log.

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

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

Damaged IP should be documented using the interactive web response system (IWRS)(please refer to IWRS manual for further details).

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

An AstraZeneca site monitor will account for all IP received at the site, for unused IP, and for appropriate destruction of unused IPs. 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. Devices sent to a patient's home must be returned to the site for traceability.

Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual (provided to the sites).

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Methods for assigning treatment groups

All patients will be centrally assigned to randomized IP using an IWRS. Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization. Randomization for adults will be stratified by region (North America vs ROW) and use of swallowed steroids at baseline (categorical, Yes/No). Adolescents will be randomized in a separate stratum with no other factors included. Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized or receive IP. There can be no exceptions to this rule.

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

6.3.2 Methods for ensuring blinding

The first 24 weeks of this study is DB design. During this portion of the study benralizumab and placebo will not be visually distinct from each other. All packaging and labelling of the IP will be done in such a way as to ensure blinding for all Sponsor and investigational site staff. Neither the patient nor any of the Investigators or Sponsor staff who are involved in the treatment, clinical evaluation and monitoring of the patients will be aware of the treatment received during the initial 24-week DB treatment period. Since benralizumab and placebo are not visually distinct, IP will be handled by an appropriately qualified member of the study team (e.g. pharmacist, Investigator or qualified designee) at the site. Following Week 24, all patients will be treated with unblinded benralizumab 30 mg administered SC Q4W until Week 52.

An AstraZeneca 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, the Sponsor must be notified immediately by the Investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list during the study, prior to database lock:

- Those carrying out the packaging and labelling of IP
- Those generating the randomization list
- The AstraZeneca Supply Chain department

The information in the randomization 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 Organization handling data, will have access to the randomization scheme during the conduct of the study.

Maintaining the blind to the patient's eosinophil counts

While not entirely assured, patients on active benralizumab treatment are expected to have lower eosinophil and basophil counts than patients on placebo. Procedures to mitigate unblinding on this basis will be in place from randomization (Visit 2/Week 0) during the entire DB treatment period, and for the first 8 weeks of the OL treatment period (up to Visit 10/Week 32):

- Hematology will be run by the central laboratory. Post-randomization (starting from Visit 2 and up to Week 32), eosinophil and basophil counts will be redacted from the full hematology reports sent back to the investigative sites. Because complete knowledge of

the remaining cell types could permit deduction of the 'eosinophil + basophil' compartment, monocyte counts will also be redacted from the full haematology reports sent back to the investigative sites.

- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases without absolute eosinophil counts, absolute basophil counts or absolute monocyte counts being revealed.
- 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 an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (e.g. administrator or another ancillary person) not directly involved in patient management, to receive and blind any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the patient's management and prior to filing the laboratory report as a source document. Similarly, eosinophil, basophil, and monocyte results must be redacted from all communications with the Sponsor.
- Esophageal biopsies will be centrally read. Additional biopsies are not to be sent to local labs in parallel. Biopsy results will be reported back to the investigative sites for the purposes of confirming eligibility criteria following Visit 1. Week 24 follow-up biopsy results will not be reported back to the investigative sites due to potential risk of unblinding.

6.3.3 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the Investigator(s) or pharmacists from the IWRS. Routines for this will be described in the IWRS user manual that will be provided to each site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator will document and report the action to AstraZeneca, without revealing the patient's treatment randomization 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 IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of

data until all decisions on the evaluability of the data from each individual patient have been made and documented.

6.4 Treatment compliance

The administration of all study treatments (both in the DB, OL, and OLE periods of the study) should be recorded in the source documents, as well as in the appropriate section of the eCRF. The study treatment provided for this study will be used only as directed in this Clinical Study Protocol (CSP).

The IP will be administered SC at the study site on treatment visits and within visit windows as specified in Table 1, Table 2 and Table 3. Any change from the dosing schedule, dose interruptions, dose discontinuations should be recorded in eCRF; dose modifications are prohibited. PRO compliance will be assessed at scheduled assessments as outlined in Table 1, Table 2 and Table 3.

If a patient misses 2 or more doses of IP (consecutively or non-consecutively) within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take 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 missed doses, should be recorded in the appropriate section of the eCRF.

6.5 Concomitant therapy

The Investigator/authorized delegate 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 medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

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

6.5.1 Background medication and related treatments

Background medications for EoE (e.g. swallowed steroids and PPI) and steroid treatments used for asthma or allergies that are inhaled or administered intranasally should be maintained at the same dose and schedule for at least 4 weeks prior to the run-in period. Patients on PPI therapy must report a stable dose for at least 8 weeks prior to the run-in period. If a medication

for EoE (including swallowed steroids, systemic steroids and PPI) is discontinued prior to screening, there should be a washout period of at least 8 weeks.

Background medication for EoE (and related treatments) should remain stable throughout the run-in period and the DB+OL treatment periods (up to Week 52) unless a change is medically indicated. Background medication use will be recorded on the eCRF. The justification and rationale for treatment changes should be documented in the eCRF source notes.

Additionally, patients should remain on a stabilized diet for treatment of their EoE for at least 6 weeks prior to the run-in period throughout the run-in period and the first 52 weeks of the study (see Section 5.3.1) unless medically indicated. Diet will be tracked using a diet questionnaire (see Section 8.11.2).

For patients who enter the OLE period after the first 52 weeks, background medications and diet for treatment of EoE may be adjusted.

Background medication is not regarded as IP but may be provided by AstraZeneca according to local regulations, in order to maintain access to these concomitant therapies from enrolment and throughout the duration of the study until the patient completes or withdraws.

6.5.2 Other concomitant treatment

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

6.5.3 Rescue medication

Rescue medication for EoE is prohibited during the first 52 weeks of the study. Patients not on PPI and/or steroid background medications for EoE at Baseline should not initiate these medications during the first 52 weeks of the study. If such a need arises during the study, the Investigator should consult with the Sponsor.

6.5.4 Restrictions

The restrictions that apply during the study are summarized in Table 10.

If, at discretion of the Investigator, a patient needs treatment with any disallowed medication or changes in background medications for EoE and related treatments, it is recommended that the Investigator contact the AZ study physician to discuss justification.

Table 10 Allowed, restricted, and prohibited concomitant medication and treatments

Unless specifically indicated, all conditions apply from enrolment throughout the study duration.

Medication	Allowed/ Restricted/ Prohibited	Details
Background (maintenance) medication for EoE (e.g. swallowed steroids and PPI), leukotriene inhibitors and steroid treatments used for asthma or allergies that are inhaled or administered intranasally	**Allowed**	Continuation of EoE therapies and medications prior to randomization are allowed. Background medications for EoE and **related treatments** should remain stable within 4 weeks prior to screening (8 weeks for PPI). During run-in and during the course of the study, these medications should remain stable unless a change is medically indicated. If such a need arises during the study, the Investigator should consult with the Sponsor.
Systemic corticosteroids (tablets, suspension, or injections; (e.g. prednisone, prednisolone or related products)	**Restricted**	Disallowed within 8 weeks prior to screening and within 4 weeks prior to endoscopy during the study. Throughout the run-in and the first 52 weeks of the study, allowed for treatment of an AE (e.g. asthma) where there is no alternative treatment available, for no more than 7 days. Allowed at clinical discretion after the first 52 weeks of the study.
Other immunosuppressive medication (including but not limited to: methotrexate, , cyclosporine, azathioprine)	**Restricted**	Allowed for treatment of an AE where there is no alternative treatment available for the duration of <4 weeks. If longer treatment is required, this should be discussed with the AZ study physician to decide on the patient's disposition. Disallowed within 8 weeks prior to screening and for other reasons throughout the study.
Immunoglobulin or blood products	**Prohibited**	Disallowed 30 days prior to screening and during the study.
Antibiotics	**Restricted**	Allowed, but should be managed according to local standards of care and the Investigator's judgment and discussed with AZ study physician based on the potential for a precipitating allergic response.
Antitussives and mucolytics	**Allowed**	

Table 10 Allowed, restricted, and prohibited concomitant medication and treatments

Unless specifically indicated, all conditions apply from enrolment throughout the study duration.

Medication	Allowed/ Restricted/ Prohibited	Details
Dermal topical steroids, topical ophthalmic and otic corticosteroids	**Allowed**	
Antihistamines and ephedrine containing medications	**Allowed**	
Xanthines	**Restricted**	Allowed in a dose equivalent to theophylline ≤400mg q day. For doses greater than 400 mg, the dose has to be stable and blood levels should be confirmed to be ≤12 mg/dL, within 8 weeks prior to screening or during the run-in period. Blood levels >12 mg/dL should be managed according to local standards of care and the Investigator's judgment and discussed with AZ study physician. It is recommended that additional increments in dose are evaluated with blood levels.
Any other marketed or investigational biologic	**Prohibited**	Disallowed if taken for any reason within 4 months or 5 half-lives, whichever is longer, prior to screening and during the study. Not recommended within 12 weeks (5 half-lives) after the last dose of IP.
Any investigational non-biologic drug	**Prohibited**	Disallowed within 30 days or 5 half-lives (whichever is longer) prior to screening, during the treatment period, and is not recommended within 12 weeks (5 half-lives) after the last dose of IP.
Subcutaneous Allergen immunotherapy (SCIT)	**Restricted**	SCIT is allowed if on stable therapy started at least 30 days prior to screening and stable dose is maintained during the study. It is recommended that patient does not receive SCIT on the same day as IP administration.
Oral and/or Sublingual allergen immunotherapy	**Prohibited**	Disallowed within 8 weeks prior to screening and during the treatment period.
Live attenuated vaccines	**Prohibited**	Disallowed within 30 days prior to randomization, during the treatment period and for 12 weeks (5 half-lives) after the last dose of IP.
Inactive/killed vaccinations (e.g., inactive influenza)	**Restricted**	Not recommended within the 7 days before or within 7 days after any IP dosing study visit.

Table 10 Allowed, restricted, and prohibited concomitant medication and treatments

Unless specifically indicated, all conditions apply from enrolment throughout the study duration.

Medication	Allowed/ Restricted/ Prohibited	Details
		Injection site for vaccine should be distant to preceding and next injection site of IP.

6.6 Dose modification

Modification of the dose of benralizumab is not permitted.

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 IP

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 end of the DB+OL treatment periods.

Patients may be discontinued from IP in the following situations.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event that, in the opinion of the Investigator, contradicts further dosing
- Severe non-compliance with the Clinical Study Protocol
- Eligibility requirement found not to be fulfilled that in the opinion of the Investigator or AstraZeneca may put the patient at risk.
  If a patient does not meet all the eligibility criteria but is randomized in error, the Investigator should inform the AZ study physician immediately to discuss potential safety concerns and the best interests of the patient and decide on further patient's disposition.
- Pregnancy.
- Lost to follow up.
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the IP requiring administration of epinephrine

- Development of helminth parasitic infestations requiring hospitalization
- Confirmed reactivation of hepatitis B virus
- If a patient misses 2 or more doses (consecutively or non-consecutively) of IP within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take place to review the patient's adherence to treatment and decide on the patient's further disposition

Before a decision to discontinue a patient from IP is instituted, the AZ study physician should be consulted regardless of the reason for discontinuation. The Investigator should contact the patient if a decision to stop IP is taken. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. The date of last IP dose, the date of IP discontinuation decision and the reason(s) for discontinuation should be documented in the eCRF. Conditions that require administration of IP to be temporarily withheld are described in Section 6.1.5.

Discontinuation of IP will be registered in the IWRS.

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

7.1.1 Procedures for early discontinuation of study treatment and at end of study

7.1.1.1 Early discontinuation of study treatment

All patients who prematurely discontinue IP (during either the DB, OL, or OLE periods) should return to the study site for an IPD visit within 4 weeks (±3 days) after the last dose of IP, and FU visit 12 weeks (±7 days) after the last dose of IP for procedures described in (Table 1, Table 2 and Table 3). The IPD visit replaces the nearest scheduled visit after IP discontinuation. Patients who have discontinued IP prior to Week 52 are not eligible to enter the OLE period.

IPD during the DB+OL treatment periods

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

- Patients are encouraged to return for all scheduled clinic visits, but without IP administration. During this time data collection should continue according to the study protocol.
  - All PRO assessments should continue at home, otherwise the patient should return the handheld device at the IPD visit.

  - An endoscopy with biopsy should be performed at the IPD visit only if ≥12 weeks have elapsed since the prior endoscopy. The endoscopy with biopsy at Week 24 should be performed. If a patient discontinues prior to week 24, the patient should be asked to return for the endoscopy at Week 24 (rather than at the IPD visit).
  - If the FU visit (12 weeks after the last dose of IP) overlaps with a scheduled visit, the procedures for the scheduled visit should be performed
- If the patient is unwilling/unable to attend the scheduled clinic visits until end of the DB+OL period, he/she will be offered a follow-up option that includes monthly telephone contact instead. The patient will be encouraged to attend the FU visit at the study site, if feasible.
  - During telephone follow-up contact(s), the Investigator will collect information about concomitant medications, AE/SAEs, diet, and healthcare resource utilization.
  - The handheld device will be returned at the IPD visit, and no further PRO assessments will be collected.

The approach taken should be recorded in the medical records. A patient that agrees to phone follow-up is not considered to have withdrawn consent or assent (if applicable) or to have withdrawn from the study.

Permanently discontinuing IP shall prompt no further changes regarding EoE therapy; patients should remain on stable background medications and stable diet for EoE during the first 52 weeks of the study, even without IP. If a patient requires initiating a background medication for EoE or related treatment during the study following discontinuation of IP, the Investigator should consult with the Sponsor (Section 6.5.3). Following discontinuation of IP, restrictions and prohibitions on concomitant medications or treatment other than background medications for EoE or related treatments no longer apply.

