Official Title of Study:

A Phase 3, Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Induction and Maintenance Study to Evaluate the Efficacy and Safety of CC-93538 in Adult and Adolescent Subjects With Eosinophilic Esophagitis

NCT Number: NCT04753697

Document Date (Date in which document was last revised): 01 September 2023

A PHASE 3, MULTICENTER, MULTINATIONAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED INDUCTION AND MAINTENANCE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-93538 IN ADULT AND ADOLESCENT SUBJECTS WITH EOSINOPHILIC ESOPHAGITIS

PROTOCOL NUMBER:	**CC-93538-EE-001**
DATE FINAL:	**30-Sep-2020**
AMENDMENT 0.1 UK	**01-Apr-2021**
AMENDMENT 0.1 DE	**23-Apr-2021**
ADDENDUM 1.2 JP	**10-Jun-2021**
AMENDMENT 0.1 ES	**13-Sep-2021**
ADMINISTRATIVE LETTER No. 01	**04-Mar-2022**
AMENDMENT 1.0	**01-Sep-2023**
EudraCT NUMBER:	**2020-004336-16**
IND NUMBER:	**119240**
SPONSOR NAME / ADDRESS:	Celgene International II Sàrl Route de Perreux 1 2017 Boudry Switzerland

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

The PPD Medical Monitoring team can be reached by contacting the PPD Safety Hotline.

24/7 PPD Medical Monitor Safety Hotline

North American Regional Contact	EMEA & APAC Regional Contact
Phone: [redacted]	**Phone:** [redacted]
Fax: [redacted]	**Fax:** [redacted]

Sponsor Clinical Trial Physician

[redacted]
Title: [redacted] Clinical Trial Physician, [redacted]
Address: 3401 Princeton Pike, Lawrenceville, NJ 08648
Phone: [redacted]
E-mail: [redacted]

The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the PPD Medical Monitor(s) or Clinical Trial Physician(s) or designee for emergency calls.

Back-up 24-hour Global Emergency Contact Call Center: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

See Electronic Signature and Date on File in Electronic Document Management System.
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SPONSOR: CELGENE INTERNATIONAL II SÀRL

[redacted] **Signature of Celgene International II Sàrl Representative**	**Date**
Printed Name of Celgene International II Sàrl Representative	

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 1.0:

The purpose of this amendment is to update the statistical methodology, revise the study discontinuation criteria [redacted], [redacted], as well as align this protocol with guidance provided across the development program. Please note that country-specific restrictions are added to this global protocol amendment, and any country specific protocol amendments will be retired.

Other edits were made throughout the protocol to correct minor errors, add clarity, and improve consistency and alignment. The Protocol Summary was updated to reflect changes in the amendment.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0

Section Number & Title	Description of Change	Brief Rationale
Title Page and Signature Pages	• Updated Sponsor address and personnel.	• Administrative changes.
Section 1:1: Disease Background: Eosinophilic Esophagitis	• Added approval for dupilumab in the United States (US).	• To provide updated information on an approved treatment for EoE.
Section 1.2.1: Mechanism of Action	• Added Bristol Myers Squibb Company (BMS) compound number.	• For clarification purposes.
Section 1.2.2: Clinical Studies	• Updated the list of CC-93538 clinical studies with additional studies.	• To provide further information on clinical studies in the CC-93538 development program.
Section 1.2.2.2 Phase 2 Study, CC-93538-AD-001	• Added new protocol section for Study CC-93538-AD-001.	• To include a brief description of the Phase 2 Study CC-93538-AD-001 evaluating CC-93538 for moderate-to-severe atopic dermatitis.
Section 1.2.2.5: Phase 1 Study, CC-93538-CP-002	• Added new protocol section for Study CC-93538-CP-002.	• To include the results of Study CC-93538-CP-002, which provide the pharmacokinetic comparability, safety, tolerability, and immunogenicity of a single subcutaneous dose of 360 mg CC-93538 using 2 different drug concentrations, 180 mg/mL and 150 mg/mL, in healthy adult subjects.
Section 1.2.2.6: Phase 1 Study, IM042-003	• Added new protocol section for Study IM042-003.	• To include the preliminary results of Phase 1 Study IM042-003 Part 1, which provides PK comparability, safety, tolerability, and immunogenicity of single SC injections of CC-93538 administered using an AI versus PFS.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.3.1.1: Benefit-Risk Assessment Section 8.1: Permitted Concomitant Medications and Procedures	• Added information related to concomitant use of coronavirus disease of 2019 (COVID-19) vaccines in subjects receiving CC-93538.	• Non-live COVID-19 vaccinations will be allowed and will be documented as a concomitant medication for this study. The efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-93538 remain unknown currently.
Section 1.3.2: Rationale for the Study Design	• Added information related to the advisory panel of patients and caregivers.	• Administrative update.
Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48	• Added a secondary endpoint to evaluate the proportion of subjects who maintained their histologic response at Week 24 to Week 48.	• To provide additional results on maintenance of response.
Table 1: Study Objectives Table 2: Study Endpoints: Induction Phase Endpoints at Week 24 Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48 Table 4: Table of Events for the Induction Phase Table 5: Table of Events for the Maintenance Phase Section 6.2: Induction Phase and Maintenance Phase Treatment Period [redacted]	[redacted]	[redacted]
Section 3.1: Study Design Section 4.1: Number of Subjects	• Added language regarding study eligibility, clarifying that in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroids or are	• Local restrictions prohibit enrollment of subjects who are naive or have had an adequate response to corticosteroids in Germany, Spain, and the United Kingdom.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.2: Inclusion Criteria Section 12.3: Subject Information and Informed Consent	intolerant to corticosteroids will be enrolled in the Phase 3 Studies. • Updated language to indicate that in Austria, Germany, Spain, and Switzerland, adolescent subjects will not be included in the Phase 3 Studies.	• Local restrictions prohibit enrollment of adolescent subjects in Germany and Spain. Adolescents will not be enrolled in Austria or Switzerland as participating sites in these countries do not serve the adolescent patient population or have decided to only enroll adult patients.
Section 4.2: Inclusion Criteria	• Updated Inclusion Criterion 8) to indicate that women that have had bilateral salpingectomy are also considered to be not of childbearing potential. • Notes included regarding restrictions on acceptable methods of hormonal contraception in Japan	• Added to clarify that women that have had a bilateral salpingectomy are not of childbearing potential. • Added clarification based on local restrictions included in the Japan country-specific protocol addendum.
Section 4.3: Exclusion Criteria	• Added clarification to Exclusion Criterion 22) for a known hypersensitivity to any ingredient in the investigational product.	• Added clarification based on local restrictions included in the Japan country-specific protocol addendum.
Section 6.2: Induction Phase and Maintenance Phase Treatment Period	• Provided guidance regarding the Week 24 dose when out of window due to EGD scheduling.	• For clarification.
Section 6.2.1 EoE Flare Assessment Visit	• Provided guidance regarding Week 24/Week 48 Visit EGD requirements for subjects that had an EGD as part of their EoE Flare assessment. • Note added to clarify samples do not need to be a pre-dose draw unless the subject is expected to dose later that day.	• For clarification.
Section 6.4.1: Esophagogastroduode-noscopy (EGD)	• Added clarification for handling incidental findings of potential clinical relevance not associated with objectives of the study.	• Provide additional guidance on handling of incidental findings found on the EGD.
Section 6.4.2.1: Modified Daily Symptom Diary (mDSD)	• Added guidance for diary completion during transition between phases or studies.	• For clarification.
Section 6.4.2.8: Entry to Maintenance Phase	• Included language to state that if the subject is eligible for the Maintenance Phase, but the Investigator does not believe it is in the best interest of the subject to continue, a discussion with the Medical Monitor will be required prior to transitioning into the Open-Label Extension study.	• Language for entry into the Maintenance Phase was updated to clarify that this decision should be made in conjunction with the Medical Monitor.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.2: Treatment Administration and Schedule	• Added language from the Germany country-specific protocol amendment that required 60-minute post-dose observation.	• To add language from the Germany country-specific protocol amendment.
Section 7.2.1: Self-Administration	• Added language from the Japan country-specific protocol addendum that provides additional clarification about self-administration.	• To add language from the Japan country-specific protocol addendum.
Section 7.2.4: Guidelines for Temporary Interruption of Dosing	• Added guidance, consistent with Study CC-93539-EE-002, on how to manage subjects who test positive for COVID-19 during the treatment period.	• To align with guidance in Study CC-93538-EE-002.
Section 8: Concomitant Medications and Procedures Section 8.1: Permitted Concomitant Medications and Procedures	• Added information related to concomitant use of COVID-19 vaccines in subjects who receive CC-93538.	• Non-live COVID-19 vaccinations will be allowed and will be documented as a concomitant medication for this study. The efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-93538 remain unknown at this time.
Section 8.2: Prohibited Concomitant Medications and Procedures	• Added further examples of immunomodulating drugs. • Also added language to clarify that corticosteroids can be used for an EoE	• For clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	flare, or used for an adverse event (AE) with consultation with the Medical Monitor, and will not result in permanent discontinuation of IP.	
Section 9.1: Overview	• Added details for database lock and the clinical study report.	• For clarification.
Section 9.2: Study Population Definitions 9.6.1: Efficacy Analysis of the Co-primary Endpoints	• Removed the Per-Protocol (PP) population.	• The PP population was removed as the specified estimands better address the objectives, and the PP population would not add additional insights.
Section 9.3: Sample Size and Power Considerations	• Updated this section using more accurate estimates from the Phase 2 study (RPC02-201) and recent published literature, and clarified the significance level (alpha).	• Updated to reflect more accurate estimates and clarify significance level (alpha).
Section 9.6.1.1: Overview of Attributes of the Main Estimand for the Co-primary Endpoints	• Updated the section title and included the main estimands for the co-primary endpoints in table format. • Updated the main estimand for the co-primary endpoint of change in dysphagia days (DD) from baseline to Week 24. The estimand strategy to handle intercurrent events (ICEs) of rescue therapy/prohibited medication use has been changed from the treatment policy estimand strategy to the composite variable estimand strategy.	• Tables were added to conform with the Sponsor's internal protocol template regarding the presentation of estimand. • Main estimand strategy was updated as the composite variable estimand strategy, which reflects treatment failure, is considered a more appropriate strategy for handling rescue/prohibited medication use than the treatment policy estimand strategy for the main estimand.
Section 9.6.1.2: Change in Dysphagia Days (DD) from Baseline to Week 24 (Induction Phase)	• Included language stating how DD are calculated. • Included language defining the missing data rule. • Added a sensitivity analysis where a minimum of 4 measurable diary days per week is required to derive a DD score for the 14-day period. • Removed a sensitivity analysis where missing daily DD scores are imputed using multiple imputation (MI). • Added a supplementary analysis for the co-primary endpoint of change in DD from baseline to Week 24 using the treatment policy estimand strategy to handle ICEs of rescue therapy/prohibited medication use.	[redacted] • Sensitivity analysis was removed as it was considered to provide very little additional insight beyond the currently specified sensitivity and supplementary analyses. • Main estimand strategy was updated from treatment policy estimand strategy to composite variable estimand strategy for handling ICEs