7.1.1.2 Discontinuation at Week 52

All patients who complete the 52-week treatment period (DB+OL treatment periods) on IP will be offered the opportunity to continue into the OLE period. If a patient chooses not to continue to the OLE period, then the patient will be considered to have completed the study; the site will perform an End of Treatment (EOT) visit at Week 52, and the patient will return for a FU visit 12 weeks (±7 days) after the last dose of IP, after which the patient exits the study. The reason for not entering the OLE period will be recorded in the eCRF.

7.1.1.3 Discontinuation of treatment in the OLE treatment period

During the OLE treatment period, a visit will be defined as an EOT visit when the study is closed at the site for any reason, including when AstraZeneca declares the end of the study (Section 4.4). When a patient discontinues IP for other reasons during the OLE, the visit will be defined as an IPD visit.

The following visits should be performed (Table 2 and Table 3) for all patients who discontinue during the OLE period:

- IPD/EOT visit – within 4 weeks (±3 days) after the last dose of IP
- Follow-Up visit – within 12 weeks (±7 days) after last dose of IP

7.2 Lost to follow-up

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

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

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

7.3 Withdrawal from the study

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

A patient who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).

If the patient and/or legal representative withdraws consent or assent (if applicable) for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent/assent.

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

A patient and/or legal representative who withdraws consent/assent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients as medically indicated. The patient will return the handheld device.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study (end of study is defined in Section 4.4).

See SoA, Table 1, Table 2 and Table 3, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8 STUDY ASSESSMENTS AND PROCEDURES

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

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

The Investigator ensures the accuracy, completeness, 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 the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue IP.

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

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

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy assessments

8.1.1 Histopathology and tissue eosinophil counts

One of the dual-primary endpoints in the study is the proportion of patients with a histologic response at 24 weeks defined as ≤6 eos/hpf across all available esophageal levels.

During the study, EGD biopsies will be conducted as per the schedule provided in Table 1, Table 2 and Table 3. EGD will be performed according to local medical practice. The biopsies will be sent to the central lab for slide preparation and for central, blinded pathology review of tissue eosinophil counts and histopathology. Centralized slide assessments and scoring from independent physician review will be performed for all biopsies.

Details pertaining to EGD biopsy collection are provided in the laboratory manual.

To confirm eligibility at Visit 2, the Visit 1 results of the central biopsy review will be communicated to the site.

The EoE Histology Scoring System (EoE-HSS) may be determined and recorded independently for all available esophageal levels by central, blinded pathology review.

8.1.2 EoE Endoscopic Reference Score

The EoE Endoscopic Reference Score (EREFS) is a scoring system for assessing the presence and severity of the major endoscopic signs of EoE, including esophageal edema, rings, exudates, furrows, and stricture.

The EREFS will be evaluated at the time of each EGD as per the schedule provided in Table 1, Table 2 and Table 3.

The EREFS will be centrally-read from video recordings and Investigator-read during the endoscopies. Centralized imaging data assessments and scoring from expert physician review will be performed for all endoscopies. Standardized methods for training Investigators on the application of EREFS to ensure the collection of quality data using this measure will be implemented. Details on the scoring will be provided to Investigators in a separate manual.

The sites will remove patient-identifying information from the imaging data header prior to sending the imaging data to the central reader.

8.1.3 Patient Reported Outcomes

Between Visit 1 and Visit 21, patients will complete all PRO assessments using a handheld device. The handheld device (or web-based back-up, in case of device failure) will be the only accepted source of PRO data in this protocol (except for PGI-S, see section 8.1.3.5). The

Investigator will ensure that patients are properly trained on the use of this device and the importance of completing assessments as scheduled.

The handheld device will be programmed at Visit 1 with reminder alarms for the daily diary. Study site staff will be able to adjust alarms for specific patient needs as required. The patient will be required to complete a training module before taking the device home.

The Investigator or designee will be responsible for monitoring patient adherence with the daily diary and follow-up as necessary to minimize missing data. Patient compliance should be checked weekly (at a minimum) to ensure that the patient is completing the assessments as scheduled. Monitoring of patient adherence to the diary is critical between Visit 1 and Visit 2 to ensure that the patient meets applicable criteria for randomization. If the patient does not meet the randomization requirements, the device will be deactivated and retained at the site for future use.

Review of patient compliance with the assessment schedule, completion of any available assessments, and logging of the visit on the handheld device should be completed prior to other study procedures.

Compliance with the assessment schedule should be reviewed weekly throughout the study. Patients with low compliance should be reminded to complete their assessments through follow-up phone calls and during site visits. Correcting poor compliance is required to ensure sufficient data are available for supporting the dual-primary endpoint of this study.

The timing and frequency for each PRO is outlined in Table 4. The schedule used in the DB+OL periods is also used for the first 24 weeks of the OLE period, though fewer PROs are assessed in the OLE period. The handheld device will be returned to the study site at Week 76.

8.1.3.1 Dysphagia Symptom Questionnaire (DSQ)

The DSQ is a PRO measure validated for patients age 12 and older with dysphagia related to EoE (Dellon et al 2013). The presence and severity of dysphagia symptoms in the past day are captured in a 4-item questionnaire.

Questions 1 and 2 utilize yes/no response capture if the patient consumed solid food that day (yes/no; unscored) and instances of food going down slowly or becoming stuck in the throat or chest (scored 0 for no and 2 for yes). Please note, if the patient reports not eating solid food, then the DSQ is considered missing for that day. Question 3 asks about the severity of dysphagia, based on actions the patient took to relieve the dysphagia at its worst point during the day. It ranges from 0 (dysphagia cleared up on its own) to 4 (patient sought medical attention for dysphagia). Question 4 asks the patient to report the worst pain experienced while swallowing food over the past 24 hours (no pain [0] to very severe pain [4]).

The total DSQ score ranges from 0 to 84, with a lower score indicating less severe dysphagia. Questions 2 and 3 are the only questions that contribute to the total DSQ score. The score is calculated by multiplying the daily scores of questions 2 and 3 by 14 days and dividing by the number of days in the past 14 days with no missing data. Question 4 is a standalone item intended to be evaluated separately. The DSQ can only be scored if there are at least 8 days with no missing data. Using anchor-based methods, the minimal clinically important differences (MCID) and clinically important difference (CID) in DSQ score (mean absolute change) were estimated to be −6.5 points and −13.5 points, respectively (Hudgens et al 2017). Using DSQ Question 2, dysphagia-free days over each 28-day period following randomization will also be summarized.

The DSQ assessments will be completed by patients daily starting at Visit 1 as described in Table 4.

8.1.3.2 EoE-3D and additional daily questions

The Eosinophilic Esophagitis Daily Dysphagia Diary (EoE-3D) is a daily diary focused on the patient experience of EoE. The diary is episode-based and uses reporting over the past 24 hours.

The EoE-3D consists of 6 items and focuses on components of an episode of dysphagia. In the EoE-3D, respondents are asked to first report on whether they experienced episodes of difficulty swallowing in the past 24 hours and if so, how many. Patients are asked to report the time at which the episode occurred to facilitate recall and subsequently respond to 3 questions on the pain, discomfort, and overall severity of the event using an 11-point numeric rating scale (0 [no] to 10 [worst]). These items are repeated for each episode reported by the respondent. Therefore, the EoE-3D allows for an assessment of the frequency count of episodes over time as well as a characterization of the severity of the episode experience over time.

Patients are also asked several additional questions to characterize their daily experience. These items will be scored separately from EoE-3D. Patients reporting no solid food consumption will be asked to report if this is due to their eosinophilic esophagitis or due to other reasons. Patients will be asked to report, via two separate questions, the severity of abdominal pain and the severity of nausea at their worst over the past 24 hours using similar 11-point numeric rating scales.

Dysphagia episode frequency will be summarized as the total number of dysphagia episodes occurring over each 28-day period following randomization. Calculation of the 28-day dysphagia episode frequency will require at least 16 days of evaluable data in the period; otherwise, the period will be set to missing.

Dysphagia related pain, discomfort and overall episode severity will be recorded for each episode. The severity of these episode characteristics (pain, discomfort, overall severity) will be summarized as 14-day mean scores. The 3 separate 14-day means will be calculated as the sum of episode response(s) divided by the number of episodes in the same 14-day period. Calculation of the 14-day mean scores will require at least 8 days of evaluable data during the period; otherwise, the mean scores will be set to missing.

Abdominal pain severity and nausea severity will be summarized individually as 14-day mean scores. Each 14-day mean score will be calculated as the sum of daily NRS responses divided by the number of days with evaluable data in the same 14-day period. Calculation of the 14-day means will require at least 8 out of 14 days of evaluable data; otherwise, the mean score will be set to missing.

The daily diary assessments, including EoE-3D, will be completed by patients daily starting at Visit 1 as described in Table 4.

8.1.3.3 Adult Eosinophilic Esophagitis Quality of Life Questionnaire (EoE-QoL-A)

The Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) questionnaire is a 30-item assessment developed specifically to capture health-related quality of life (HRQoL) in patients with EOE (Taft et al 2011). The assessment is divided into 5 domains: eating/diet impact, social impact, emotional impact, disease anxiety and swallowing anxiety. Patient response is captured via a 5-point rating scale. Overall and domain scores are calculated by taking the mean of item responses.

The EoE-QoL-A assessments will be completed by patients weekly (ie., every 7 days) starting from Visit 1 as described in Table 4.

8.1.3.4 Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2, Children and Teens Report (PEESS)

The Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2, Children and Teens Report (PEESS) is an 18-item assessment of EoE symptom severity and frequency validated for use in patients age 8 to 18 years. The recall period is one month. The first 18 questions alternate between a question about a given symptom's frequency (never, almost never, sometimes, often, almost always) and a question about the symptom's severity (face rating scale with drawings representing not bad at all, a little bad, kind of bad, bad, very bad). The remaining two questions ask about frequency of eating less food than others and frequency of needing more time to eat than others. The overall score ranges from 0 to 80, with higher scores representing more severe and frequent EoE symptoms.

The PEESS will be completed only by patients who are age 18 years or under at Visit 1. The assessment will be completed monthly as described in Table 4 and as per the schedule provided in Table 1, Table 2 and Table 3.

8.1.3.5 Patient Global Impression of Severity

Patient Global Impression of Severity (PGI-S) is a single item designed to capture the patient's perception of overall symptom severity over the past 14 days using a 6-point categorical response scale (no symptoms to very severe symptoms).

The PGI-S assessment will be completed by patients on the device every two weeks (i.e., every 14 days) starting from Visit 1 as described in Table 4. At Visit 21 and Visit 28 (or IPD/EOT visit if before Visit 28), PGI-S will be administered by interview and the data will be entered into the eCRF.

8.1.3.6 Patient Global Impression of Change

Patient Global Impression of Change (PGI-C) is a single item assessment to capture the patient's perception of change in health status. The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point scale (Much better, Moderately better, A little better, About the same, A little worse, Moderately worse, Much worse).

The PGI-C assessment will be completed by patients weekly (i.e., every 7 days) starting 7 days after Visit 2 as described in Table 4.

8.1.3.7 SF-36 (Version 2), Acute Recall

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

Two types of thresholds have been developed for interpretation of SF-36v2 scores. The first type is suitable for comparing group mean scores and is generally referred to as the MCID. The second type is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (QualityMetric 2011). Threshold values for the SF-36v2 scale and summary measures are provided in Table 11.

The SF-36v2 assessment should be completed using the handheld device as described in Table 4. If the SF-36v2 is not complete by the time the patient arrives at the site, the patient

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

Table 11 Threshold values for the SF-36v2 scale and summary measures

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

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

8.1.3.8 Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions (WPAI+CIQ)

The WPAI+CIQ consists of questions about how health and health-related issues impact the ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss. The questionnaire will be completed using the handheld device.

The WPAI+CIQ assessment should be completed using the handheld device as described in Table 4. If the WPAI+CIQ is not complete by time the patient arrives at the site, the patient will complete the WPAI+CIQ at the site using the handheld device prior to other study procedures.

8.1.4 EndoFLIP (esophageal distensibility) – sub-study

EndoFLIP (Endolumenal Functional Lumen Imaging Probe) is an imaging tool utilizing high-resolution impedance planimetry to investigate pressure and cross-sectional area relationships during serial volumetric distention, thereby measuring both esophageal distensibility and compliance.

At select sites, EndoFLIP will be performed by an EndoFLIP expert at the time of endoscopy as per the schedule provided in Table 1. The data obtained from the EndoFLIP measurements will be analysed with a FLIP analytic software and reviewed by an EndoFLIP expert.

Details on the procedure will be available in a separate EndoFLIP Guide provided to the sites.

8.1.5 Early Time Point Sub-study

In asthmatic patients, the enhanced ADCC activity of benralizumab results in the rapid and nearly complete depletion of eosinophils in the blood, as well as depletion of eosinophils in the lung tissue, sputum, and bone marrow as early as 4 weeks post dose (Busse et al 2013,

Kolbeck et al 2010, Laviolette et al 2013). Rapid depletion of eosinophils in esophageal tissue has also been observed (Freeman et al 2020).

To generate early time point evidence and demonstrate the impact of eosinophil depletion in tissue and to understand its relationship with endoscopic findings and symptom response, additional endoscopies will be performed in an Early Time Point Sub-study according to the SoA (Table 1). Additional blood samples will also be collected (see Table 1).

Adult patients at participating sites will be offered the opportunity to participate in the Early Time Point Sub-study. Approximately 20 patients are targeted to participate in this sub-study.