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
		of rescue therapy/prohibited medication use.
Section 9.6.1.3: Eosinophilic Histologic Response at Week 24 (Induction Phase)	• Updated language to indicate that missing data for the binary efficacy endpoints will be imputed using the MI approach rather than non-responder imputation.	[redacted]
Section 9.6.1.3: Eosinophilic Histological Response at Week 24 (Induction Phase) Section 9.6.3: Analysis of Secondary Efficacy Endpoints Section 9.6.4.1: Analyses Method	• Removed language stating that the stratified Newcombe confidence interval (CI) will be provided for binary efficacy endpoints.	• The method for handling missing data for the binary efficacy endpoints has been changed from non-responder imputation to MI; therefore, the Newcombe CIs cannot be provided.
Section 9.6.2: Analysis of Key Secondary Efficacy Endpoints	• Added supplemental analyses using the treatment policy estimand strategy to handle ICEs of rescue therapy/prohibited medication use.	[redacted]
Section 9.6.4: Control of the Type I Error Rate	• Added language and updated the hierarchical testing procedure to include two secondary endpoints at Week 48 in the overall population and testing of the co-primary endpoints and two secondary endpoints at Week 48 in the Steroid Inadequate Responders/Intolerant subgroup.	• Updated for consistency [redacted] to align with development objectives.
Section 9.6.5: Subgroup Analyses	• Added "on stable dietary modification (eg, elimination diet for the treatment of allergy or EoE [yes versus no])" to the list of subgroups that will be assessed. • Removed language regarding a criterion for conducting the subgroup analyses.	• Added to better understand CC-93538 treatment response in the presence of other EoE concomitant therapies. • Language was removed as this information will be specified and discussed in the statistical analysis plan.
Section 10.5: Reporting of Serious Adverse Events	• Modifications were made for reporting of serious adverse events (SAEs) that occur prior to treatment but after signing the informed consent form/assent.	• All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by completing in EDC.
Section 10.6: Adverse Events of Special Interest	• Added text denoting the Sponsor will also identify Adverse Events of	• For clarification.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	Special Interest (AESI) programmatically. • Clarified that AESIs must be entered into EDC.	
Section 10.7: Expedited Reporting of Adverse Events	• Gastroesophageal reflux disease (GERD) and dysphagia are not considered anticipated serious events, and as such they will not be excluded from expedited reporting of AEs to the United States Food and Drug Administration per the CC-93538 Safety Surveillance Plan.	• Per the Safety Surveillance Plan for CC-93538, following review of data from randomized controlled trials in EoE, including Study RPC02-201, anticipated severe events have not been identified for the EoE patient population; therefore, dysphagia and GERD are being removed as serious anticipated events from the CC-93538-EE-001 protocol.
Section 11.2: Study Discontinuation	• Removed reasons other than withdrawal of consent (WOC) and lost to follow-up (LTFU) as reasons why subjects discontinue from study. Death and Other remain as they are standard.	• [redacted] since subjects can continue on study without being on investigational product, the main reasons for subjects to discontinue from the study should be due to Lost to Follow-Up (LTFU) or Withdrawal of Consent (WOC).
Section 14.3: Investigational Medicinal Product Quality Issues	• An Investigator Memo was provided in 2021 to inform sites of the new process on reporting any issues with investigational product and this language is now reflected in this amendment.	• Updated to reflect the current internal processes.
All	• Minor formatting and typographical corrections.	• Minor edits that do not change the content of the protocol were made to improve readability and consistency.

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled Induction and Maintenance Study to Evaluate the Efficacy and Safety of CC-93538 in Adult and Adolescent Subjects with Eosinophilic Esophagitis

Indication

CC-93538, also known as BMS-986355 (nonproprietary name, cendakimab), is a recombinant humanized, high-affinity neutralizing (immunoglobulin G1 kappa [IgG1κ]) monoclonal antibody (mAb) selective for interleukin-13 (IL-13). CC-93538 binds to IL-13, thus preventing its interaction with both IL-13 receptors, IL-13 receptor alpha 1 (IL-13Rα1) and IL-13 receptor alpha 2 (IL-13Rα2). Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, and IL-13 has been shown to be a key driver of disease pathology in patients with EoE.

Globally, the Phase 3 program includes a multicenter, multinational, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EoE (Study CC-93538-EE-001) with a separate, optional Open-Label Extension Study (OLE; Study CC-93538-EE-002). However, in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy will be enrolled in the studies. Also, in Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

Results of the Phase 2 Study, RPC02-201, in adult subjects with EoE showed that administration of CC-93538 180 mg and 360 mg subcutaneously (SC) weekly for 16 weeks reduced the mean esophageal eosinophil count (the primary endpoint) and improved other inflammatory parameters. A greater reduction in dysphagia symptoms was observed with the 360 mg dose although it did not reach statistical significance. The study also demonstrated the safety and tolerability of CC-93538 in adult subjects with symptomatic EoE treated with one of 2 dose levels (CC-93538 180 mg or 360 mg SC) compared to placebo. CC-93538 was generally safe and well tolerated for up to 68 weeks of treatment (including data from a 52-week CC-93538 Open-Label Extension). These data support the continued development of CC-93538 as a novel treatment for EoE. The single pivotal Phase 3 study is designed to confirm and extend the findings obtained from the positive Phase 2 study with CC-93538.

Objectives (Primary and Secondary)

<u>Primary Objectives</u>

- To assess the efficacy of CC-93538 versus placebo in reducing dysphagia symptoms at 24 weeks
- To assess the efficacy of CC-93538 versus placebo in reducing esophageal eosinophil counts at 24 weeks

Secondary Objectives

- To assess the efficacy of CC-93538 versus placebo at 24 weeks in improving:
  - Endoscopic features of EoE
  - Histologic features of EoE
- To assess the persistence of effect of CC-93538 at 48 weeks in reducing:
  - Dysphagia symptoms
  - Esophageal eosinophil counts
- To assess the persistence of effect of CC-93538 through administration of a less frequent dosing regimen at 48 weeks in reducing:
  - Dysphagia symptoms
  - Esophageal eosinophil counts
- To assess the persistence of effect of CC-93538 at 48 weeks in improving:
  - Endoscopic features of EoE
  - Histologic features of EoE
- To evaluate the time to and frequency of EoE flare events and use of rescue therapy during the study
- To evaluate the safety and tolerability of CC-93538 including the characterization of the immunogenicity profile
- To assess trough concentrations of CC-93538 in subjects with EoE

See Section 2 for a complete list of study objectives, including all [redacted] objectives.

Study Endpoints (Primary and Secondary)

Induction Phase Endpoints

For endpoints listed below with statistical comparisons, the CC-93538 360 mg SC once weekly treatment arm (2 active arms combined) will be compared to the placebo arm.

Co-primary endpoints at Week 24:

- The mean change in dysphagia days (DD), evaluated over the prior 14-day period using the modified Daily Symptom Diary (mDSD), from baseline to Week 24
- The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count $\leq$ 6/high-power field (hpf) at Week 24

Key secondary endpoints at Week 24:

- The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf at Week 24
- The mean change in the endoscopic features of EoE as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to Week 24

- The mean change in the mean adjusted histology grade score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 24
- The mean change in the mean adjusted histology stage score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 24
- The mean change in the modified Daily Symptom Diary (mDSD) composite score from baseline to Week 24
- Additional secondary endpoints at Week 24:
- The proportion of subjects with a ≥ 50% decrease in dysphagia days (DD) from baseline at Week 24
- The mean change in dysphagia days (DD) over time from baseline through Week 24
- The mean change in the modified Daily Symptom Diary (mDSD) composite score over time from baseline through Week 24
- The time to event of EoE flare during the Induction Phase
- The time to event of use of rescue therapy during the Induction Phase
- The proportion of subjects with an EoE flare during the Induction Phase
- The proportion of subjects with use of rescue therapy during the Induction Phase
- Safety and tolerability evaluated by the incidence, severity, and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities, and the presence of anti-drug antibodies
- Measurements of trough concentrations of CC-93538 in subjects with EoE during the Induction Phase

Maintenance Phase Endpoints

For endpoints listed below with statistical comparisons, the 2 CC-93538 dosing regimens (360 mg SC once weekly and 360 mg SC once every other week) will be compared to placebo separately.

Secondary endpoints at Week 48:

- The mean change in dysphagia days (DD), evaluated over the prior 14-day period using the modified Daily Symptom Diary (mDSD), from baseline to Week 48
- The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 48
- The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf at Week 48
- The mean change in the endoscopic features of EoE as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to Week 48
- The mean change in the mean adjusted histology grade score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 48
- The mean change in the mean adjusted histology stage score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 48

- The mean change in the modified Daily Symptom Diary (mDSD) composite score from baseline to Week 48
- The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 48 among subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 24
- The time to event of EoE flare during the study (Induction and Maintenance Phases)
- The time to event of use of rescue therapy during the study (Induction and Maintenance Phases)
- The proportion of subjects with an EoE flare during the study (Induction and Maintenance Phases)
- The proportion of subjects with use of rescue therapy during the study (Induction and Maintenance Phases)
- Safety and tolerability evaluated by the incidence, severity, and relationship to CC-93538 of AEs, SAEs, clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities, and the presence of anti-drug antibodies
- Measurements of trough concentrations of CC-93538 in subjects with EoE during the Maintenance Phase

See Section 2 for a complete list of study endpoints including all [redacted] endpoints.

Study Design

Study CC-93538-EE-001 is a Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EoE. The study will incorporate a 24-week Induction Phase followed by a 24-week Maintenance Phase.

Following a 4-week Screening Period, subjects meeting all inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the 24-week Induction Phase. Subjects (N ≈ 399) will be randomized (1:1:1) to receive CC-93538 360 mg subcutaneously (SC) once weekly (2 of the 3 treatment arms) or matching placebo, in a double-blind manner for 24 weeks. Subjects are required to have at least 4 dysphagia days (DD) as assessed with the dysphagia modified Daily Symptom Diary (mDSD) over the prior 2 consecutive weeks (14 days) before baseline and histologic evidence of EoE, defined as a peak count of ≥ 15 eosinophils per hpf at any 2 levels (proximal, mid, distal) of the esophagus; both assessments will be conducted when not receiving anti-inflammatory therapy. Further, eligibility also includes a previous proton pump inhibitor trial without a complete response. Treatment assignment at baseline will be stratified based on steroid responder status to ensure an equal balance in the treatment arms.

After completion of Week 24 of the Induction Phase, subjects will be eligible to enter the Maintenance Phase if none of the conditions that would disqualify subjects from continuing have been met including the need for endoscopic intervention or concomitant use of rescue therapy for a severe EoE flare (refer to Section 6.4.2.7). The Maintenance Phase treatment arms include 360 mg SC once every week, 360 mg SC once every other week, and matching placebo. Approximately half of the subjects receiving CC-93538 360 mg SC once weekly during the

Induction Phase will continue on the same dosing regimen for the Maintenance Phase while the other half of the subjects will continue on the less frequent regimen of 360 mg SC once every other week per the original randomization assignment. Subjects previously randomized to placebo will remain on placebo.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests, esophagogastroduodenoscopy (EGD), clinical symptom assessment, subject-reported outcomes, serum CC-93538 concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and AE assessments will be performed according to the Table of Events presented in Table 4 (Induction Phase) and Table 5 (Maintenance Phase). [redacted]

Subjects experiencing an EoE flare in the Induction or Maintenance Phase may continue to participate with concomitant rescue therapy as needed and will be eligible to enter the Open-Label Extension (OLE) study only following completion of Week 24 of the Induction Phase or Week 48 of the Maintenance Phase, respectively. Subjects with an EoE flare requiring rescue therapy during the Induction Phase will not be eligible to enter the Maintenance Phase.

Following Induction, subjects not entering the Maintenance Phase or OLE study will return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively, after final investigational product (IP) administration for the assessment of safety and clinical status. Similarly, subjects completing the Maintenance Phase who do not participate in the OLE study will complete the Interim and the Final Safety Follow-up Visits (at 8 and 16 weeks, respectively) after final IP administration. Subjects who discontinue the study prematurely will be asked to complete an Early Termination (ET) Visit and return for the 2 Safety Follow-up Visits.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

The study population will consist of males and females aged 12 to 75 years (inclusive) with EoE who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy, as defined in Section 4.2, Inclusion Criterion 5 (Steroid Inadequate Responders/Intolerant; approximately 70% of the study population) as well as subjects who are naïve or have had an adequate response to corticosteroid therapy (Steroid Responders/Naïve; approximately 30% of the study population). Approximately 369 adults (aged 18 to 75 years) and 30 adolescents (aged 12 to 17 years) with a weight of ≥ 40 kg will be enrolled in the study.

However, in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy will be enrolled in the study. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

Note: Countries or sites with local restrictions that prohibit enrollment of adolescents (aged 12 to 17 years inclusive) will only enroll subjects who are 18 years of age or older. Enrollment of adolescent subjects will begin only after the applicable regulatory requirements for enrolling subjects in that age group have been satisfied and the necessary health authority approvals have

been granted. Where national or regional guidelines for the definition of adolescence differ from the definition stated above, the national or regional guidelines may be used to determine eligibility.

Length of Study

The maximum duration of subject participation in this study is approximately 72 weeks. Subjects will participate up to 4 weeks in the Screening Period (the screening EGD may be completed up to 8 weeks prior to Day 1), 24 weeks in the Induction Phase Treatment Period, and 24 weeks in the Maintenance Phase Treatment Period of the study. Following Induction, subjects not entering the Maintenance Phase or OLE study will have Interim and Final Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration for the assessment of safety and clinical status. Similarly, subjects completing the Maintenance Phase who do not participate in the OLE study will have Interim and Final Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration; for these subjects, the maximum duration is approximately 71 weeks. However, as an exception, the maximum duration of participation will be approximately 72 weeks for subjects permanently discontinuing IP during the Maintenance Phase but who continue study participation through Week 48, as the Interim and Final Safety Follow-up Visits will occur 8 and 16 weeks after the last study visit instead of the last dose of IP.

The End of Study is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary, [redacted] analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

Subjects will be randomized 1:1:1 to the following treatment arms for the 24-week Induction and 24-week Maintenance Phases:

- CC-93538 360 mg SC once weekly for 24 weeks followed by CC-93538 360 mg SC once weekly for 24 weeks
- CC-93538 360 mg SC once weekly for 24 weeks followed by CC-93538 360 mg SC once every other week for 24 weeks. During the Maintenance Phase, matching placebo will be administered once every other week on alternate weeks to maintain the blind.
- Matching placebo SC once weekly for 24 weeks followed by matching placebo SC once weekly for 24 weeks

The CC-93538 360 mg SC dose will be administered by 2 injections of 1.2 mL each provided in 150 mg/mL pre-filled syringes (PFS). Matching placebo will also be administered as 2 injections of 1.2 mL.

Overview of Key Efficacy Assessments

- Number of dysphagia days (DD) and modified Daily Symptom Diary (mDSD) composite score using the mDSD instrument
- Enumeration of esophageal eosinophil count (peak esophageal eosinophil count) by analysis of hematoxylin and eosin (H&E) stained esophageal biopsies

- EoE Endoscopic Reference Score (EREFS)
- EoE histology scoring system (EoEHSS)

For additional detail about key efficacy assessments, please refer to the Table of Events (Table 4 and Table 5).

Overview of Key Safety Assessments

- Type, frequency, severity, seriousness, and relationship of AEs to IP
- Clinically significant changes in vital signs, physical examinations, and laboratory findings
- Presence of and clinical effects of anti-drug antibodies (ADAs)

For additional detail about key safety assessments, please refer to the Table of Events (Table 4 and Table 5).

Statistical Methods

The primary population for assessing efficacy will be the intent-to-treat (ITT) population which consists of all randomized subjects regardless of whether or not the subject received IP (CC-93538 or placebo).

Analysis details not explained in the statistical section of the protocol (Section 9), will be provided in the Statistical Analysis Plan (SAP). In addition, the statistical analysis and analysis population for the European Union (EU) will be described in the SAP.

Sample Size

A total sample size of 399 subjects (266 subjects for CC-93538 and 133 subjects for placebo) with a 20% dropout rate at the end of the Induction Phase (212 subjects for CC-93538 and 106 subjects for placebo) will provide at least 90% power to detect a difference of -2.79 change in DD from baseline at Week 24 and at least 90% power to detect a difference of 15% at Week 24 in histologic response with a two-sided significance level (alpha) of 0.05. These calculations were based on a 2 sample t-test assuming a pooled standard deviation (SD) of 4.76 for change in DD from baseline and the chi-square test to compare the difference in 2 independent proportions for the histologic response assuming a true placebo response proportion is 0.05.

Efficacy Analysis

Change in DD: The mean change in DD, evaluated over the prior 14-day period using the mDSD, from baseline to Week 24 is one of the 2 co-primary endpoints for the Induction Phase. The primary analysis will be conducted on the ITT population based on an analysis of covariance (ANCOVA) model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline DD values included in the model. The comparison between CC-93538 360 mg SC once weekly and placebo for change in DD from baseline at Week 24 will be made using the difference in least squares (LS) Mean at a 5% 2-sided significance level. Point estimates for the mean difference between the 2 treatment groups using the adjusted LS Mean changes and corresponding 95% Wald CI will be reported. In addition, adjusted LS Means with standard error

(SE), arithmetic means with standard deviation (SD), and arithmetic mean changes with SD will be summarized by treatment group.

Histologic Response: The other co-primary endpoint, the eosinophilic histologic response is defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 24. The primary analysis of the eosinophilic histologic response will be conducted on the ITT population using the Cochran-Mantel-Haenszel (CMH) test at a 2-sided 5% significance level, stratified by Steroid Inadequate Responders/Intolerant status. For treatment comparison between CC-93538 360 mg SC once weekly and placebo, the 2-sided 95% CI for the difference in proportions using the CMH weights and the 2-sided p-value from the CMH test will be provided.