All patients recruited up to and including the date when the required number of patients have been achieved for the primary analysis (minimum of 170 patients including approximately 40 adolescents and 130 adults) will contribute to the primary analysis, including any patients already recruited to the Early Time Point Sub-study. If at this time sufficient patients have not been recruited to the Early Time Point Sub-study, recruitment may be extended for sub-study patients only. Sub-study patients recruited after recruitment to the primary analysis population is completed will not be included in the primary efficacy analyses, and will be reported in a later analysis.

8.2 Safety assessments

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

8.2.1 Clinical safety laboratory assessments

See Table 12 for the list of clinical safety laboratory tests to be performed and see the SoA (Table 1, Table 2 and Table 3) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

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 center as source data for laboratory variables.

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

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded in the patient's medical records.

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory.

Table 12 Laboratory safety variables

Clinical chemistry		Hematology	Urinalysis
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Color
BUN (blood urea nitrogen)	Potassium	Platelet count	Ketones
Calcium	Sodium	Red blood cell (RBC) count	Microscopy including WBC/high power field (HPF), RBC/HPF
Chloride	Total bilirubin	WBC count (absolute and differential)[a]	pH
CO_2 (carbon dioxide)[b]	Uric acid		Specific gravity
Creatinine	Creatine kinase		
Cholesterol, total			

[a] Eosinophil, basophil, and monocyte counts and differentials will be redacted from the central laboratory reports starting from Visit 2 (see Section 6.3.2).
[b] Measured as bicarbonate.

8.2.1.1 Other laboratory assessments

Serology

Blood samples for the hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C antibody (anti-HCV), and the HIV-1 and HIV-2 antibodies will be taken according to the SoA (Table 1, Table 2 and Table 3). The analysis will be performed at the central laboratory. Any low-positive or indefinite results must be confirmed prior to determining the patient's eligibility.

For patients that are HBsAg positive or anti-HBc positive at Visit 1, hepatitis B e-antigen (HBeAg), hepatitis D antibody (anti-HDV) and hepatitis B-virus (HBV) DNA testing will be performed. For these subjects that are HBsAg positive or anti-HBc positive, ALT and HBV DNA will be drawn monthly at on-site visits to monitor for hepatitis B reactivation. Similarly, if patient is using self-administration option, this assessment will be performed at on-site visits.

Instructions for sample collection, processing, storage, and shipment will be found in the central laboratory manual.

8.2.2 Pregnancy test

A serum pregnancy test will be done for WOCBP during the run-in period. A urine pregnancy test will be performed for WOCBP at each on-site treatment visit prior to IP administration. The frequency of urine pregnancy testing is adjusted after week 52 according to the SoA. A positive urine test result must be confirmed with a serum pregnancy test. If a serum test is positive, the patient should be excluded.

The following tests are applicable to female patients only and will be conducted as per the schedule provided in Table 1, Table 2 and Table 3, as applicable.

- FSH: The test will be performed at Visit 1 only to confirm postmenopausal status in women <50 years of age who have been amenorrheic for ≥12 months. This test is to be sent to and analysed at the central laboratory.
- Serum beta- human chorionic gonadotropin (HCG): The test will be performed at Visit 1 for WOCBP (defined in inclusion criterion 10). This test is to be sent to and analysed at the central laboratory.
- Urine HCG: The dipstick test will be performed at the study site for WOCBP as per the schedule provided in Table 1, Table 2 and Table 3. At each on-site treatment visit, the test will be performed before IP administration. This kit is to be provided by the central laboratory and analysed locally at the sites. Between on-site pregnancy tests, WOCBP should be encouraged to follow contraceptive measures and to carefully monitor for pregnancy. If the urine test result is positive, the patient should contact the site and should not administer IP.

8.2.3 Physical examinations

Physical examinations (complete or brief) will be done in accordance with the schedule provided in Table 1, Table 2 and Table 3. Baseline data will be collected at the randomization visit (Visit 2) before first dose of IP. Any new findings or aggravated existing abnormalities, judged as clinically significant by the Investigator, will be reported as an AE as described in Section 8.3.7.

The complete physical examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular, and respiratory system.

8.2.3.1 Weight and height

The patient's height and weight will be measured in accordance with the schedule provided in Table 1, Table 2 and Table 3. The patient's weight will be recorded in kilograms and height will be recorded in centimetres.

Weight and height measurements will be performed in light clothing and without shoes.

8.2.4 Vital signs

Pre-dose vital signs, including pulse rate, blood pressure, respiratory rate will be assessed in accordance with the schedule provided in Table 1, Table 2 and Table 3.

It is recommended that vital signs are assessed before any interventional study procedures (blood test collection, IP administration), and prior to administration of EoE maintenance therapy, if possible.

Blood pressure and pulse measurements will be assessed while sitting with a completely automated device. Manual techniques will be used only if an automated device is not available. The pulse rate and blood pressure should be measured after the patient has been resting for at least 5 minutes in a quiet setting without distractions (e.g., television, cell phones). The pulse rate will be obtained before blood pressure.

The respiration rate will be obtained after the patient has been resting for at least 5 minutes, by counting the number of breaths (how many times the chest rises) for 1 minute.

8.2.5 Electrocardiograms

Single 12-lead electrocardiograms (ECG) will be obtained in accordance with the schedule provided in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. The ECG results will be interpreted locally.

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printouts will be signed and dated by the Investigator and stored at the study site. Any findings will be recorded in the eCRF.

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

8.3 Collection of adverse events

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

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up on AEs see Section 8.3.2.1.

8.3.1 Method of detecting AEs and SAEs

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

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from time of signature of informed consent or assent (if applicable) form, throughout the treatment period and including the follow-up period/last contact with the patient (including the phone follow-up period).

SAEs will be recorded from the time of signing of informed consent form.

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

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

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

8.3.2.1 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 Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.

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

8.3.3 Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the end of the study (database lock) 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 AEs/SAEs at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum NCI CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for serious AE

- Date Investigator became aware of serious AE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Causality assessment in relation to study procedure(s)
- Description of the SAE

The grading scales found in NCI CTCAE version 5.00 will be utilized for all events. For those events without assigned CTCAE grades, the Investigator should assign the CTCAE criteria based on the CTCAE definitions. A copy of the CTCAE version 5.00 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality collection

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

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

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

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized 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 fulfill any of

the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.3.8 and Section 8.3.9.

8.3.8 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of EoE. Events which are unequivocally due to EoE 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. Outcomes associated with EoE, such as food impaction, and symptoms or signs, such as dysphagia, vomiting, heartburn, and abdominal pain will be recorded as AEs only when:

- The event is serious according to definitions, see Appendix B.
- The patient discontinues IP due to the event.
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing EoE history (defined as within 1 year of Visit 1) as judged by the Investigator.

Outcomes associated with EoE that do not fulfil any of the above criteria will be captured under healthcare resource utilization (see Section 8.10).

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a stricture that requires dilatation should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. Interventions that occur due to disease progression will be collected and analysed as healthcare resource utilization measures (see Section 8.10).

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

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

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

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

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

If the electronic data capture system is not available, then the Investigator or other study site staff reports a SAE to the appropriate Sponsor representative by telephone.

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

The reference document for definition of expectedness/listedness is the Investigator's Brochure for benralizumab.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study patient has received any IP

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

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

8.4.2.1 Maternal exposure

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defects) 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 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

8.4.3 Paternal exposure

Pregnancy of a patient's partner will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented for conceptions occurring from the date of the first administration of IP until 12 weeks (5 half-lives) after the last administration of IP.

8.4.4 Overdose

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

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

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.5 Device Constituent Deficiencies

In a combination drug-device IP (e.g. APFS), the Device Constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and incorrect information supplied by the manufacturer.

SADE (Serious Adverse Device Effect) is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.
The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.4.5.1 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.

8.4.6 Medication error

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

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

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

8.4.7 Management of IP-related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, corticosteroids, etc, and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F 4.

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

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both, and at least 1 of the following: a) respiratory compromise; 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 F 2.

Patients will have had a pre-assessment (i.e. vital signs) prior to IP administration and should be observed after IP administration for any acute drug reactions in line with clinical practice.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator. If local analysis of serum tryptase is unavailable, there will be an option to have the sample analysed at the central lab.

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.

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.

Serum will be collected pre-dose in accordance with the schedule provided in Table 1, Table 2 and Table 3.

8.5.1 Determination of drug concentration

Samples for determination of benralizumab concentration in serum will be analysed for all patients receiving benralizumab at an appropriate contract laboratory on behalf of AstraZeneca, using a validated bioanalytical method.

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

8.5.2 Storage and destruction of pharmacokinetic samples

Samples may be stored for a maximum of 5 years from the date of the last patient's last visit (end of study is defined in Section 4.4), after which they will be destroyed.

Guidance regarding handling, transport, and destruction of human biological samples is provided in Appendix C.

8.6 Pharmacodynamics

Blood eosinophil levels are an important marker of the pharmacodynamic effect of benralizumab and will be assessed as part of the hematology safety testing, see Section 8.2.1.

[redacted]

[redacted]

8.7 Genetics

8.7.1 Optional exploratory genetic sample

A blood sample for DNA isolation will be collected at one time point only 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. The blood sample should be collected at randomization (Week 0); however, it may be taken at any visit until the last study visit. In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient.

Adolescent patient samples will not be collected for optional genetic research.

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 Laboratory Manual.

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. Deoxyribonucleic acid (DNA) is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

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

8.8 [redacted]

[redacted]

[redacted]

[redacted]

8.9 Immunogenicity

Blood samples for determination of ADA in serum will be assayed at the discretion of AstraZeneca by bioanalytical test site operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report. ADA samples may also be further tested for characterization of the ADA response. Neutralizing antibodies (nAb) may be assessed on ADA positive samples. Samples will be collected according to the SoA (Table 1, Table 2 and Table 3), labelled, stored and shipped as detailed in the Laboratory manual.

8.10 Healthcare resource utilization

Healthcare resource utilization data, associated with medical encounters related to EoE, will be collected in the eCRF by the Investigator or designee for all patients throughout the study. The data may be used as input to cost analyses for example cost utility analysis or cost effectiveness analysis. Protocol-mandated procedures, tests, and encounters are excluded.

At visits when healthcare use is being collected, as specified in the SoA (Table 1, Table 2 and Table 3) the Investigator should ask the patient if they have had any need to seek medical treatment for EoE or an EoE-related episode (e.g., an intervention for food impaction or stricture requiring dilatation) since last healthcare resource utilization assessment during the previous scheduled visit.

8.11 Other assessments

8.11.1 [redacted]

[redacted]

[redacted]

8.11.2 Diet questionnaire

A diet questionnaire will be completed at Visit 1, monthly between Visit 2 and Visit 28 (Week 104), and thereafter at 3-month intervals in accordance with the schedule provided in Table 1, Table 2 and Table 3. The Investigator or designee will interview the patient and enter the information via a web portal.

The diet questionnaire is a tool to capture patient-reported diet and eating behaviors related to EoE. The questionnaire will consist of sections related to initiation or discontinuation of elimination diets and the defining parameters of these diets. Further, the questionnaire will ask patients to characterize EoE-related eating behaviours or self-initiated symptom management techniques.

8.11.3 Patient Testing Due to Public Health Crisis

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

9 STATISTICAL CONSIDERATIONS

All patients recruited up to and including the date when the required number of patients have been achieved for the primary analysis (minimum of 170 patients including approximately 40 adolescents and 130 adults) will contribute to the primary analysis. If at this time sufficient patients have not been recruited to the Early Time Point Sub-study, recruitment may be extended for sub-study patients only. Sub-study patients recruited after recruitment to the primary analysis population is completed will not be included in the primary efficacy analyses, and will be reported in a later analysis.

The primary database lock is targeted to occur when all patients randomised for the primary analysis have completed the 24-week DB treatment period, including those who have had the opportunity to complete at least 52 weeks of follow-up (i.e., DB+OL treatment periods). The primary CSR for the study will be written based on this analysis and all data reported up to the primary database lock will be included. Additional analyses may be performed after the last patient completes 52 weeks of follow up and/or when sufficient patients numbers and follow

up in the Early Time Point Sub-study is achieved, if this was not available at the primary analysis.

The final database lock will occur after the last patient completes the OLE period and FU visit. Data reported at this analysis will be presented in an addendum to the primary analysis CSR.

9.1 Statistical hypotheses

For the first primary endpoint of proportion of patients achieving a histological response at Week 24, the null hypothesis is that the odds of responding on benralizumab 30mg Q4W is equal to the odds of responding on placebo (this can be interpreted as the proportion of responders on benralizumab 30 mg Q4W is equal to the proportion of responders on placebo). The alternative hypothesis is that the odds of responding on benralizumab 30 mg Q4W is not equal to the odds of responding on placebo, i.e.:

H_0: Odds ratio (benralizumab 30 mg / Placebo) = 1

H_1: Odds ratio (benralizumab 30 mg / Placebo) ≠ 1

For the second primary endpoint of change from baseline in DSQ score at Week 24, the null hypothesis is that the change in DSQ for patients on benralizumab 30 mg Q4W is equal to the change in DSQ for patients on placebo. The alternative hypothesis is that the change in DSQ for patients on benralizumab 30 mg Q4W is not equal to the change in DSQ for patients on placebo, i.e.:

H_0: Difference in change from baseline in DSQ at Week 24 (benralizumab 30 mg – Placebo) = 0

H_1: Difference in change from baseline in DSQ at Week 24 (benralizumab 30 mg – Placebo) ≠ 0

Hypothesis testing for the primary analyses will be performed at the 2-sided 5% significance level. If the p-value is less than 0.05 and the treatment effect favors benralizumab, reject H_0 and accept H_1.

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

9.2 Sample size determination

Approximately 170 patients will be randomized in a 1:1 ratio to benralizumab or matching placebo. This will provide >95% power for the first primary endpoint of proportion of patients achieving histological response to demonstrate an increase from 20% or less on

placebo, to 50% on benralizumab at the 2-sided 5% significance level. This is a conservative estimate of the likely placebo histological response rate as lower placebo rates have been reported in previous EoE studies (Hirano et al 2017, Dellon et al 2017). The power calculation for the second primary endpoint of the change from baseline in DSQ score at Week 24 is based on detecting similar effect sizes (mean difference in change from baseline of the PRO / standard deviation) as seen in previous studies (Hirano et al 2017, Hudgens et al 2017, Lucendo et al 2017). Assuming an effect size of 0.6, which equates to a 7.2-point difference in change in the DSQ, 85 patients per arm will allow >95% power for statistical significance at the 5% 2-sided level. The high level of power for the primary endpoints will ensure stronger statistical evidence can be demonstrated in this single Phase 3 study.

The amount of missing data for the histological response rate endpoint is expected to be low, based on rates previously reported; 96% of patients in Hirano et al 2017 had peak eosinophil counts available at Week 12; 94% of patients in Dellon et al 2017 had evaluable post-treatment DSQ and biopsy data at Week 12. There is some uncertainty in the amount of missing data for the DSQ endpoint at Week 24 given the limited data available to date on this tool and differences in length of follow-up between this study and the referenced trials. However measures are in place in the protocol to limit missing data by excluding non-compliance during the run-in period and monitoring overall compliance with the PRO on an ongoing basis. In addition, patients who discontinue randomised therapy are accounted for in the analyses using a composite estimand strategy. Given this estimand strategy which imputes outcomes for the most likely potential source of missing data, it is considered un-likely that there will be much remaining missing data in the analyses, but with missing data rates at Week 24 as high as 25%, the study still maintains >90% power for statistical significance under the assumptions highlighted above.

Success in the adolescent population will be dependent on demonstrating broadly consistent results with the overall population. With 20 adolescents per arm there is a high chance of demonstrating consistent effects, if they truly exist. For the histological response rate at Week 24 endpoint, there is a 99% chance of observing an adolescent treatment difference that is at least half of the overall population effect, assuming the true histological response rates are 65% on benralizumab and 10% on placebo. For the change in DSQ endpoint at Week 24 there is an 86% chance of observing an adolescent treatment difference that is at least half of the overall population effect, assuming the true treatment effect for the DSQ endpoint is as outlined in the sample size justification above.

The focus of the Early Time Point Sub-study is to characterise the time profile of tissue eosinophil depletion with benralizumab, with contextualisation versus the placebo control arm. Therefore the sample size of this sub study has been chosen to adequately characterise the changes in tissue eosinophils over time. For example, 10 patients per arm provides >80% power for statistical significance at the 2-sided 5% level to detect a difference between

benralizumab and placebo in the % change from baseline in tissue eosinophils of at least 80% (eg 20% increase on placebo versus 60% reduction on benralizumab). A pooled standard deviation of 60 is assumed in these calculations based on the dupilumab phase 2 data on % tissue eosinophil reduction at week 12, where a 14% increase on placebo versus 93% reduction on dupilumab was observed (Hirano et al 2017).

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
All patients analysis set	All patients screened for the study, to be used for reporting of disposition and screening failures.
Full analysis set	All randomized patients who received at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomized treatment irrespective of whether or not they have been prematurely discontinued, according to the ITT principle. Patients who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The Safety analysis set consists of all patients who have received at least one dose of IP. Erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received active IP is classified as active. Safety summaries and ADA data will be based on this analysis set and for whom any post-dose data are available.
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 (e.g. received wrong dose) and who had at least 1 quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set.
OL benralizumab analysis set	All patients who start or carry on receiving at least 1 dose of benralizumab after the end of the Week 24 DB treatment period.
OLE benralizumab analysis set	All patients who carry on receiving at least 1 dose of benralizumab after the end of the Week 52 DB + OL treatment periods.

ADA Anti-drug antibodies; DB Double-blind; IP Investigational product; ITT Intent-to-Treat; OL Open-label; OLE Open-label extension period ; PK Pharmacokinetic

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until the primary database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before 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.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP. Details are described in the SAP.

9.4.1 Efficacy analyses

9.4.1.1 General principles

The primary efficacy analyses will be based on the DB placebo-controlled first 24 weeks of the study (DB period). In this part of the study all efficacy analyses will use the full analysis set (FAS) as defined above, and patients will be analysed according to their randomized treatment, following the Intention-to-Treat principle.

A composite estimand strategy will be used for the primary analyses of endpoints at week 24, whereby any patient with intercurrent events of IP discontinuation, an increase of background therapy or addition of a new therapy for EoE, or having a dilation procedure will be considered as treatment failures at week 24. For the histologic response rate endpoint, patients with these intercurrent events prior to week 24 will be considered non-responders at week 24; for the change in DSQ at week 24 endpoint, and for other change from baseline continuous endpoints, any patient experiencing the described intercurrent events will have their week 24 value imputed using return to baseline multiple imputation methods.

All patients who prematurely discontinue from IP or have any changes to background therapies for EoE are asked to come in for all visits and study assessments up to week 52. Therefore, sensitivity analyses can be performed to assess the robustness of the efficacy results to these estimand approaches and missing data assumptions as described in individual endpoint analysis methods and Section 9.4.1.2 below.

Analyses will include factors or strata (as appropriate) for each of region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline, to ensure any imbalances in these factors are adjusted for in the treatment effects estimated. However, in the instance of convergence issues/small strata for stratified analyses, presence of strictures at baseline may be removed if necessary.

All analyses of Week 52 endpoints will be descriptive as no placebo control is available at that timepoint and so no hypothesis testing will be performed. Week 52 analyses will primarily be presented on the FAS, but a repeat of key analyses may also be produced on the OL benralizumab analysis set to ensure only patients who switched to receive benralizumab after 24 weeks are included in the denominator for that group and to ensure a meaningful

interpretation of the placebo-to-benralizumab patients. Full details of the Week 52 analysis groupings and methods will be provided in the SAP.

Demography and baseline characteristics will be summarized by treatment group for the FAS. In the event that there are major differences between the FAS and safety analysis set, these summaries will also be repeated for the safety analysis set.

9.4.1.2 Primary analysis method

Histological response rate

The first of the primary dual endpoints, the proportion of patients achieving a histological response at Week 24, will be compared between benralizumab and placebo using a CMH test stratified by region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline. The results of the analysis will be presented using an odds ratio, together with its associated 95% confidence intervals (CIs) and 2-sided p-value. Results will also be transformed into a difference in proportions for ease of interpretation. The number and percentage of histological responders will also be summarized by randomized treatment with confidence intervals around the proportions.

A sensitivity analysis to the CMH test may be performed using a logistic regression with covariates.

The analysis of histological response rate at Week 24 will include data collected at the Week 24 visits including a window of +/−2 weeks. Patients with no biopsy data at Week 24 will be considered non-responders. Sensitivity analyses may be performed including all post-baseline biopsy data to assess the impact of any additional data collected that may have been outside of the Week 24 window.

Change from baseline in Dysphagia Symptom Questionnaire (DSQ)

The second of the dual-primary endpoints, the change from baseline in DSQ score at Week 24, will be compared between the benralizumab and placebo treatment groups using a composite estimand strategy where subjects with the intercurrent events described above at or before week 24 will have their change from baseline value imputed at each timepoint from the time of the intercurrent events occurring onwards using return-to-baseline multiple imputation. This method will impute values multiple times for the change from baseline drawing from a normal distribution with mean 0 and variance as a function of the number of completers and variance of the completers, $Vimp = (1 + 1/N_c)*V_c$. For each imputation

dataset, the change from baseline in DSQ score at Week 24 will then be analyzed using an analysis of covariance (ANCOVA) model.

The model will include change from baseline in DSQ score at Week 24 as the dependent variable, baseline DSQ score as a continuous covariate, and region, swallowed steroids used at baseline (categorical, Yes/No), and presence of strictures at baseline as categorical covariates. The model will be used to estimate the mean change from baseline at Week 24 for each treatment group and the difference versus placebo, with corresponding 95% confidence limits. A p-value, corresponding to a 2-sided test, will be presented to compare the benralizumab and placebo treatment groups. Results will be combined across the imputations using Rubin's rule (Rubin et al 1986, Rubin et al 1987).

Descriptive statistics to summarize reasons for non-evaluable daily DSQ score data due to the patient reporting no solid food consumption will be provided. Full details will be defined in the SAP.

To support the change from baseline in DSQ results, clinically meaningful within patient change responder categories will be defined and proportion of responders summarized by visit. The threshold used to define responder categories will be explored using the data generated in this study using anchor based methods supplemented with empirical cumulative distribution functions and probability density functions; results will also be presented using the MCID of -6.5 points presented in the literature (Hudgens 2017). Additional analyses to characterize patient dysphagia experience and correlations between the two primary endpoints may also be explored. Full details will be defined in the SAP.

9.4.1.3 Analysis methods for secondary efficacy variables

Analyses of the secondary variables will follow the same treatment failure approach to handle intercurrent events as described above for the primary endpoints (non responder imputation for binary endpoints, return to baseline multiple imputation for continuous endpoints).

The key secondary endpoint of percent change from baseline in tissue eosinophils at Week 24 will be compared between the benralizumab and placebo treatment groups using an analysis of covariance (ANCOVA) model. The dependent variable will be percent change from baseline eosinophils at Week 24, and baseline eosinophils along with treatment, region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline as covariates.

The key secondary endpoints of change from baseline in EoE-HSS grade and stage scores at Week 24 will be compared between benralizumab and placebo treatment groups using ANCOVA models similarly as above.

The key secondary endpoint of change from baseline in centrally-read EREFS at Week 24 will be compared between the benralizumab and placebo treatment groups using an ANCOVA model. The dependent variable will be the change from baseline in centrally-read EREFS score at Week 24, baseline centrally-read EREFS score and treatment will be included as covariates along with region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of strictures at baseline. The primary analysis of change in centrally-read EREFS at Week 24 will include centrally-read data collected at the Week 24 visit including a window of ±2 weeks. In addition, exploration into the concordance between site recorded and centrally-read data may be performed. Full details will be specified in the SAP.

The key secondary endpoint of treatment responder rate at Week 24 is a composite endpoint of histological response and clinically meaningful improvement from baseline in DSQ (30% improvement) (Hudgens et al 2017Dellon et al 2014). The endpoint will be analyzed using logistic regression with treatment response as the dependent variable, and covariates of treatment, region, use of swallowed steroids at baseline, and presence of strictures at baseline. The results of the analysis will be presented using an odds ratio, together with its associated 95% confidence intervals (CIs) and 2-sided p-value. Results will also be transformed into a difference in proportions for ease of interpretation.

To support the primary histological response rate endpoint, further summaries and analyses of tissue eosinophil counts and EoE-HSS from centrally-read biopsies will be performed. These will include summaries of number of patients achieving histological response to certain levels will be produced (<1, 1 to ≤6, 7 to <15 eos/hpf, etc.).

Other continuous secondary endpoints collected by visit up to Week 24 including changes from baseline in PEESS, EoE QoL-A, changes in SF-36v2 scores, and changes in EoE-3D and daily assessments will be analysed using ANCOVA in a similar way to that described for the change in DSQ primary endpoint. For these analyses the dependent variable will be the change from baseline in the respective continuous endpoint at Week 24, and each will include the relevant baseline score as a covariate. Additional responder analyses and descriptive summaries of the PRO assessments will be produced to further characterize patient symptomatology and health status.

Categories of PGI-C, PGI-S and percentage of patients with relevant procedures and healthcare resource utilization during the study will be summarized by visit and during the study. No formal analyses will be performed.

Change from baseline in EndoFLIP scores at Week 24 will be analysed using an ANCOVA model with change in EndoFLIP score as the dependent variable and baseline score along with treatment and other covariates (region, use of swallowed steroids at baseline (categorical, Yes/No), and presence of stricture at baseline) as explanatory variables.

Descriptive summary statistics and graphical data displays will be used for Week 52 efficacy data and all analyses of data in the OLE, no formal statistical analyses will be performed. Details will be provided in the SAP.

9.4.1.4 Sensitivity analyses

Sensitivity analyses for the primary and key secondary endpoints based on different estimand strategies and different missing data mechanism assumptions including those expected to more conservative, will be used to explore the robustness of any treatment effect including other multiple imputation approaches and tipping point analyses. Full details of sensitivity analyses will be pre-specified in the SAP and documented prior to database lock of the study.

Sensitivity analyses may also be considered to explore the effect of extreme outliers on individual endpoints, such as rank based methods. Full details of these will be pre-specified in the SAP.

9.4.1.5 Subgroup analysis

Analyses of the primary endpoints will be performed to explore the consistency of the treatment effect across key pre-defined subgroups. These will include but are not limited to explorations into background medications at baseline and prior response to background medications, presence of strictures at baseline, dietary restrictions, and duration of EoE. Full details of all subgroup analyses and statistical modelling including possible testing of interaction between treatment group and covariates will be described in the SAP.

9.4.2 Safety analyses

Safety analyses will be performed using the safety analysis set.