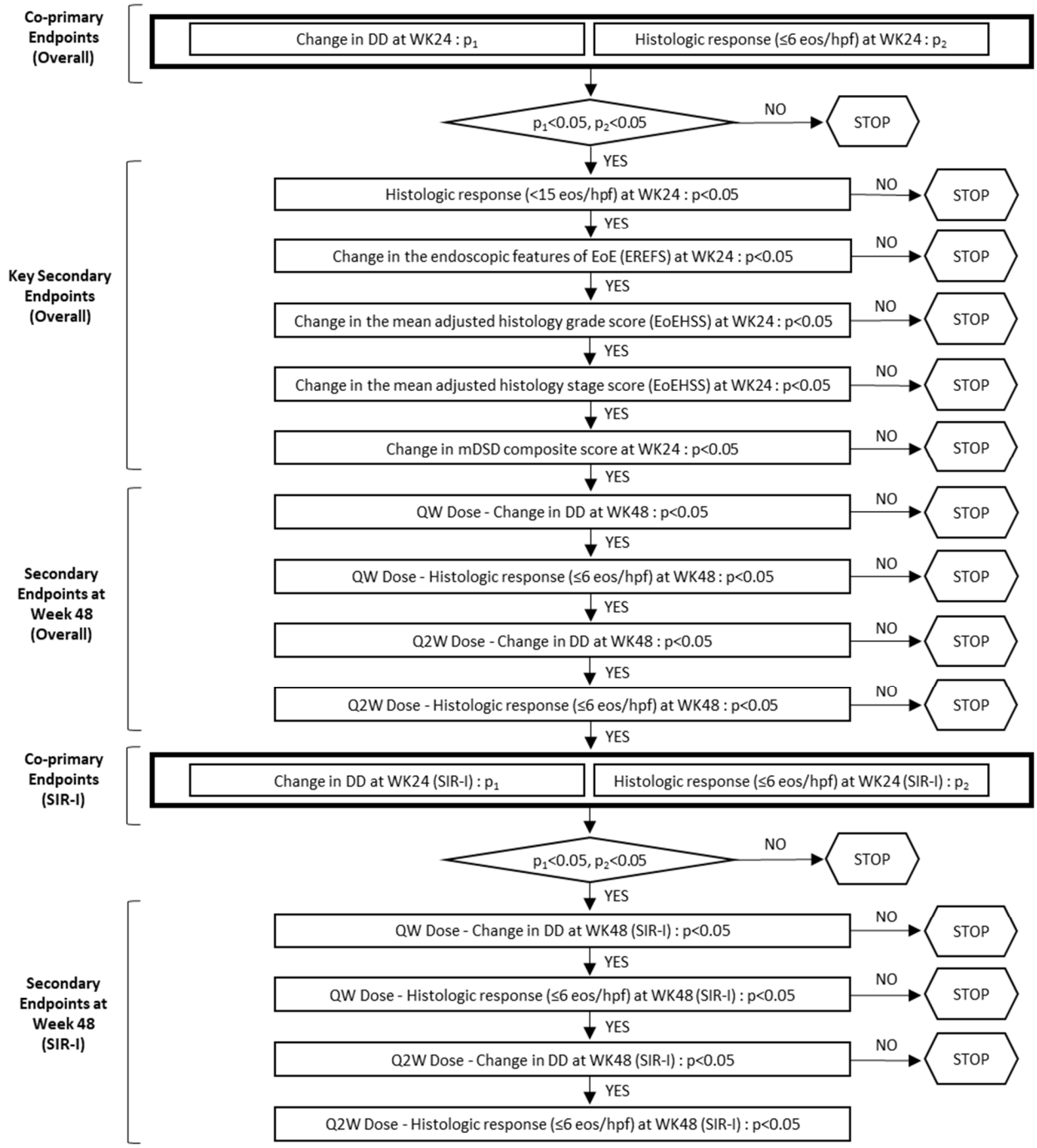
The following are the intercurrent events (ICEs) of interest:

1) Treatment discontinuation in subjects without the use of concomitant rescue therapy or prohibited medication (subjects remain in the study)
2) The use of concomitant rescue therapy or prohibited medication which may impact the efficacy assessment for CC-93538 regardless of treatment discontinuation

For ICE number 1, the treatment policy estimand strategy will be used where all observed data after the ICE will be included in the primary analysis regardless of the occurrence of the ICE. For ICE number 2, a composite variable estimand strategy will be used where data after rescue therapy or prohibited medication which may impact the efficacy assessment will be set as non-responders for histologic response and worst possible value for change in DD. A missing at random (MAR) multiple imputation approach will be applied for missing data.

Multiplicity Adjustment

A hierarchical testing procedure will be employed to control the overall type I error rate at 0.05 for the co-primary endpoints, key secondary endpoints, and two secondary endpoints at Week 48 in the overall population. In addition, the hierarchical testing procedure includes testing of the co-primary endpoints and two secondary endpoints at Week 48 in the Steroid Inadequate Responders/Intolerant subgroup. Below is the schematic for this hierarchical testing procedure for the United States and other non-European Union regions.



Abbreviations: DD = dysphagia day(s); EoE = eosinophilic esophagitis; EoEHSS = EoE histology scoring system; eos = eosinophils; EREFS = EoE Endoscopic Reference Score; hpf = high-power field; ITT = intent-to-treat; mDSD = modified daily symptom diary; SIR-I = Steroid Inadequate Responders/Intolerant; WK = week

Note: p_1 and p_2 represent the p-values for the 1st co-primary endpoint of change in DD and 2nd co-primary endpoint of histologic response, respectively.

Safety Population

The safety population will consist of all subjects who received at least one dose of IP. The assessment of safety will include AEs, SAEs, AEs leading to discontinuation of study treatment, changes from baseline in laboratory values and vital signs, and incidence and type of laboratory, vital signs, and physical examination abnormalities. Safety data will be summarized by treatment group using descriptive statistics.

External Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) will be convened and will be comprised of physician experts with experience in treating subjects with EoE and a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified conflict of interest. During the study, the DMC will review selected data (to be specified in the DMC charter) on a regular basis for the assessment of benefit-risk and determination of study continuation. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, for the DMC members for each scheduled meeting. Operational details for the DMC, including a blinding plan to assure that all personnel involved in the conduct of the study remain blinded to the results of data reviews, will also be described in the DMC charter.

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1 INTRODUCTION

1.1 Disease Background: Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, debilitating, allergic/immune-mediated disease due to chronic esophageal inflammation with the development of dysphagia that affects food intake and quality of life. The disease is characterized by symptoms related to esophageal dysfunction and by eosinophil-predominant inflammation of the esophageal mucosa.

While eosinophils are present in specific regions of the gastrointestinal (GI) tract, they are not normally found in the esophagus. Patients with EoE demonstrate esophageal tissue infiltration of significant numbers of eosinophils and other pro-inflammatory cells, including mast cells and B and T lymphocytes (Mulder, 2011), the latter characterized by an enrichment of CD4+ T regulatory and type 2 cytokine producing effector type 2 T helper (Th2) cells (Wen, 2019). This infiltrating cellular profile along with over expression of cytokines, particularly interleukin-13 (IL-13) and interleukin-5 (IL-5), strongly suggests that EoE is a type 2 cell-mediated inflammatory disease. Many patients with EoE have other atopic diseases including asthma and food allergies, supporting the view that EoE likely represents a disease in which type 2 cells and eosinophils play key pathogenic roles (Straumann, 2012).

Interleukin-13 is a pleotropic cytokine that has been shown to have a critical role in the immunopathogenesis of type 2 inflammation characteristic of EoE (Wechsler, 2014). Pre-clinical and in vitro modeling have shown that IL-13 is overexpressed in the esophageal mucosa of EoE subjects and induces a gene transcript profile that overlaps with the EoE-specific esophageal transcriptome (Blanchard, 2007). Interleukin-13 modulates cellular and molecular pathways involved in eosinophil recruitment (Brightling, 2010), esophageal barrier function (Sherrill, 2014), and tissue remodeling and fibrosis (Zuo, 2010). Simulated altered expression of IL-13 and simulated blockade of IL-13 in animal models have also been shown to cause fluctuations in EoE disease status, esophageal function, and other related clinical consequences (Zuo, 2010; Kottyan, 2014; Rothenberg, 2015a).

The extensive tissue remodeling, including epithelial thickening, and fibrosis that also characterizes EoE leads to esophageal stricture and narrowing. Esophageal dysfunction, with symptoms of dysphagia (the most common symptom), chest pain and upper abdominal pain, and food bolus impaction is a direct consequence of these structural changes (Straumann, 2012). Natural history studies and molecular endotype analysis in adults demonstrate that EoE is a progressive fibrostenotic disease that, if not treated, usually leads to stricture formation (Shaheen, 2018; Shoda, 2018). The risk of stricture formation is proportional to the duration of untreated disease (Schoepfer, 2013; Dellon, 2014). If left untreated, EoE transitions to a more fibrotic state that is associated with increased morbidity and further decreased quality of life.

In the United States (US), the prevalence of EoE increases with age and peaks in the age range of 30 to 44 years (Dellon, 2018a). An internal analysis conducted in March of 2019 using US commercial claims data demonstrated an increasing EoE prevalence rate over the last several years (MarketScan Database, 2018). From 2011 to 2017, the prevalence for individuals aged 0 to 64 years was 4.15 (95% confidence interval [CI]: 4.09 to 4.21) per 10,000 persons in 2011 and 10.73

(95% CI: 10.58 to 10.88) per 10,000 persons in 2017. Further, in 2017, adolescent patients, which will be included in the Phase 3 program, made up 10.7% of the total patients with EoE aged 12 to 64 years.