The first analysis of safety data will include only data from the DB, placebo-controlled first 24 weeks of the study (DB period). Patients will be analysed according to the treatment they received (benralizumab or placebo). A second analysis of safety data will include all data reported in the study for patients receiving benralizumab from the start of treatment. Safety data from patients' entire duration on benralizumab during the DB period, along with the benralizumab OL period and OLE period will be summarized. Additional safety data presentations based on the OL benralizumab set will be included to summarise safety data from patients who switched from placebo to receive benralizumab after 24 weeks, with only their safety data while receiving benralizumab included. If there is considerable drop out between the first 52 weeks of the study and the OLE, additional safety summaries may be produced on the OLE benralizumab analysis set to avoid any concern around rollover bias between parts of the study. Full details of the groupings and analysis periods will be provided in the SAP.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP. Details are described in the SAP.

Adverse events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AZ/designee.

Safety data will be presented using descriptive statistics unless otherwise specified in the SAP.

Adverse events will be presented for each treatment group by system organ class and preferred term, including the number and percentage of patients reporting at least 1 event, number of events and exposure-adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of patients with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

Separate AE tables will be provided taking into consideration the relationship as to IP assessed by the Investigator, maximum intensity, seriousness, death and events leading to discontinuation of IP, as well as other action taken related to IP.

An additional table will present number and percentage of patients with most common AEs (frequency of ≥3%).

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, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Plot of frequencies and risk differences (forest plots) between treatment arms will be presented for the most common AEs and other specific events of interest. Estimates and confidence intervals based on the Miettinen-Nurminen method will also be presented for the most common AEs and any other specific events of interest included in the structured assessment of benefit risk.

Full details of AE analyses will be provided in the SAP.

Treatment emergent

The following events are considered treatment emergent:

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

Clinical laboratory safety assessments

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis.

Vital signs and weight

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Minimum, Q1, median, Q3, and Maximum. Frequency tables cover number and percentage of patients in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters (systolic and diastolic blood pressure, pulse, respiration rate, oral temperature) and body weight will be presented for observed values and change from baseline.

Changes in vital signs and weight will be examined according to Table 1. Table 2 and Table 3. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented.

Details of vital sign analyses will be provided in the SAP.

Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

9.4.3 Immunogenicity analyses

Anti-drug antibodies to benralizumab will be summarized using descriptive statistics at each visit. The impact of ADA on PK and eosinophil level may be assessed. The potential association of ADA with safety and efficacy may be evaluated. Further details will be provided in the SAP.

9.4.4 Other analyses

Pharmacokinetic and pharmacodynamic exploratory analyses will be described in the SAP finalized before database lock.

The focus of the Early Time Point Sub-study is to characterise the time profile of tissue eosinophil depletion with benralizumab, with contextualisation versus the placebo control arm. Analyses will focus on summarising and plotting the tissue eosinophils and change in eosinophils over time, any statistical testing performed will be considered exploratory. Exploration into the relationship between tissue eosinophil depletion and symptom improvements will be performed using scatterplots and time profile plots of absolute values and changes from baseline in these measures together on a patient level if appropriate. Full details of these analysis, and those of other exploratory endpoints will be pre-defined in an analysis plan which will be finalized before the primary database lock.

9.4.5 Methods for multiplicity control

To account for multiplicity testing for the primary endpoints (histological response rate and changes from baseline in DSQ at Week 24) and the key secondary endpoints listed below, a hierarchical testing strategy will be used to strongly control the overall type 1 error rate at the 0.05 level.

If the null hypothesis for the first primary endpoint of histological response rate at 24 weeks is not rejected (i.e. p-value >0.05), no null hypotheses will be rejected for any other endpoint in the study. If the null hypothesis is rejected for the first dual-primary endpoint, then hierarchical fixed-sequence testing will continue at the α=0.05 level moving to the second dual-primary endpoint of change from baseline in DSQ at Week 24 and subsequently to the key secondary endpoints in the following order:

- Percent change from baseline in tissue eosinophils at Week 24
- Change from baseline in EoE-HSS grade score at Week 24
- Change from baseline in EoE-HSS stage score at Week 24
- Change from baseline in EREFS at Week 24
- Treatment responder rate at Week 24

At any time that a null hypothesis cannot be rejected (i.e. p-value >0.05), further testing will stop and no subsequent null hypothesis in the testing hierarchy will be rejected. It is noted that for the purpose of US marketing approval both primary endpoints would need to be statistically significant.

9.5 Interim analyses

No formal interim analysis is planned for this study.

9.6 Independent Data monitoring committee (IDMC)

An IDMC will be utilized for this study. Section A 5 provides more details on the rationale for and the remit of the committee.

10 REFERENCES

Aceves et al 2014
Aceves SS. Remodeling and Fibrosis in Chronic Eosinophil Inflammation. Dig Dis. 2014;32:15 21.

Bleecker et al 2016
Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 study. Lancet. 2016;29:2115-27.

Busse et al 2013
Busse WW, Molfino NA, Kolbeck R. Interleukin-5 receptor-directed strategies. In: Lee JJ, Rosenberg HF, eds. Eosinophils in Health and Disease. London: Elsevier; 2013:587-91.

Dellon et al 2013a
Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). Am J Gastroenterol. 2013;108:679–92.

Dellon et al 2013b
Dellon, E. S., Irani, A. M., Hill, M. R., & Hirano, I. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Alimentary Pharmacology & Therapeutics, 38, 634–42.

Dellon et al 2014
Dellon ES, Jensen ET, Martin CF, Shaheen NJ, Kappelman MD. The Prevalence of eosinophilic esophagitis in the United States. Clin Gastroenterol Hepatol. 2014;12:589-96.

Dellon et al 2017
Dellon ES, Katzka DA, Collins MH, Hamdani M, Gupta SK, Hirano I, on behalf of the MP-10-06 Investigators. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis. Gastroenterology. 2017;152:776–786.

Dellon et al 2018
Dellon ES, Liacouras CA, Molina-Infante J, Furuta GT, Spergel JM, Zevit N, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology. 2018; 1-12.

Freeman et al 2020
Freeman R, Richeson B, Peterson KA. Mo1218 Efficacy of benralizumab, a monoclonal antibody that binds to IL-5R, in the treatment of Eosinophilic gastrointestinal disorders: a series of 8 patients. Gastroenterology. 2020;158(6) S-831

FDA 2009
U.S. Department of Health and Human Services Food and Drug Administration. Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.

FDA 2019
Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Draft guidance for industry. Eosinophilic Esophagitis: Developing Drugs for Treatment. February 2019.

FDA 2020
Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Eosinophilic Esophagitis: Developing Drugs for Treatment. September 2020.

FitzGerald et al 2016
FitzGerald JM, Bleecker ER, Nair P, Kom S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 study. Lancet. 2016;29:2128-41.

Hirano et al 2017
Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M et al. Dupilumab Efficacy and Safety in Adult Patients With Active Eosinophilic Esophagitis: a Randomized Double-Blind Placebo Controlled Phase 2 Trial. Presented at World Congress of Gastroenterology ACG, Orlando, Florida, USA, 13-18 October 2017.

Hudgens et al 2017
Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. Journal of Patient-Reported Outcomes. 2017;1(1):3.

Jacobsen et al 2012
Jacobsen EA, Helmers RA, Lee JJ, Lee NA. The expanding role(s) of eosinophils in health and disease. Blood 2012;120(19):3882-90.

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

Kolbeck et al 2010
Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, et al. MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell- mediated cytotoxicity function. Allergy Clin Immunol. 2010;125:1344-53.

Kuang et al 2019
Kuang FL, Legrand F, Makiya M, Ware J, Wetzler L, Brown T, Magee T, Piligian B, Yoon P, Ellis JH, Sun X, Panch SR, Powers A, Alao H, Kumar S, Quezado M, Yan L, Lee N, Kolbeck R, Newbold P, Goldman M, Fay MP, Khoury P, Maric I, Klion AD. Benralizumab for PDGFRA-Negative Hypereosinophilic Syndrome. N Engl J Med. 2019. Apr 4;380(14):1336-46.

Laviolette et al 2013
Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. J Allergy Clin Immunol. 2013;132:1086-96.

Legrand et al 2017
Legrand F, Li Kuang F, Makiya MA, Ware J, Wetzler L, Brown T, et al. Benralizumab in hypereosinophilic syndromes: predictors of response. Poster presentation at 10th Biennial Symposium of the International Eosinophil Society, Gothenburg, Sweden, 19-23 July 2017. Program available online at URL: http://www.eosinophil-society.org/UserFiles/file/IES17-FP-4web.pdf.

Lieberman et al 2010
Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol . 2010 Sep;126(3):477-80.e1-42. [cited 22 Apr 2019] Available from: URL: https://www.jacionline.org/article/S0091-6749(10)01004-3/abstract.

Lucendo et al 2017
Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterology Journal. 2017; 5(3):335–58.

Nair et al 2017
Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al for the ZONDA Study Investigators. Oral glucocorticoid–sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376:2448-58.

NCT01642212
NCT01642212 - OBS in Adolescent and Adults With EOE: A Phase II, Randomized, Double-Blind, Placebo Controlled, Study With an Open Label Extension. [Study on record on ClinicalTrials.gov] Available at URL: https://clinicaltrials.gov/ct2/show/NCT01642212.

QualityMetric 2011
QualityMetric, I. User's manual for the SF-36v2 Health Survey (3 ed.). 2011. Lincoln, RI.

Reilly et al 1996
Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. Clin Drug Invest 1996; 11(5):278-88.

Rubin et al 1986
Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. Journal of the American Statistical Association 81: 366-374. 1986

Rubin et al 1987
Rubin DB. Multiple Imputation for Nonresponse in Surveys. 1987. New York: Wiley.

Sampson et al 2006
Sampson H, Muñoz-Furlong A, Campbell R, Adkinson F, Bock A, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7. [cited 22 Apr 2019] Available from: URL: https://www.jacionline.org/article/S0091-6749(05)02723-5/fulltext.

Taft et al 2011
Taft TH, Kern E, Kwiatek MA, Hirano I, Gonsalves N, Keefer L. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. Aliment Pharmacol Ther. 2011 Oct;34(7):790-8.

The COREOS Collaborators 2022
COREOS Collaborators:, Ma C, Schoepfer AM, Dellon ES, Bredenoord AJ, Chehade M, Collins MH, Feagan BG, Furuta GT, Gupta SK, Hirano I, Jairath V, Katzka DA, Pai RK, Rothenberg ME, Straumann A, Aceves SS, Alexander JA, Arva NC, Atkins D, Biedermann L, Blanchard C, Cianferoni A, Ciriza de Los Rios C, Clayton F, Davis CM, de Bortoli N, Dias JA, Falk GW, Genta RM, Ghaffari G, Gonsalves N, Greuter T, Hopp R, Hsu Blatman KS, Jensen ET, Johnston D, Kagalwalla AF, Larsson HM, Leung J, Louis H, Masterson JC,

Menard-Katcher C, Menard-Katcher PA, Moawad FJ, Muir AB, Mukkada VA, Penagini R, Pesek RD, Peterson K, Putnam PE, Ravelli A, Savarino EV, Schlag C, Schreiner P, Simon D, Smyrk TC, Spergel JM, Taft TH, Terreehorst I, Vanuytsel T, Venter C, Vieira MC, Vieth M, Vlieg-Boerstra B, von Arnim U, Walker MM, Wechsler JB, Woodland P, Woosley JT, Yang GY, Zevit N, Safroneeva E. Development of a core outcome set for therapeutic studies in eosinophilic esophagitis (COREOS). J Allergy Clin Immunol. 2022 Feb;149(2):659-670.

Wen et al 2017
Wen T, Rothenberg ME. Clinical Applications of the Eosinophilic Esophagitis Diagnostic Panel. *Front Med (Lausanne)*. 2017 Jul 14;4:108. doi: 10.3389/fmed.2017.00108.

Wang et al 2017
Wang B, Yan L, Yao Z, Roskos LK. Population pharmacokinetics and pharmacodynamics of benralizumab in healthy volunteers and patients with asthma. CPT Pharmacometrics Syst Pharmacol. 2017;6(4):249-57.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

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

- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., 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 protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- AstraZeneca will be responsible for obtaining the 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 participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (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.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

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

Patients must be informed that their participation is voluntary for the entire study 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 authorized 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 and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) (or assent forms, if applicable) must be provided to the patient and/or legal representative.

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

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

The ICF will contain a separate section that addresses the use of remaining samples for future research projects. Adult patients will give a separate agreement to allow any remaining specimens to be used for future 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. 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.

At sites selected for the EndoFlip and/or [redacted] sub-studies, and/or the Early Time Point Sub-study, the ICF will contain separate sections with additional information on those sub-studies. If a patient's partner becomes pregnant during or within 12 weeks after the study, 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.

A 4 Data Protection

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

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure 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 authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Independent Data Monitoring Committee

An independent DMC consisting of 2 clinicians (including at least 1 EoE expert) and a statistician will be used for this study to monitor overall patient safety. The IDMC will receive patient profiles including safety data and unblinded patient laboratory results on a regular basis and will meet to discuss the data as needed. Based on their review, the IDMC may recommend changes to the study design or conduct or that individual patients be discontinued from the study for safety reasons.

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

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

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

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

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

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

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

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

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

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

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

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

A 9 Study and Site Closure

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

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

The Investigator may initiate study-site closure at any time, provided there is reasonable cause with sufficient notice and approval 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

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

A 10 Publication Policy

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

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

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

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

An adverse event 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 unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

B 2 Definitions of Serious Adverse Event

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

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

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

B 3 Life Threatening

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

B 4 Hospitalization

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

B 5 Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

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

B 6 Intensity Rating Scale:

The grading scales found in NCI CTCAE version 5.00 will be utilized for all events. For those events without assigned CTCAE grades, the Investigator should assign the CTCAE criteria based on the CTCAE definitions. A copy of the CTCAE version 5.00 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

B 7 A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

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

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

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug 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
- An error or situation that could have led to an error was identified and intercepted before the patient received the drug

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

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

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

- Errors related to or resulting from IWRS - 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) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in OL studies, even if an AZ product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

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

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

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

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

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

C 2 Withdrawal of informed consent/assent for donated biological samples

If a patient and/or legal representative withdraws consent/assent 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 where mandatory sampling conforms with the clinical safety laboratory test requirements, then the patient is withdrawn from IP. In the case where a patient and/or legal representative allows for collection and analysis of biological samples (for clinical safety laboratory tests) but specifically withdraws his/her consent/assent for the use of samples for exploratory research or retention of samples for exploratory research after the end of the study, the patient does not need to be discontinued from IP and will be allowed to continue participation in the study.

The Investigator or designee:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented

- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

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, are capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

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

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are 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 study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**

- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used

Appendix D Genetics

D 1 Use/Analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; 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 healthcare and to the discovery of new diagnostics, treatments or medications.

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

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

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

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

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All adult 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 fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol 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 within 120 days of genetic sample collection
- Age <18 years

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 Clinical Study Protocol and Appendix C 2.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at randomization (Week 0). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE); such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Week 0, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

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

An additional second code will be assigned to the blood 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 organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).

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

Ethical and regulatory requirements

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

Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must give separate consent for this. The consent will be covered in Addendum to the main ICF. The Investigator 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 AZ study physician or an Investigator might know a patient's identity and also have access to his or her genetic data. In addition, Regulatory Authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

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

AstraZeneca and its designated organizations 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 organizations 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 Statistical Analysis Plan may be prepared where appropriate.

Appendix E Best Practice Guidelines For Completing PRO Assessments

Patients will complete PRO assessments at home using a handheld device. PRO assessments must be collected in a systematic way to ensure data integrity. The following best practice guidelines should be followed when collecting PRO data via handheld device:

- Provide the right environment
  - Patients should complete the PRO questions in a quiet and private location without help from others.
- Purpose of the PRO assessments
  - Discuss the purpose of the PRO assessments with the patients. Reinforce that these are standardized questions designed to capture the patient experience in the study.
  - Inform patients that each PRO assessment is independent of the others. Some questions may be very similar or seem repeated, but it is important to answer each question independently.
- Help with procedural questions
  - Make sure the patient understands how to complete the PRO assessment. Assessment instructions are usually self-explanatory, but staff may answer questions about procedural issues like what it means to "tick a box".
- Avoid bias: do not clarify the meaning of questions or responses
  - Sometimes patients will ask site staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the patient that you cannot clarify items. Remind them that there are no right or wrong answers. Inform the patient that they should select the response that best answers the question as they understand it.
  - If a patient becomes unable to independently use the handheld device during the treatment period of the study (e.g. unable to read due to vision problems), then the patient should be exempted from completing PRO questionnaires used for efficacy endpoints (DSQ, EoE-3D, PGI-C/S, EoE-QoL-A, SF-36) and may continue in the study with external help for symptom severity and background/rescue medication use questionnaires completion. Patient's exemption in this regard must be pre-approved by an AZ study physician/delegate and appropriately documented.
- No time limits
  - Although most PRO assessments require only a few minutes to complete, the patient should be given as much time as is needed.
- Train the patient on handheld device usage
  - Train patients on how to use the handheld device using the materials and training provided by the device vendor.

  - Provide guidance on whom the patient should call if they have problems with the device.

- Monitor compliance
  - Minimizing missing data is a key aspect of study success. Compliance with device completion must be checked weekly (at a minimum) to ensure that the patient is completing the assessments as scheduled. Follow-up with patients via phone and at the visits is required to ensure sufficient data are available for supporting the dual-primary endpoint of this study.

Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management

F 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [e.g. IgG and immune complex-mediated]) and nonimmunologic. The clinical criteria for defining anaphylaxis for this study are listed in Section F 2 of this Appendix. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section F 3 of this Appendix. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected at 90 minutes ± 30 minutes after the event; analysis for serum tryptase may be performed at a local laboratory. If local analysis of serum tryptase is unavailable, there will be an option to have the sample analysed at the central lab. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

F 2 Clinical Criteria for Defining Anaphylaxis 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 (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST 1 OF THE FOLLOWING:

   (a) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence).

2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula).
   (b) Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

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

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

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

Immune Complex Disease

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

F 3 Signs and Symptoms and Management of Acute Anaphylaxis

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

- Diffuse erythema
- Pruritus
- Urticaria and/or angioedema
- Bronchospasm
- Laryngeal edema
- Hypotension
- Cardiac arrhythmias
- Feeling of impending doom
- Unconsciousness
- Shock

Other earlier or concomitant signs and symptoms can include:

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

- Headache
- Uterine cramps
- Generalized warmth

F 4 Management of Acute Anaphylaxis

F 4.1 Immediate intervention

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

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

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

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

(a) Establish and maintain airway.

(b) Administer oxygen.

(c) Establish venous access.

(d) Normal saline IV for fluid replacement.

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

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

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

(d) Consider systemic corticosteroids.

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

(f) Consider glucagon for patient taking β-blocker.

(g) Consider atropine for symptomatic bradycardia.

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

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

Adapted from Kemp et al 2008.

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/Assent/Re-assent of Study Patients During Study Interruptions

During study disruptions, 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/assent/re-assent 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 G 2 to G 66. Local and regional regulations and/or guidelines regarding 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 consent/reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

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

opportunity to re-screen a patient in addition to that detailed in Section 5.4**.** The procedures detailed in Section 8 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 adverse events, concomitant medication, diet questionnaire, review compliance of PRO assessments, and healthcare resource utilization to be reported and documented. Scheduled blood sample collection and endoscopies will be performed as soon as the patient can safely attend subsequent site visit.

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 regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures patients safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

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 should 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 e.g., details of self-administration, PRO, signs and symptoms.

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AEC	absolute eosinophil count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HCV	hepatitis C antibody
anti-HDV	hepatitis D antibody
APFS	accessorized prefilled syringe
AST	aspartate aminotransferase
CI	confidence interval
CID	clinically important difference
CMH	Cochran-Maentel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CSP	Clinical Study Protocol
CSR	clinical study report
DB	double-blind
DNA	deoxyribonucleic acid
DSQ	Dysphagia Symptom Questionnaire
DUS	disease under study
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	electrocardiogram
eCRF	electronic case report form
EDP	EoE Diagnostic Panel
EGID	eosinophilic gastrointestinal disease
EGD	esophagogastroduodenoscopy
EGPA	eosinophilic granulomatosis with polyangiitis
EndoFLIP	Endolumenal Functional Lumen Imaging Probe
EoE	eosinophilic esophagitis
EoE-3D	Eosinophilic Esophagitis - Daily Dysphagia Diary

Abbreviation or special term	Explanation
EoE-HSS	Eosinophilic Esophagitis - Histology Scoring System
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life Questionnaire;
eos	eosinophils
EREFS	Endoscopic Reference Score
FAS	full analysis set
FSH	follicle stimulating hormone
FU	follow up
GCP	Good Clinical Practice
GI	gastrointestinal
HBc	hepatitis B core
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B-virus
HCG	human chorionic gonadotropin
HCP	Health Care Professional
HES	hypereosinophilic syndrome
HIV-1/2	human immunodeficiency virus-1/2
hpf	high power field
HRQoL	health-related quality of life
HSS	histology scoring system
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IL-5	interleukin-5
IL-5Rα	IL-5 receptor alpha subunit
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IPD	investigational product discontinuation (visit)
IP	investigational product
IRB	Institutional Review Board

Abbreviation or special term	Explanation
IWRS	interactive web response system
mAb	monoclonal antibody
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect models for repeated measures
nAb	neutralizing antibody
OL	open-label
OLE	open-label extension
PDGFRA	platelet-derived growth factor receptor alpha
PEESS	Pediatric Eosinophilic Esophagitis Symptom Severity Module, Version 2, Children and Teens Report
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PPI	proton pump inhibitor
PRO	Patient Reported Outcome
PT	preferred term
Q4W	every 4 weeks
Q8W	Every 8 weeks
RNA	ribonucleic acid
ROW	Rest of World
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan
SC	subcutaneous(ly)
SF-36v2	Short Form-36 Version 2.0
SoA	schedule of activities
SOC	system organ class
TEAEs	treatment-emergent adverse events
TPV	Third Party Vendor
ULN	upper limit of normal
WBC	white blood cell (count)
WOCBP	women of childbearing potential
WPAI+CIQ	Work Productivity and Activity Impairment questionnaire plus Classroom Impairment Questions

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 5 (CSP ver 6.0): 30-April-2021

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 the early time point sub-study. The sub-study aims to generate early time point evidence of eosinophil depletion in tissue and to understand its relationship with endoscopic findings and symptom response. In addition, some minor clarifications were made to ensure 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 1.1 Schedule of Activities (SoA) Table 1	SoA updated with additions of: -endoscopies (with esophageal biopsies and EREFS) - PK - Hematology, WBC w/ differential, and blood sampling [redacted] - Esophageal tissue for histopathology and [redacted] analyses at week 4 and week 12, and a footnote to clarify that this applies only for patients in the Early Time Point Sub-study.	To indicate assessments added for the Early Time Point Sub-study.	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 1.1 Schedule of Activities (SoA) Table 2 Section 1.2 Synopsis, Table 6 Section 3 Objective and Endpoints, Table 8	Addition of EndoFLIP procedure at selected sites at Week 104 EndoFLIP added as an endpoint at week 104	To evaluate the longer-term effect of benralizumab on esophageal distensibility.	Non-Substantial
Section 1.2 Synopsis, Table 5 Section 3 Objective and Endpoints, Table 7 Table 8 Study Objectives for the OLE Period	Addition of the objective and endpoints for the Early Time Point Sub-study.	The Early Time Point Sub-study was added to the study since the previous amendment.	Substantial
Section 5.1 Inclusion criteria #5b	Wording *added*: *An average of* at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) between Visit 1 and Visit 2 *and at least 2 days per week with an episode of dysphagia in the 2 weeks prior to randomization*	For clarification	Substantial
Section 5.1 Inclusion criteria #6	Wording *added:* (a) Must complete 70% of daily *DSQ* diaries between Visit 1 and Visit 2; AND (b) Must have completed at least 8 of 14 daily *DSQ* diaries in the 14 days prior to randomization	For clarification	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 5.2 Exclusion criteria #27	Addition of an exclusion criterion; 'Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)'	To align with the protocol template	Substantial
Section 8.1.5 Early time point sub-study Section 9 Statistical considerations Section 9.2 Sample size determination Section 9.4.4 Other analyses Appendix A 3	New section added for the Early Time Point Sub-study. New paragraph added regarding the Early Time Point Sub-study. Text added: *and/or the Early Time Point Sub-study*	Sub-study added to generate early time point evidence of eosinophil depletion in tissue and to understand its relationship with symptom response.	Substantial
Section 8.4.2.1, 8.4.3 and Appendix B 2	'Congenital abnormality' updated to 'Congenital anomaly'.	To align with regulatory requirements	Non-Substantial
Throughout	Minor editorial or administrative changes that do not substantially alter the document.	For better consistency and clarity	Non Substantial