In the European Union (EU), the prevalence of EoE was reported to be between 1.4 in 10,000 persons (Dellon, 2015), and 4.8 in 10,000 persons (Giriens, 2015). A pooled estimate from a meta-analysis of population-based studies in North America, Europe, and Australia placed the prevalence of EoE somewhere in the middle of the range (2.27 per 10,000; 95% CI: 1.34 to 3.60) (Arias, 2016). Further, a rise in the incidence of EoE in multiple countries has been reported (Moawad, 2018). Moreover, an additional meta-analysis of studies mainly conducted in North America (US and Canada) and Europe reported a pooled prevalence of 3.42 per 10,000 inhabitants with a 95% CI: 2.31 to 4.75 (Navarro, 2019).

Although the definitive etiology of EoE is unknown, several factors that influence the risk of EoE have been identified. Eosinophilic esophagitis is a disorder most likely triggered by food and/or aeroallergens (de Bortoli, 2017). Disease pathogenesis involves activation of epithelial inflammatory pathways, impaired barrier function, increased production and/or activity of transforming growth factor-β, and induction of allergic inflammation by eosinophils and mast cells (Rothenberg, 2015b).

The diagnosis of EoE is based on symptoms related to esophageal dysfunction, the presence of eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥ 15 eosinophils per high-power field (or approximately 60 eosinophils per mm^2), and assessment of other causes that may be responsible for, or contributing to, symptoms and esophageal eosinophilia, particularly gastroesophageal reflux disease (GERD) (Dellon, 2018b).

The clinical manifestations commonly observed in adults with EoE include dysphagia, food impaction, chest pain that is often centrally located and may not respond to proton pump inhibitors (PPIs), GERD-like symptoms/refractory heartburn, and upper abdominal pain (Kapel, 2008; Sgouros, 2006; Gonsalves, 2006; Shoda, 2018). The clinical manifestations of EoE observed in adolescents include dysphagia and food impactions (Furuta, 2015).

The management of EoE includes pharmacologic, endoscopic, and dietary interventions, as outlined in a 2011 consensus statement (Liacouras, 2011) and guidelines provided by the United European Gastroenterology group (Lucendo, 2017). Response to a trial of PPI therapy was previously used to rule out diagnosis of EoE. However, recent studies have demonstrated that the demographics, endoscopic features, EoE [redacted] and gene expression profiles do not reliably distinguish EoE from PPI-responsive esophageal eosinophilia. Therefore, consensus recommendations have now advocated removal of a PPI trial for the purposes of establishing a diagnosis of EoE (Dellon, 2018b; Molina-Infante, 2016). Proton pump inhibitors are instead viewed as a viable treatment alternative for EoE (through off-label use) with an overall clinical response and histologic response rate of 30% to 70% (Lucendo, 2017). Given the ease of administration and long-term clinical experience, PPIs have been positioned as a first-line pharmacological option for most patients with EoE (Dellon, 2018b; Lucendo, 2017). For patients without symptom and histologic improvement after PPI therapy, PPI therapy is discontinued. The

current standard of care for both naïve and relapsing patients also includes topical corticosteroids (swallowed or inhaled preparations) as first line treatment (as an add-on to PPIs or as stand-alone). Overall response rates are 60% to 80%. However, the majority of patients relapse within 1 to 4 months following discontinuation, requiring additional courses of therapy, and most patients lose response even if the steroids are continued long-term. Nevertheless, steroids continue to be prescribed mostly off-label. Although the orodispersible tablet formulation of budesonide (Jorveza™) was approved in the EU in early 2018 for the treatment of EoE in adults over 18 years of age, it is not currently approved in the US. The US Food and Drug Administration (FDA) has more recently approved dupilumab as a new treatment for EoE in adults and pediatric patients 12 years and older, weighing at least 40 kg (US FDA, 2022). Dupilumab was also approved in the European Union (EU) to treat EoE in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy in January 2023 (European Medicines Agency, 2023). Dupilumab is a monoclonal antibody against interleukin (IL)-4 receptor alpha that blocks IL-4 and IL-13 cosignaling through a shared receptor component, decreasing type 2 inflammation. Weekly treatment with dupilumab for 24 weeks in the pivotal study demonstrated histologic remission (defined as a peak esophageal intraepithelial eosinophil count of ≤ 6 per high-power field) in approximately 60% of patients and improvements in symptomatic scores (Dellon, 2022; Straumann, 2022). Dupilumab's approval marks the introduction of the use of biologics in the EoE treatment paradigm (Nhu, 2022).

Non-pharmacologic treatment strategies include dietary therapy and endoscopic dilations. Dietary therapy usually consists of an elemental formula, a six-food elimination diet (SFED), or targeted elimination diet (Dellon, 2012). Challenges to this approach include difficulty in compliance, effects on quality of life and social activities because patients have to avoid common foods such as milk and gluten (Straumann, 2018), and the frequent need for endoscopies to properly assess response to changes in food exposure. Dilation of esophageal strictures has been reported to be effective for relieving dysphagia in adults and children with EoE (Lucendo, 2018), but it has no effect on underlying inflammation (Schoepfer, 2010; Robles-Medranda, 2010) and is not free of procedural complications (Schoepfer, 2014a). Dilation is often reserved for patients who have failed other therapy. However, dilation may be required as initial therapy in EoE patients (often adults) who have high-grade strictures (Dellon, 2013; Furuta, 2007).

Despite the recent advances in EoE treatment, significant unmet need still exists for a new and effective immunomodulatory treatment with an improved safety and tolerability profile, especially for long-term management.

1.2 Investigational Product: CC-93538

1.2.1 Mechanism of Action

CC-93538, also known as BMS-986355 (nonproprietary name, cendakimab), is a recombinant, humanized, high-affinity neutralizing (immunoglobulin G1 kappa [IgG1κ]) monoclonal antibody (mAb). CC-93538 is highly selective for human IL-13 and was generated by humanization of a rodent anti-human IL-13 mAb, which was identified using hybridoma technology through

immunization of mice with human Q110 variant recombinant IL-13. The fragment, crystallizable (Fc) region of CC-93538 is mutated at residues L240A and L241A in the heavy chain hinge/CH2 region to reduce effector function as suggested by literature reports (Hezareh, 2001; Lo, 2017). CC-93538 is produced by mammalian cell expression.

IL-13 is a cytokine that is expressed by a large number of cell types including most leukocytes, mast cells, epithelial cells, fibroblasts, and smooth muscle cells (Brightling, 2010). CC-93538 has high affinity for wild-type IL-13 and a common variant of IL-13, Q110, which is associated with and enhances human allergic inflammation (Vladich, 2005). CC-93538 binds an IL-13 epitope, comprised of residues in helix A and helix D (Ying, 2010). This binding in turn prevents IL-13 from binding to both IL-13 receptor alpha 1 (IL-13Rα1) and IL-13 receptor alpha 2 (IL-13Rα2) (Ying, 2010), where IL-13Rα1 and IL-13Rα2 may be implicated in inflammation and in the progression of tissue remodeling or fibrosis in EoE, respectively (Doran, 2017; Hershey, 2003; Fichtner-Feigl, 2006; Fichtner-Feigl, 2008).

1.2.2 Clinical Studies

CC-93538 has been investigated in a Phase 1 clinical study in healthy adults and adults with mild-to-moderate controlled asthma, Study M10-378; a Phase 2 clinical study in adults with moderate-to-severe atopic dermatitis, Study CC-93538-AD-001; and a Phase 2 clinical study in adults with EoE, Study RPC02-201. Additional Phase 1 single-dose pharmacokinetic (PK) studies in adult healthy volunteers, RPC02-1901, CC-93538-CP-001, and CC-93538-CP-002, were also completed, and preliminary results are available for a fourth PK study, IM042-003 Part 1.

1.2.2.1 Phase 1 Study, M10-378

The PK of CC-93538 was examined in healthy adults (between 18 and 55 years of age, inclusive) and adults with mild-to-moderate asthma in Study M10-378. The PK data included results from 16 healthy subjects after intravenous (IV) infusion over the 0.3 mg/kg to 10.0 mg/kg CC-93538 dose range, 12 subjects with mild-to-moderate asthma after IV infusion over the 0.3 mg/kg to 10.0 mg/kg dose range, and 8 subjects with mild-to-moderate asthma after SC administration of 0.3 or 3.0 mg/kg for 3 weekly doses. After IV administration, the exposures, as determined by CC-93538 area under the curve (AUC) and observed maximum serum concentration (Cmax), increased in a dose-dependent manner and were similar in healthy subjects and subjects with asthma. The median time to the observed maximum concentration (tmax) for CC-93538 following SC administration in subjects with asthma was approximately 108 hours or 4.5 days. The mean estimated volume of distribution at steady state for CC-93538 ranged from 69.7 to 97.7 mL/kg, and the mean systemic clearance for CC-93538 ranged from 0.106 to 0.154 mL/hr/kg. The mean terminal elimination half-life (t½) for CC-93538 ranged from 16.4 to 26.7 days. See Section 1.2.2.7 for PK results from Phase 2 Study RPC02-201.

In Study M10-378, CC-93538 was well tolerated and had an acceptable safety profile when administered as a single dose up to 10.0 mg/kg IV or as 3 weekly doses of 0.3 and 3.0 mg/kg SC. There were no deaths. One serious adverse event (SAE) of bunionectomy which was considered unrelated to study drug was reported in a healthy subject. The adverse event (AE) profile in healthy adults was similar to that observed in subjects with asthma. No dose-related increases or

administration-specific trends in treatment-emergent AEs (TEAEs) were observed. No subjects discontinued study treatment due to a TEAE. No infusion-related reactions were reported. Anti-drug antibodies (ADAs) were detected in approximately 28% (10 of 36 subjects) of subjects receiving CC-93538 but were usually transient and did not interfere with CC-93538 PK.