Amendment 4 (CSP ver 5.0): 11-Feb-2021

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 update the duration of the OLE-period to at least 1 year (variable duration) and to include the option of at-home or remote location self-IP administration after week 52. Inclusion/exclusion criteria were clarified, the primary estimand approach for the analyses of study data was updated to a composite strategy to more accurately account for the occurrence of the described intercurrent events which are considered to reflect a treatment failure outcome. In addition, some minor clarifications were made to ensure 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 1.1 Schedule of Activities (SoA)	Reference to compliance as a specific criterion for eligibility to the OLE period was taken out to emphasize that all patients who complete the 52-week treatment period on IP may continue into the OLE period.	To align with changes made in amendment 2.	
Section 1.1 Schedule of Activities (SoA) Section 1.2 Synopsis Section 4.1 Overall design Section 4.4 End of study definition	Text revised regarding duration of the OLE period.	To clarify that the OLE period is intended to allow each patient at least 1 more year of OL treatment and that the duration of the OLE period is flexible.	Non-Substantial
Section 1.1 Schedule of Activities (SoA) Table 1	The schedule of activities was updated to include references to CSP section for ‘Serum for total IgE’ and ‘serum tryptase’. Updates to serology footnote regarding monitoring of patients who are HBsAg positive or anti-HBc positive.	Corrected reference section. To clarify how this would occur if the patient are using self-administration option.	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 1.1 Schedule of Activities (SoA) Table 2	Heading adjusted, V28 with assessments and a footnote with a subsequent footnote renumbering added. Brief physical exam and vital signs were removed from some visits and PGI-S (via interview) was added to Visit 21, 28 and EOT/IPD (if before Visit 28). Some assessments were moved from visit 27 to visit 28. Updates to serology footnote regarding monitoring of patients who are HBsAg positive or anti-HBc positive.	To have first year of the OLE in a separate table and the fourth endoscopy scheduled at V28 and not at EOT, since the OLE will continue. Footnote was added to indicate which visits that can be conducted remotely with self IP admin, and at these visit brief PE and vital signs were removed. PGI-S was added to have a measure of the patient's perception of overall symptom severity. Update to serology footnote to clarify how this would occur if the patient are using self-administration option.	Non-Substantial
Section 1.1 Schedule of Activites (SoA) Table 3	A new table was added, Table 3; therefore all subsequent table numbers have been updated.	To have OLE from week 104 (the second year of the OLE period and beyond) in a separate table.	Non-Substantial
Section 1.1 Schedule of Activities (SoA) Table 4 Section 1.2 Synopsis, Table 6 Section 3 Objective and Endpoints, Table 8 Section 8.1.3.5 Patient Global Impression of Severity	PGI-S schedule updated. PGI-S administration was added to Visit 21 and Visit 28 (or at IPD/EOT if before Visit 28) and will at these visits occur by interview (i.e. Not via the device) and be entered into the eCRF. PGI-S was entered as an endpoint in the OLE	To include PGI-S as an endpoint in the OLE measuring the patient's perception of overall symptom severity after the handheld PRO device is returned, and to clarify when PGI-S will be administered on the device and when it will be administered by interview.	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 1.2 Synopsis, Table 5 and Table 6 Section 3 Objective and Endpoints, Table 7 and Table 8 Study Objectives for the OLE Period	Addition of the objective and endpoint for; the [redacted] and WPAI+CIQ	It was missing from the tables	Non-Substantial
Section 1.2 Synopsis, Overall design Section 4.1 Overall design	Wording on background medications updated	To align with Inclusion criteria #7 on background medications	Non-Substantial
Section 1.2 Synopsis, Overall design Section 4.1 Overall design	Revised text on how diet will be tracked during the study	Correction	Non-Substantial
Section 1.2 Synopsis Section 6.1.4 Optional At-home or Remote-Location IP administration Section 6.1.4.1 Optional Remote Visits for Patients doing At-Home or Remote-Location IP administration Section 8.2.2 Pregnancy test	New text/sections added to provide guidance on the optional self IP administration after week 52 (if allowed by local guidance) Clarified procedure for urine pregnancy testing for WOCBP in case of IP self-administration	To describe procedures if optional self-administration is implemented during the OLE	Non-Substantial
Section 1.3 Schema	Figure updated	To include the fourth endoscopy, the variable OLE duration and to clarify restrictions on background medications and diet	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 2.3 Benefit/risk assessment	The requirement for observation of the patient following IP administration was changed from 1 hour to be 'in line with clinical practice at the site'. Wording added regarding self IP administration during the OLE.	These safety requirements have been updated. Wording was also added to include risk minimisation for patients who select to do the optional/remote location IP administration during the OLE.	Non-Substantial
Section 4.2 Scientific rational for study design	'During the run-in' was added to the fifth bullet of 'Key features of this study include'.	To clarify that EoE-related diet and background medications are to be kept stable also during the run-in period.	Non-Substantial
Section 5.1 Inclusion criteria # 7 Section 5.2 Exclusion criteria # 21	Wording added: 'during the run-in period and' Wording added: 'and during'	To clarify that background medications taken for EoE and related treatments should be stable also during the run-in period	Non-Substantial
Section 5.2 Exclusion criteria # 5	Revised – text *added* 'Esophageal dilation performed within 8 weeks prior to screening *and prior esophagaeal surgery that would impact the assessments for EoE'*	Added as this may impact EoE assessments	Substantial
Section 5.2 Exclusion criteria # 6	Revised – text *added*. Use of a feeding tube, or *having a pattern of* not eating solid food daily during the run-in period	Added for clarification	Non-Substantial
Section 5.2 Exclusion criteria # 15 Section 6.5.4 Restrictions, Table 10	Troleandomycin removed	Safety requirements have been updated	Non-Substantial
Section 5.3 Lifestyle restrictions	Corrected the number of the inclusion criterion referred to in the first paragraph, from 4 to 9	Correction	Non-Substantial
Section 5.3.1 Meals and dietary restrictions	Wording updated that patients should remain on stabilized diet for treatment of their EoE also during the run-in period	For clarification	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 5.4 Screen failures	The first criterion for when re-screening is not allowed was reworded	To align with inclusion criteria #4	Non-Substantial
Section 6.1, Table 9	Dosage level added	For clarity	Non-Substantial
Section 6.1 Treatment administered	Paragraph added to inform when IP will be administered at site and when it may be administered at home/remotely by the patient	To align with addition of the optional self-administration during the OLE	Non-Substantial
Section 6.1.2 IP administration Section 8.4.7 IP administration at the study site	Wording revised regarding how patients should be monitored after IP administration- changed from '1 hour' to be 'in line with clinical practice at the site'	Safety requirements have been updated	Non-Substantial
Section 6.2 Preparation/handling/storage/accountability	Wording on where IP will be administered was removed	Since wording is included in new section in 6.1	Non-Substantial
Section 6.2 Preparation/handling/storage/accountability	Revised, text *added* that patient or caregiver may administer IP, and that *'Devices sent to patients home must be returned to the site for traceability'*	As IP may be self-administered at home or remote location	Non-Substantial
Section 6.5.4 Restrictions, Table 10	For 'background medication for EoE' and for 'Systemic corticosteroids', wording was added to the third column describing details, to include also the run-in period	To clarify that; -Background medications taken for EoE and related treatments should be stable also during the run-in period -Systemic corticosteroid is restricted also during the run-in period	Non-Substantial
Section 8.1.3 Patient reported outcomes	Wording on when PRO assessments will be performed on a handheld device was adjusted.	For clarification	Non-Substantial
Section 8.1.3.1 Dysphagia Symptom Questionnaire (DSQ)	Wording added to note that if the patient reports not eating solid food, then the DSQ is considered missing for that day.	For clarification	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 8.2.1.1 Other laboratory assessments	Wording was updated and added regarding monitoring of patients that are HBsAg positive or anti-HBC positive.	To clarify how this would occur if the patient is using self-administration option	Non-Substantial
Section 8.11.2 Diet Questionnaire	Wording updated on when the diet questionnaire will be completed	To clarify how this would occur during in the OLE, Year 2 and beyond	Non-Substantial
Section 9.4.1 Efficacy Analyses Section 1.2 Synopsis	Updated estimand strategy to a composite strategy where the occurrence of intercurrent events such as increase of background medication or addition of a new therapy for EOE are considered treatment failure events and handled as such in the analyses.	To better account for intercurrent events considered to be a negative outcome in the analyses.	Non-Substantial
Section 9.4.2 Safety Analyses, Adverse Events	Wording added that information on frequencies and risk differences between treatment arms will be presented for the most common AEs and other specific events of interest.	For clarification	Non-Substantial
A 3Informed consent process	Updated wording-	The time period was changed based on updated safety recommendations	Non-Substantial
Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management	Timing for collection of a blood sample to measure serum tryptase was changed from ‘as soon as possible, at 60 (±30) minutes after the event, and at discharge’ to at 90 (±30) after the event	To optimize timing of sample collection for measuring serum tryptase	Non-Substantial
Appendix A.9 Study and Site Start and Closure	Modified section heading from ‘Study and Site Closure’. Added Suggested Text for study start date	To comply with EU Clinical Trials Regulation No 536/2014 requirements (38) for definition of start of recruitment and ct.gov definition of study start.	Non-Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Throughout	Updated wording of the stratification factor from 'steroids at baseline' to 'use of swallowed steroids at baseline (categorical, Yes/No)'	For clarification	Non Substantial
Throughout	Reference to Interactive Voice Response System (IVRS) was removed	Interactive Voice Response System (IVRS) will not be used	Non Substantial
Throughout	Minor editorial or administrative changes that do not substantially alter the document have been made where applicable are not individually listed	For better consistency and clarity	Non Substantial

Amendment 3 (CSP ver 4.0): 26-Aug-2020

This amendment includes only corrected numbering of inclusion criteria.

Amendment 2: 31-July-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. [redacted] In addition,

inclusion/exclusion criteria were clarified, and Table 9 of Restrictions (Section 6.5.4) was updated with clarifications regarding medications allowed, restricted and prohibited prior to screening. Finally, some minor clarifications were made to ensure 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; Appendix G	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a patient is not able to visit a study site to ensure that the clinical trial can continue whilst 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 Schedule of Activities (SoA)1.1 (Schedule of Activities), Table 1 and Table 2	[redacted]	[redacted]	Non-substantial
Section 1.1 (Schedule of Activities), Table 1	The schedule of activities was updated to include references to CSP section for 'Serum for total IgE' and 'serum tryptase'.	Corrected reference section.	Non-substantial
Section 1.1 (Schedule of Activities), Table 1	Healthcare resource utilization removed from V1.	Healthcare resource utilization removed from V1 for simplification, as V2 is seen as baseline for this assessment.	Non-substantial
Section 1.1 (Schedule of Activities), Table 2	• ADA/nAb was added to the EOT/IPD visits. • A footnote was added to emphasize that all samples for PK and ADA/nAB must be taken prior to IP administration.	• Added for complete analysis of ADA/nAb. • Added for clarification.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 1.1 (Schedule of Activities), Table 1 and Table 2	• Urine pregnancy test added at the 12 week Follow-up visit. • Text revisions:" Laboratory assessments: Hematology, WBC w/differential ~~"Only eosinophils will be measured at the FU visit"~~ was replaced with "*Only WBC w/differential will be measured at the FU visit."*	• Added for final confirmation that pregnancy has not occurred during the study. • Change needed due to limitations at the central lab; eosinophils are only analyzed as part of the WBC w/differential.	Non-substantial
Section 1.1 (Schedule of assessments), Table 4	Schedule of ePRO assessment: Time for completion of daily diaries was extended on Day n+1 from 4:00 in the previous version to 4:59. Schedule of ePRO assessment: Frequency of PGI-S assessment was reduced from weekly to every two weeks.	• Evening completion was extended to match ePRO specifications and training material. • PGI-S frequency was adjusted to match recall period.	Non-substantial
Section 1.2 (Synopsis), Overall design; Section 4.1 (Overall design); Section 7.1.1.2 (Discontinuation at Week 52)	Reference to compliance as a specific criterion for eligibility to the OLE period was taken out to emphasize that all patients who complete the 52-week treatment period on IP may continue into the OLE period.	Wording was changed to clarify eligibility for the OLE period.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 5.1 (Inclusion Criteria)	Text revisions: • #5: Must be symptomatic at Visit 1 (~~run-in-period~~ *screening*) and Visit 2 (randomization): - A patient reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to ~~the run-in period~~ *Visit 1* - At least 2 days *per week* with an episode of dysphagia (Daily DSQ ≥2) ~~per week~~ between Visit 1 and Visit 2 ~~(randomization)~~ • #7: May be on background medications for EoE ……for at least 4 weeks *(8 weeks for PPI)* prior to ~~the run-in period~~ *screening.* ~~Patient on PPI therapy must report~~ *If a* ~~a~~ ~~stable dose~~ *medication* for ~~at least 8 weeks~~ *EoE (including swallowed steroids, systemic steroids and PPI) is discontinued* prior to ~~the run-in~~ *screening, there should be a washout period of at least 8 weeks.* • #8: Body weight of at least 35 kg (inclusion criterion removed) • #9 (previously #10): WOCBP must agree to use a highly effective form of birth control (confirmed by the Investigator) from randomization throughout the study duration and ~~within 16 weeks~~ *for at least 12 week* after last dose of IP.	• Inclusion criterion #5 was updated to clarify the symptom criteria. • Inclusion criterion #7 was updated to add details on a washout period for background medications for EoE. A washout period is needed to ensure that discontinuation of the medications will not affect baseline assessments. • Align to approved product profile and dosing instructions • The time period was changed based on updated safety recommendations.	Substantial

Section 5.2 (Exclusion Criteria)	Text revisions: • #5: Added new exclusion criterion: Esophageal dilation performed within 8 weeks prior to screening.	• An 8-week period is needed after an esophageal dilation to stabilize symptoms and findings prior to baseline assessments.	Substantial
	• #13 (previously #16) : Helminth parasitic infection diagnosed within 24 weeks prior to screening that has not been treated with or has failed to respond to standard of care therapy. (formerly time of consent/assent).	• Simplification of language.	
	• #15 (previously #18): A prohibition period of 8 weeks prior to screening was added for immunosuppressive medications.	• An 8-week period is needed after discontinuation of immunosuppressive treatment to stabilize symptoms and findings prior to baseline assessments	
	• #16 (previously #19): Receipt of immunoglobulin or blood products within 30 days prior to screening. (formerly time of consent/assent)	• Simplification of language.	
	• #17 (previously #20):Receipt of live attenuated vaccines 30 days prior to randomization.(formerly time of consent/assent).	• The decisive time period is the time before randomization, to separate the effects of IP from effects of the vaccine.	
	• #18: Added new exclusion criterion: Receipt of inactivated/killed vaccinations (e.g., inactive influenza) within 1 week prior to randomisation.	• Addition made for completeness and alignment with the instruction already included in Table 9.	
	• #19 (previously #21): Receipt of any marketed or investigational biologic …within 4 months or 5 half-lives prior to screening, whichever is longer. (formerly time of consent/assent)	• Simplification of language.	
	• #20: Added new exclusion criterion: Receipt of oral and/or sublingual allergen immunotherapy within 8 weeks prior to screening.	• An 8-week period is needed after oral and/or sublingual allergen immunotherapy to stabilize symptoms and findings prior to baseline assessments.	