1.2.2.2 Phase 2 Study, CC-93538-AD-001

Study CC-93538-AD-001 is an ongoing, Phase 2, multicenter, global, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of CC-93538 in adult subjects with moderate-to-severe atopic dermatitis. A total of 220 subjects were randomized in the study, and the clinical study conduct is complete. The study results were still being analyzed, and the clinical study report (CSR) was not yet final at the time of this amendment.

1.2.2.3 Phase 1 Study, RPC02-1901

Study RPC02-1901 was a Phase 1, randomized, open-label, single-dose parallel-group study to characterize the PK of CC-93538 in healthy adult subjects following a single 360 mg IV infusion or 360 mg SC administration using the 150 mg/mL formulation. Twenty-four healthy adult subjects were randomized to receive a single CC-93538 360 mg dose either via IV infusion (N = 12) or SC injection (N = 12). Following SC administration, the absorption of CC-93538 was slow with a median tmax of approximately 144 hours (approximately 6 days). CC-93538 showed a long elimination t½ of approximately 475 to 497 hours (approximately 20 to 21 days) and a small volume of distribution of approximately 5 L. The SC bioavailability of CC-93538 was estimated to be approximately 53%. Anti-CC-93538 antibodies were detected in 10 of 24 subjects. Of those 10 subjects, 3 had pre-existing antibodies and there was no indication that the response increased after treatment. Thus, in 7 out of 24 (29%) subjects, treatment-induced ADAs were detected. Of those 7 subjects for which treatment-induced ADAs were detected, the ADA titers were low for 6 of them. However, 1 subject had titers that were higher than the others (20- to 50-fold). Despite this, there was no indication that exposure was impacted in that subject or in any of the subjects who had treatment-induced antibodies. None of the subjects who had treatment-induced ADAs had TEAEs suspected by the Investigator to be related to CC-93538.

There were no deaths, SAEs, AEs leading to discontinuation, or infusion/injection site or hypersensitivity reactions. The most frequently reported (2 or more subjects) TEAEs were headache and viral infection. A single 360 mg IV infusion or SC administration of CC-93538 (for each route of administration) was well tolerated and had an acceptable safety profile in healthy adult subjects in Study RPC02-1901.

1.2.2.4 Phase 1 Study, CC-93538-CP-001

Study CC-93538-CP-001 was a Phase 1, randomized, open-label, single-dose study to evaluate the PK of CC-93538 in healthy Japanese and Caucasian adult subjects. Forty-eight subjects (24 Japanese and 24 Caucasians) received either a single 180 mg or 360 mg SC dose of CC-93538. Preliminary results show that following SC administration of either 180 mg or 360 mg CC-93538, the absorption of CC-93538 was slow with a median tmax of 5.4 to 7.5 days. A long elimination t½ of approximately 18.7 to 23.4 days and a small volume of distribution of approximately 7.4 to 9.8 L were observed. The 90% CI for the least squares geometric mean ratios for Cmax and AUC

from a combined dose analysis were found to be approximately within the typical 80% to 125% bound. These data suggest that the PK of CC-93538 is similar between Japanese and Caucasian subjects.

Anti-drug antibodies were detected in 20 of 48 subjects. Of the 20 subjects (41.7%) with positive anti-CC-93538 antibody response, 12 TEAEs were reported; 1 of which (injection site pain) was considered by the investigator to be related to study drug. There was no indication that CC-93538 exposure was impacted in any of the subjects with positive ADAs, and ADA response did not impact the safety of CC-93538 following a single 180 mg or 360 mg SC dose. There were no deaths, SAEs, or TEAEs leading to study discontinuation. All TEAEs were mild to moderate in severity. The only TEAEs reported in 2 or more subjects included upper respiratory tract infection, cough, back pain, headache, and anaemia. Overall, CC-93538 was well tolerated and had an acceptable safety profile in healthy Japanese and Caucasian adult subjects following a single SC dose of 180 mg or 360 mg.

1.2.2.5 Phase 1 Study, CC-93538-CP-002

Study CC-93538-CP-002 was an open-label, randomized, parallel design study to evaluate the PK comparability, safety, tolerability, and immunogenicity of a single SC dose of 360 mg CC-93538 using 2 different drug concentrations, 180 mg/mL and 150 mg/mL, in healthy adult subjects. A total of 52 subjects were enrolled and randomized 1:1 to receive a single 360 mg SC dose of CC-93538 using either 180 mg/mL (one injection of 2.0 mL) or 150 mg/mL (two injections of 1.2 mL each) drug concentrations.

Following SC administration of either the 150 mg/mL or 180 mg/mL concentrations, the statistical comparison of PK parameters for CC-93538-CP-002 showed that the point estimate for the ratios of geometric least squares means of peak and total exposure parameters for the comparison of 180 mg/mL versus 150 mg/mL treatments were close to 1 and their 90% CI were contained entirely within 80% to 125%, indicating the two formulations were biocomparable. The nonparametric analysis of serum CC-93538 tmax using Hodges-Lehmann showed the median difference between these treatments was not statistically significant.

The two concentration products of CC-93538, 150 mg/mL or 180 mg/mL, administered as a single dose of 360 mg, were both safe and well tolerated in healthy adults. No differences were observed in safety, tolerability, or immunogenicity. Anti-drug antibodies developed on Day 56 or later in 8 subjects total (5 subjects receiving 150 mg/mL and 3 subjects receiving 180 mg/mL). The ADA profiles were similar between subjects receiving 150 mg/mL and 180 mg/mL. There was no indication that the ADA response impacted the safety, tolerability, and PK of CC-93538 following a single SC dose of 360 mg using either 150 mg/mL or 180 mg/mL. ADAs were not associated with differences in safety, tolerability, or PK.

Overall, 17 of 52 subjects (32.7%) reported at least one TEAE. The majority of TEAEs were mild to moderate in severity. The most frequent TEAEs reported included injection site bruising (2 subjects from each treatment group) and coronavirus disease 2019 (COVID-19). No other TEAEs were reported in more than one subject. Overall, only 2 subjects reported at least one TEAE related to study drug (frequent bowel movements [one subject from the 150 mg/mL treatment group] and

injection site pain [one subject from the 180 mg/mL treatment group]). No deaths or SAEs were reported, and no subject had a TEAE that led to early discontinuation from the study. All TEAEs were recovered/resolved by the end of the study.

1.2.2.6 Phase 1 Study, IM042-003

Study IM042-003 was an open-label, randomized, 2-part parallel design study to compare the PK of single subcutaneous injections of CC-93538 administered with an autoinjector (AI) versus PFS, and to evaluate the PK of CC-93538 when administered by the AI at different injection sites, in healthy subjects. A total of 104 subjects were enrolled. In Part 1 of the study, 64 subjects were randomized 1:1 to receive CC-93538 360 mg SC either by PFS or by AI in the abdomen. In Part 2 of the study, 40 subjects were randomized 1:1 to receive CC-93538 360 mg SC by AI in either the upper arm or the upper thigh area. Part 2 began enrollment after the completion of Part 1; the results of which will be included in the final CSR.

In Part 1 of the study, following SC administration of CC-93538 360 mg, either by PFS or AI, the preliminary statistical comparison of PK parameters showed that the 90% confidence interval (CI) for the ratios of geometric least squares means of peak and exposure parameters for the comparison of PFS vs AI were contained entirely within 80% to 125%, indicating the 2 devices (PFS and AI) are biocomparable.

Overall, 27 of 64 subjects (42.2%) reported at least one TEAE. There were 14 subjects (43.8%) who reported 29 TEAEs after receiving CC-93538 with the PFS and 13 subjects (40.6%) reported 18 TEAEs after receiving CC-93538 with the AI. The most frequently reported TEAEs were arthropod bite (7 subjects), increased alanine aminotransferase (ALT) (5 [7.8%] subjects), and headache (4 [6.3%] subjects). Other TEAEs reported in more than one subject included injection site erythema, muscle strain, blood creatine phosphokinase (CPK) increased, and constipation. Except for one event of asymptomatic moderate CPK elevation which was determined not to be related to study drug by the Investigator, all TEAEs were mild in severity and were recovered/resolved at the end of the study. No deaths or SAEs were reported, and no subject had a TEAE that led to early discontinuation from the study. The safety profile of CC-93538 was comparable between subjects receiving a single dose of 360 mg/2 mL by PFS or AI.

Anti-drug antibodies (ADAs) were detected in 10 subjects (4 in the PFS arm and 6 in the AI arm [one subject in the AI arm had existing ADAs at baseline]). ADA profiles were similar between subjects receiving CC-93538 with the PFS or AI. There was no indication that the ADA response impacted the safety, tolerability, or PK of CC-93538 following a single SC dose of 360 mg with the PFS or AI.

The two presentations of CC-93538, given by PFS or AI, administered as a single dose of 360 mg, were well tolerated and had an acceptable safety profile in healthy adults. No differences were observed in safety, tolerability, or immunogenicity.

1.2.2.7 Phase 2 Study, RPC02-201

Study RPC02-201 was a Phase 2, multicenter, multinational, randomized, double-blind, placebo-controlled parallel-group clinical study to evaluate the efficacy and safety of CC-93538 in adult

subjects with EoE (Hirano, 2019). Subjects were stratified 1:1 by previously defined steroid refractory status, as determined by the Investigator (47% of enrolled subjects were steroid refractory). After a Screening Period to determine eligibility, adult subjects with EoE were randomly assigned in a 1:1:1 ratio to receive either CC-93538 180 mg (N = 31), CC-93538 360 mg (N = 34), or placebo (N = 34) weekly for 16 weeks during the double-blind (DB) Treatment Period. Subjects received an IV load of either CC-93538 (5 mg/kg or 10 mg/kg) or placebo prior to SC dosing. An optional Open-Label Extension (OLE) for an additional 52 weeks where all subjects received 360 mg CC-93538 SC weekly was available for subjects completing the DB Treatment Period. Of the 99 subjects randomized and dosed, 86 (86%) entered the OLE and 66 (66.7%) subjects completed Week 52 of the OLE.

In Study RPC02-201, the primary endpoint (changes in esophageal eosinophil count) was met. The mean changes from baseline to Week 16 in mean esophageal eosinophil count measured in the 5 most inflamed high-power fields (hpfs) from the esophageal biopsies in the placebo, CC-93538 180 mg, and CC-93538 360 mg groups were -4.42, -94.76, and -99.90, respectively. The difference in mean change from baseline to Week 16 between each CC-93538 group and the placebo group was statistically significant ($p < 0.0001$) for each comparison. Ad hoc analysis showed statistically significant differences between both dose groups and placebo in the subgroups, subjects known to be steroid-refractory and subjects not known to be steroid-refractory. CC-93538 significantly reduced peak esophageal eosinophil count and increased the number of subjects with < 15 eosinophils/hpf. CC-93538 also improved inflammatory features of EoE including the endoscopic appearance of the esophageal mucosa and improvements in histologic changes including fibrosis parameters characteristic of EoE.

Mean reductions in the subject's and clinician's global assessment of disease severity score were significant with the 360 mg dose. Improvements in dysphagia symptoms based on mean change from baseline to Week 16 in the Dysphagia Symptom Diary (DSD) composite score, as assessed by the DSD instrument over the prior 2 weeks were also observed (although not statistically significant; the study was not powered for this endpoint) with the 360 mg dose (-6.41 in the placebo group compared to -13.31 in the CC-93536 360 mg group). Ad hoc analysis revealed a numerically greater decrease in DSD composite score was observed in the CC-93538 360 mg group compared with the placebo group for the subgroup of subjects known to be steroid-refractory; however, the difference trended toward but did not reach statistical significance ($p = 0.0547$). An ad hoc analysis of the change from baseline to different time points in the DSD composite score demonstrated statistically significant differences between CC-93538 360 mg and placebo at Week 8 ($p = 0.0197$) and Week 12 ($p = 0.0460$) in subjects known to be steroid refractory.

Long-term treatment with CC-93538 360 mg showed sustained improvements in esophageal eosinophil count and other inflammatory features of EoE. In the OLE, the treatment of subjects with weekly CC-93538 360 mg SC doses demonstrated continued improvement in subjects who transitioned from placebo and those who originally received the CC-93538 180 mg or 360 mg dose in the DB Treatment Period of the study.

Results from the Phase 2 Study, RPC02-201, suggest that CC-93538 at doses of 180 mg and 360 mg weekly was well tolerated and had an acceptable safety profile in subjects with EoE. The

most frequently occurring related TEAEs (> 5% in the total CC-93538 group) in the DB Treatment Period, shown with incidences in the placebo, CC-93538 180 mg, and CC-93538 360 mg groups, respectively, were upper respiratory tract infection (2.9%, 9.7%, 11.8%), headache (8.8%, 9.7%, 8.8%), and arthralgia (0%, 12.9%, 2.9%). Injection site reaction TEAEs, were reported for 17.6%, 12.9%, and 26.5% of subjects in the placebo, CC-93538 180 mg, and CC-93538 360 mg groups, respectively. The most frequently occurring TEAEs in the OLE assessed as at least possibly related to study drug (> 3%) were headache and injection site hematoma (4.7% each), and injection site erythema, nasopharyngitis, and upper respiratory tract infection (3.5% each). Injection site reaction TEAEs were reported for 18.6% of subjects in the OLE Population. No deaths were reported. Three subjects experienced 1 SAE each in the DB Treatment Period, including 2 subjects in the placebo group (1 with appendicitis and 1 with umbilical hernia, both moderate) and 1 subject in the CC-93538 360 mg group (severe appendicitis). All SAEs in the DB Treatment Period were assessed as unrelated to study drug. Six subjects experienced 1 SAE each in the OLE, of which 2 had severe, possibly related events (cholecystitis acute and abortion spontaneous) and 4 had unrelated or unlikely related events (moderate asthma, diverticulitis with perforation, schizophrenia, and femur fracture due to motorcycle accident). Anti-drug antibodies were assessed and were not associated with any safety findings.

Mean CC-93538 serum trough concentration (Ctrough) values for subjects in the 360 mg dose group were approximately 2-fold of mean CC-93538 Ctrough values for subjects in the 180 mg dose group at each visit, suggesting a dose-proportional increase in exposure. During the OLE, mean CC-93538 Ctrough values were similar across double-blind randomized treatment groups by OLE at Week 12, with these levels sustained through OLE at Week 52. CC-93538 trough concentration data showed steady state was reached between Weeks 12 and 16 of dosing, consistent with the t½.

These Phase 2 data indicate that targeting IL-13 with CC-93538 significantly improves many of the important disease and symptomatic features of EoE and is well tolerated. The data support the further study of CC-93538 as a novel treatment for EoE.

Refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the investigational product (IP).

1.3 Rationale

1.3.1 Study Rationale and Purpose

There is strong preclinical evidence for the role of IL-13 in the underlying pathophysiology of EoE. Results of the CC-93538 Phase 2 EoE study indicate that targeting IL-13 with CC-93538 significantly improved many of the important disease features of EoE and was well tolerated. In this study (RPC02-201) of 99 adult subjects with EoE, weekly administration of CC-93538 360 mg SC reduced mean esophageal eosinophil count and improved other inflammatory and symptomatic parameters. These results support the continued development of CC-93538 as a novel treatment for EoE. The single pivotal Phase 3 study is designed to confirm and extend the findings obtained from the positive Phase 2 study with CC-93538.

1.3.1.1 Benefit-Risk Assessment

As few treatment options exist for patients with EoE, there is an unmet need for new pharmacotherapies targeting the pathophysiology of EoE with a safety and tolerability profile acceptable for long-term treatment. Based on the clinical safety and efficacy data with CC-93538 reported to date, including results from the completed Phase 2 EoE study, the benefit-risk assessment of CC-93538 supports further development in EoE and other inflammatory conditions. The overall safety profile of CC-93538 remained consistent with the information that has been presented in the Investigator's Brochure (IB). Please refer to the IB for additional information.

While CC-93538 is a biologic immunomodulator targeting IL-13, it was well tolerated in the Phase 2 study conducted in EoE subjects, without an increased risk of serious infection. Other immunomodulatory biologics in development or marketed for type 2 inflammatory diseases with a related mechanism of action, for example, dupilumab (targeting the interleukin-4 [IL-4] receptor), lebrikizumab (targeting IL-13), and tralokinumab (targeting IL-13) also have not been associated with an increased risk of serious viral infections. Although targeted coronavirus disease 2019 (COVID-19) related research with these agents is limited, small studies conducted in patients with atopic dermatitis from high endemic areas (eg, Lombardy, Italy) provide supplemental, real-world evidence that there does not appear to be an increased risk for COVID-19 infection in patients treated with dupilumab (Carugno, 2020), which has a mechanism of action similar to CC-93538.

In order to minimize the overall risk to subjects, this protocol has inclusion and exclusion criteria appropriate to the population and proposed treatments (see Section 4.2 and Section 4.3). Exclusionary screening tests will be used to identify latent tuberculosis (TB), viral hepatitis, human immunodeficiency virus (HIV), and other risk assessments, such as a detailed assessment of medical history, will be performed. Each study visit will include an assessment for AEs, and subjects who develop an intercurrent illness between study visits are encouraged to contact the Investigator, who will determine if a clinical assessment is required. The Sponsor has also developed guidance for Investigators on how to manage a subject with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporarily interrupting or permanently discontinuing IP (Section 7.2.4 and Section 7.2.5), and criteria for reinitiating IP on resolution of a COVID-19 infection (Section 7.2.4). To facilitate reporting of COVID-19 events that occur during the study, all AEs and SAEs related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID-19 must be reported from the time of consent (Section 10.1). In addition, such AEs or SAEs will also trigger additional data collection through specialized electronic case report (eCRF) forms, which will allow the Sponsor to further evaluate these events.

While the global coronavirus disease 2019 (COVID-19) pandemic has been identified as a potential risk to clinical trial subjects in general, and it may particularly affect individuals with underlying chronic diseases, the overall benefit-risk for participation in this EoE study with CC-93538 is considered favorable. The individual benefit-risk considerations regarding COVID-19 infection remains the responsibility of the Investigator. Testing to exclude COVID-19 infection prior to enrollment and to inform decisions about subject care during the study should follow local standard practice and requirements. Non-live COVID-19 vaccination is allowed and will be

documented as a concomitant medication within the study. The efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-93538 are unknown.

1.3.2 Rationale for the Study Design

The Phase 3 program includes a multicenter, multinational, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EoE (Study CC-93538-EE-001, the core Phase 3 study) with a separate, optional Open-Label Extension Study (OLE; Study CC-93538-EE-002). The core Phase 3 study will enroll both subjects who have had an inadequate response to or are intolerant to corticosteroid therapy (Steroid Inadequate Responders/Intolerant; approximately 70% of the study population) as well as subjects who are naïve or have had an adequate response to corticosteroid therapy (Steroid Responders/Naïve; approximately 30% of the study population). The study includes a 24-week Induction Phase followed by a 24-week Maintenance Phase, for a total study duration of 48 weeks. A double-blind, placebo-controlled treat-through design with allowance for use of concomitant rescue therapy has been chosen, as it enhances subject recruitment and retainment for evaluation of relevant short-term as well as the long-term efficacy of CC-93538 in EoE.