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 5.3 (lifestyle restrictions)	Text revisions: Women of childbearing potential must use highly effective contraceptive methods …for ~~16~~ *12* weeks (5 half-lives) after last administration of the IP. Patients must abstain from donating blood, plasma, or platelets from the time of informed consent or assent (if applicable) and for ~~16~~ *12* weeks (5 half-lives) after last dose of IP.	The time period was changed to 12 weeks based on updated safety recommendations.	Non-substantial
Section 5.4 (Screen failures)	Text revisions: Screening in order to confirm a patient-reported average of at least 2 days per week with an episode of dysphagia over the 4 weeks prior to ~~the run-in period~~ *visit 1 or to confirm at least 2 days per week with an episode of dysphagia (Daily DSQ ≥2) between Visit 1 and Visit 2.*	Wording was added to clarify that re-screening is not allowed if patients fail to meet inclusion criterion #5.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 6.1 (Treatments administered)	Text revisions: • (Before IP administration): "All applicable visit procedures, including sample collection of [redacted], PK, and ADA samples and on-site PRO assessments, should be completed prior to IP administration. If the patient cannot tolerate a particular visit procedure(s) during the visit, IP can be administered, and the procedure should be re-scheduled for a different date, preferably within the visit window." • (IP administration): Added wording about training in IP administration.	• The mentioned visit procedures need to be performed before IP administration • Training in IP administration was added to have patients prepared for self-administration in case of study disruption.	Non-substantial Substantial
Section 6.4 (Treatment compliance)	Text revisions: "The administration of all study treatments (both in the DB, OL, and OLE periods of the study) should be recorded in *the source documents, as well as in* the appropriate section of the eCRF."	Wording was added to emphasize the need to note IP administrations in source documents.	Non-substantial
Section 6.5.1 (Background medication and related treatments)	Added wording about a washout period needed after discontinuation of a medication for EoE.	A washout period is needed to ensure that discontinuation of the medication will not affect baseline assessments.	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Section 6.5.4 (Restrictions)	Clarifications were added to Table 9 regarding allowed, restricted and prohibited medications: • Immunoglobulins, blood products and investigational non-biologic drugs were added to the table as prohibited. • A clarification was added that it is allergen immunotherapy administered subcutaneously that is restricted, whereas oral and sublingual allergen immunotherapy is prohibited.	• Additions made for alignment with the exclusion criteria. • Allergen immunotherapy may have different effects on EoE disease depending on the route of administration.	Substantial
Section 8.1.3.5 (Patient Reported Outcome)	The recall period for the Patient Global Impression of Severity (PGI-S) instrument was specified.	Added for clarification.	Non-substantial
Section 8.1.3.4 (EndoFLIP (esophageal distensibility) – sub-study	Requirement for performing EndoFLIP prior to obtaining esophagal biopsies was removed.	Update made based on feedback from external experts.	Non-substantial
Section 8.2.3 (Physical examination)	Text removed: "For the brief physical examination, only information on whether the assessment was performed or not is to be recorded."	A separate instruction for the brief physical examination is not needed as it is the same as for the complete physical examination.	Non-substantial
Section 8.4.3 (Paternal exposure)	The time period required after the last IP dose for follow-up and documentation of pregnancies was changed from 16 to 12 weeks.	The time period was changed based on updated safety recommendations.	Non-substantial
Section 8.4.5 (Device Constituent Deficiencies)	New Section 8.4.5 added: Device Constituent Deficiencies including 8.4.5.1 SADE reporting	To ensure compliance with new regulatory guidance.	Non-substantial
Section 8.9 (Immunogenicity)	Detailed and specific descriptions of the collection and analysis of immunogenicity samples were omitted and other documents describing these details were referenced.	Language updated to allow for evolving approach to immunogenicity analyses.	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
[redacted]	[redacted]	[redacted]	[redacted]
8.11.3 (Patient Testing Due to Public Health Crisis)	Section included if patient testing is performed due to the public health crisis, the results may be documented for this study.	Section added for test results secondary to public health crisis to be collected allowing for an evaluation of the public health crisis on the study.	Non-substantial
Section 9.4.3 (Immunogenicity analyses)	Text revisions: "Anti-drug antibodies to benralizumab will be summarized using descriptive statistics at each visit~~by treatment group~~. ~~The ADA titres time profiles of benralizumab by treatment group will be generated~~. The impact of ADA on PK and eosinophil level ~~will~~ *may* be assessed. The potential association of ADA with safety and efficacy ~~will~~*may* be evaluated. Further details will be provided in the SAP."	Updated wording to align with evolving AZ process.	Non-substantial
Appendix A 1 (Regulatory and Ethical Considerations)	Text revised and added 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 A 3(Informed consent Process)	Text revisions: • "The ICF will contain a separate section that addresses the use of remaining samples for future projects. Adult patients will give a separate agreement to allow any remaining specimens to be used for future research." • [redacted]	• The section was updated to clarify that future exploratory research is relevant for adults only. [redacted]	Substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
Appendix A 6 (Dissemination of clinical study data)	Text revisions: A description of this clinical study will be available on http://~~astrazenecaclinicaltrials~~*astrazenecagrouptrials.pharmacm.com.*	Section updated with correct weblink.	Non-substantial
Appendix A 7 (Data quality assurance)	Section updated to note that the eCRF is only signed electronically and not physically, as was stated in the previous version.	Clarification of the eCRF signature process.	Non-substantial

Version 2.0, 01 November 2019
Changes to the protocol are summarised below:

Section 1.1 (Schedule of Activities): The schedule of activities was updated to remove IgE allergen testing and add assessments for serum tryptase and plasma sampling. The visit schedule for the OLE period was updated to have the final dose of benralizumab at Week 100 with the EOT occurring at Week 104. The specific tests for hepatitis B and C serology were clarified. All visit windows were calculated from Visit 2. The PEESS assessment was added to the PRO assessments collected during the 52-week study period (DB+OL) and OLE period. An additional table was added to clarify the schedule for all PRO assessments.

Section 3 (Objectives and Endpoints): The secondary and other endpoint measures were updated as follows:

- Change from baseline in dysphagia associated pain, and discomfort as captured by the EoE-3D
- Changes from baseline in abdominal pain and nausea as captured by the daily diary
- Dysphagia-free days as captured by the DSQ
- Frequency of dysphagia episodes as captured by the EoE-3D

The exploratory endpoints during the 52-week study period (DB+OL) and the OLE period were updated to include EoE-related transcriptomic profile, tissue histology and immunohistochemistry, [redacted] and PEESS.

Section 4.1 (Overall Design): This section was updated to clarify that patients on PPI therapy must report a stable dose for at least 8 weeks prior to the run-in period. Stratification by region for adults was clarified as North American vs Rest of World.

Target recruitment for adolescents was updated for approximately 20 adolescent patients per arm.

Section 5.1 (Inclusion Criteria): Inclusion criterion #4 was updated to clarify the definitions of EoE diagnoses. Inclusion criterion #5 was updated to clarify the definition of symptomatic EoE. Inclusion criterion #6 was updated to clarify the definition of daily diary adherence. Inclusion criterion #7 was updated to require patients on PPI therapy report a stable dose for at least 8 weeks prior to enrolment. Inclusion criterion #10 was updated to clarify the definition of a highly effective method of contraception.

Section 5.2 (Exclusion Criteria): Exclusion criterion #5 was updated to exclude patients who do not report eating solid food daily during the run-in period. Exclusion criterion #18 was updated to exclude patients with any concomitant use of systemic corticosteroids.

Section 5.4 (Screen failures): Study procedures for re-screening were clarified such that all study procedures scheduled for Visit 1 should be repeated at the re-screening visit, with the exception of the EGD and biopsy, which should be completed at the discretion of the Investigator. The inclusion/exclusion criteria that cannot be failed in order to be considered for re-screening were added, and it was specified that re-screened patients should sign a new ICF.

Section 6.3.1 (Methods for assigning treatment groups): The stratification by region for adults was clarified: North America vs Rest of World.

Section 6.3.2 (Methods for Ensuring Blinding): The text was updated to indicate that in instances in which the Investigator requires an eosinophil, basophil, or monocyte count test for managing safety issues, AstraZeneca should be notified of all such cases without absolute eosinophil counts, absolute basophil counts or absolute monocyte counts being revealed.

Section 6.5.1 (Background medication and related treatments): This section was updated to indicate that patients on PPI therapy must report a stable dose for at least 8 weeks prior to the run-in period.

Section 6.5.4 (Restrictions): Clarifications were added to Table 9 (Allowed, restricted, and prohibited concomitant medication and treatments) regarding allowed and restricted steroid use.

Section 7.1 (Discontinuation of IP): Confirmed reactivation of hepatitis B virus was added as a study-specific criterion for discontinuation.

Section 8.1.3 (Patient Reported Outcomes): The description of the PRO device was updated to be a handheld device. The weekly review of PRO compliance was clarified.

Section 8.1.3.1 (Dysphagia Symptom Questionnaire): Calculation of the DSQ score was clarified and the assessment of dysphagia-free days over each 28-day period was added.

Section 8.1.3.2 (EoE-3D and additional daily questions): The text was updated to clarify how dysphagia episode frequency will be calculated and summarized. Specifics regarding the analyses of dysphagia-related pain/discomfort/overall episode severity and abdominal pain/nausea severity were added.

Section 8.1.3.3 (EoE-QoL-A): The text was updated to reflect that both overall and domain scores will be calculated.

Section 8.1.3.4 (PEESS): The PEESS was added for completion only by patients who are age 18 or under at Visit 1. The assessment will be completed as per the schedule provided in Table 4.

Section 8.1.3.6 (PGI-C): The text was updated to indicate that the PGI-C assessment will be completed by patients weekly starting 7 days after Visit 2.

Section 8.2.1 (Clinical safety laboratory measurements): The text was updated to indicate that the date, time of collection and results (values, units and reference ranges) of additional safety samples will be recorded in the patient's medical records. The text was clarified to include differentials in the eosinophil, basophil, and monocyte counts to be redacted starting from Visit 2.

Section 8.2.1.1 (Other laboratory measurements): The text was updated to indicate that blood samples for hepatitis B core antibody testing will be taken during the run-in period with additional monitoring as needed. This section was updated to include a description of the monitoring requirements for patients that are HBsAg positive or anti-HBc positive at Visit 1. The description of the assessments for total IgE and IgE allergen testing was removed from this section.

Section 8.2.2 (Pregnancy test): This section was updated to clarify that FSH and serum HCG tests would be sent to and analysed at the central laboratory.

Section 8.2.4 (Vital signs): This section was updated to clarify that oral temperature will be measured.

Section 8.3.2.1 (Regulatory Reporting Requirements for SAEs): The section was added to describe the regulatory reporting requirements for SAEs.

Section 8.3.4 (Adverse event data collection): This section was updated to include collection of maximum NCI CTCAE grade and administration of treatment for each AE and description of SAEs.

Section 8.5.1 (Determination of drug concentration): This section was updated to clarify that samples will be analysed for all patients receiving benralizumab.

[redacted]

Section 8.9 (Immunogenicity): This section was updated to clarify that samples will be analysed for all patients receiving benralizumab.

Section 8.11.1 (Diet Questionnaire): This section was updated to clarify that interview data will be entered by the investigator via a web portal.

Section 9.2 (Sample size determination): This section was updated to clarify the assumptions of the sample size calculation.

Section 9.4.1.1 (General principles): The general principles of the analyses that include presence of strictures at baseline as a covariate were clarified to indicate that in the instance of convergence issues/small strata for stratified analyses, presence of strictures at baseline may be removed if necessary.

Section 9.4.1.2 (Primary analysis method): This section was updated to indicate additional analyses to characterize patient dysphagia experience and correlations between the two primary endpoints may be explored. This section was also updated to indicate that sensitivity analyses for missing data will be collected for change from baseline in DSQ

score. Sensitivity analyses of the primary endpoint related to non-evaluable daily DSQ score data were removed.

Section 9.4.1.3 (Analysis methods for secondary efficacy variables): The histological response levels were revised to <1, 1 to ≤6, 7 to <15 eos/hpf, etc. This section was also updated to indicate that responder analyses and descriptive summaries will be provided for all PRO assessments.

Section 9.4.1.4 (Sensitivity analyses): This section was updated to describe the sensitivity analyses that will be performed for the primary and key secondary endpoints.

Section 9.4.2 (Safety analyses): The definition of baseline values for the safety analyses was added. The collection of vital sign parameters was clarified to include systolic and diastolic blood pressure, pulse, respiration rate, and oral temperature. Collection of body weight was also added.

Section 9.4.5 (Methods for multiplicity control): This section was clarified to note that for the purpose of US marketing approval both primary endpoints would need to be statistically significant.

Appendix A-5 (Independent Data Monitoring Committee): The description of the IDMC was updated.

Appendix B-6 (Intensity Rating Scale): This section was clarified to indicate that grading scales NCI CTCAE V5.00 will be utilized for all events with a CTCAE grading. Considerations for other AE intensity grading (e.g., mild, moderate, severe) were removed.

Appendix H (Daily Diary [DSQ, EoE-3D, and other symptom questions]): The PRO instruments contained in this appendix were removed.

Appendix I (EoE-Qol-A): The EoE-Qol-A PRO instrument was removed.

Global: The word ‘optional’ was removed from the description of the OLE period. Participation in the OLE period will be offered to all patients who are eligible.

Version 1.0, 10 July 2019
Original Protocol (Initial creation)

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d3255c00001-csp-v7		
Document Title:	D3255C00001 Clinical Study Protocol version 7	
Document ID:	Doc ID-004158106	
Version Label:	6.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
05-Apr-2022 14:21 UTC	[redacted]	Content Approval
05-Apr-2022 16:25 UTC	[redacted]	Management Approval
08-Apr-2022 15:55 UTC	[redacted]	Content Approval
06-Apr-2022 14:34 UTC	[redacted]	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.