An advisory panel of patients with EoE and their caregivers has been consulted and input has been sought on the protocol design and development of patient-facing materials and recruitment initiatives. A series of 3 advisory boards took place between March 2021 and March 2022. The feedback and insights from these members of the EoE community have been considered in the trial awareness and recruitment materials developed for the study. The Sponsor has ongoing partnerships with US-based and global Patient Advocacy Groups to deliver trial awareness initiatives for the study.

1.3.2.1 Justification of Co-Primary Endpoints

The selection of the co-primary clinical endpoint, the mean change in dysphagia days (DD), evaluated over the prior 14-day period using the dysphagia modified Daily Symptom Diary (mDSD), from baseline to Week 24, for Induction Phase Week 24 is based on qualitative patient interviews conducted in the validation study EVA-20655, Assessment of the Content Validity and Reproducibility of the Dysphagia Daily Symptom Diary (DSD) in Patients with Eosinophilic Esophagitis. In Study EVA-20655, patients reported dysphagia as the hallmark symptom of EoE. The assessment of the number of DD over a 14-day period using the mDSD captures the symptoms of dysphagia most often described by patients in Study EVA-20655: trouble swallowing, food going down slowly, and food getting stuck in the throat. This is aligned with the Food and Drug Administration's (FDA's) draft and final guidance for developing drugs for the treatment of EoE noting that clinical trials of new medications for EoE should evaluate the treatment effect on both signs/symptoms and inflammation associated with EoE (FDA, 2019; FDA, 2020). Results of post hoc analyses of Phase 2 data indicate that change in DD is a responsive measure of dysphagia symptoms based on anchoring analyses using the Global Assessment of Disease Severity-Subject (GADS-S) and Global Impression of Change in EoE Symptoms (GIC-EoE) instruments. Further, the post hoc analysis of mean change in DD from baseline showed a nominal significant difference

in the 360 mg SC once weekly group compared to placebo. The number of DD, a frequency measure of symptoms important to the patient, is associated with severity information, as it is highly correlated to the mDSD composite score which incorporates severity of symptoms into the score. Therefore, assessment of DD, which captures the symptoms of dysphagia most relevant to patients, has been chosen as the co-primary clinical endpoint for the Phase 3 program.

For the co-primary histologic endpoint, eosinophilic histologic response is defined as a peak esophageal eosinophil count ≤ 6/hpf, across all available esophageal levels, at Week 24, as this is the threshold recommended in the draft and final FDA guidance for developing drugs for the treatment of EoE (FDA, 2019, FDA, 2020). This threshold is also supported by the report of a retrospective cohort trial utilizing the University of North Carolina EoE Database (Wolf, 2015). The study generated receiver operator characteristic curves for symptom and endoscopic response at different eosinophil count cutpoints (eosinophils/hpf) on 199 patients. The cutpoints examined were < 30 eosinophils/hpf, < 20 eosinophils/hpf, < 15 eosinophils/hpf, < 10 eosinophils/hpf, < 5 eosinophils/hpf, < 3 eosinophils/hpf, ≤ 1 eosinophils/hpf, and 0 eosinophils/hpf. Among patients achieving a similar cut-off of < 5 eosinophils/hpf, 90% had endoscopic response, 86% had clinical response, and 79% had both symptomatic and endoscopic response. Finally, this threshold provides confirmation of significant histologic response as it surpasses the current eosinophil threshold required for the diagnosis of EoE, which is ≥ 15 eosinophils/hpf (Wolf, 2015).

1.3.3 Rationale for Dose, Schedule, and Regimen Selection

Based on results from the Phase 2 Study RPC02-201, the CC-93538 360 mg SC once weekly dose was selected for Phase 3. In addition, this study is designed to test if induction of response at the 360 mg SC once weekly dose level followed by continued treatment at a lower dose level through administration of a less frequent dosing regimen would provide a similar persistence of response. PK modeling demonstrated the average exposure for the 180 mg dose once weekly and the 360 mg dose once every other week is very similar. The fluctuation between Cmax and Ctrough is larger in the 360 mg dose administered every other week compared to the 180 mg dose administered every week but this is not expected to result in any clinically relevant differences between the 2 regimens. Further, a dose higher than 360 mg SC once weekly is not expected to provide additional therapeutic benefit, as trough concentrations observed in the 360 mg SC once weekly dose during the DB Treatment Period in the Phase 2 study exceeded the estimated in vitro EC_{95} (95% of the maximal effective concentration) for IL-13 neutralization. Data from Study RPC02-201 also provide support that the intravenous (IV) loading dose (10 mg/kg) is not required to achieve optimal efficacy. Subjects in the placebo group from the DB Treatment Period who transitioned to the CC-93538 360 mg SC regimen without receiving the IV loading dose in the OLE showed improvement in dysphagia symptoms and comparable reduction in eosinophil count at Week 12 of the OLE as was observed at Week 16 of the DB Treatment Period for subjects treated with CC-93538 360 mg with the IV loading dose. These subjects also showed a mean Ctrough concentration (56.8 µg/mL) approximately 5-fold higher than the half maximal effective concentration (EC_{50}; 10 µg/mL) at Week 2 of the OLE. Collectively, PK and efficacy data support the IV loading dose is not needed to achieve optimal efficacy.

Therefore, because (1) the CC-93538 360 mg once weekly regimen has shown an effect on both histological and clinical endpoints in Study RPC02-201, (2) the CC-93538 180 mg once weekly regimen has shown a relevant histological but not clinical effect in the same study, and (3) the CC-93538 360 mg once every other week regimen is not expected to achieve concentrations different than the 180 mg once weekly regimen, the 360 mg once weekly dose was selected for the Induction Phase and the 360 mg once weekly and 360 mg once every other week doses were selected for the Maintenance Phase.

1.3.4 Rationale for Choice of Comparator Compounds

The study design employs a comparison to placebo which is intended to minimize bias and to provide an accurate determination of efficacy and safety findings attributable to CC-93538 administration. In addition, at the time of study initiation, there were no comparators available for subjects with EoE who have had an inadequate response or are intolerant to corticosteroid therapy.

1.3.5 Rationale for [redacted] Potential Predictive [redacted]

EoE is characterized by eosinophil-predominant inflammation and additional pathogenesis including esophageal tissue remodeling and over-expression of [redacted] that are thought to play a role in EoE disease pathogenesis, such as [redacted] in esophageal [redacted] tissue as well as [redacted] assessment will be evaluated for potential diagnostic or prognostic importance.

2 STUDY OBJECTIVES AND ENDPOINTS

The objectives for this study are listed in Table 1, and the study endpoints are described in Table 2 for the Induction Phase and Table 3 for the Maintenance Phase.

Table 1: Study Objectives

Primary Objectives
The primary objectives of the study are: • To assess the efficacy of CC-93538 versus placebo in reducing dysphagia symptoms at 24 weeks • To assess the efficacy of CC-93538 versus placebo in reducing esophageal eosinophil counts at 24 weeks
Secondary Objectives
The secondary objectives are: • To assess the efficacy of CC-93538 versus placebo at 24 weeks in improving: – Endoscopic features of eosinophilic esophagitis (EoE) – Histologic features of EoE • To assess the persistence of effect of CC-93538 at 48 weeks in reducing: – Dysphagia symptoms – Esophageal eosinophil counts • To assess the persistence of effect of CC-93538 through administration of a less frequent dosing regimen at 48 weeks in reducing: – Dysphagia symptoms – Esophageal eosinophil counts

Table 1: Study Objectives

• To assess the persistence of effect of CC-93538 at 48 weeks in improving: – Endoscopic features of EoE – Histologic features of EoE • To evaluate the time to and frequency of EoE flare events and use of rescue therapy during the study • To evaluate the safety and tolerability of CC-93538 including characterization of the immunogenicity profile • To assess trough concentrations of CC-93538 in subjects with EoE
[redacted]

Table 2: Study Endpoints: Induction Phase Endpoints at Week 24

For endpoints listed below with statistical comparisons, the CC-93538 360 mg SC once weekly treatment arm (2 active arms combined) will be compared to the placebo arm.

Induction Phase Endpoints at Week 24			
Endpoint	**Name**	**Description**	**Timeframe**
Co-primary	Change in DD Clinical Response	The mean change in dysphagia days (DD), evaluated over the prior 14-day period using the modified Daily Symptom Diary (mDSD), from baseline to Week 24	Week 24
	Eosinophil Histologic Response (≤ 6/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/high-power field (hpf) at Week 24	Week 24

Table 2: Study Endpoints: Induction Phase Endpoints at Week 24

For endpoints listed below with statistical comparisons, the CC-93538 360 mg SC once weekly treatment arm (2 active arms combined) will be compared to the placebo arm.

Induction Phase Endpoints at Week 24			
Endpoint	**Name**	**Description**	**Timeframe**
Key Secondary	Eosinophil Histologic Response (< 15/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf at Week 24	Week 24
	EREFS	The mean change in the endoscopic features of eosinophilic esophagitis (EoE) as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to Week 24	Week 24
	EoEHSS Grade Score	The mean change in the mean adjusted histology grade score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 24	Week 24
	EoEHSS Stage Score	The mean change in the mean adjusted histology stage score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 24	Week 24
	mDSD Composite Score	The mean change in the modified Daily Symptom Diary (mDSD) composite score from baseline to Week 24	Week 24
Additional Secondary	DD Clinical Responder Definition	The proportion of subjects with a ≥ 50% decrease in dysphagia days (DD) from baseline at Week 24	Week 24
	Kinetics and Onset of Clinical Response	The mean change in dysphagia days (DD) over time from baseline through Week 24	Through Week 24
	Kinetics and Onset of Clinical Response	The mean change in the modified Daily Symptom Diary (mDSD) composite score over time from baseline through Week 24	Through Week 24
	Time to Event	The time to event of EoE flare during the Induction Phase	Through Week 24
	Time to Event	The time to event of use of rescue therapy during the Induction Phase	Through Week 24
	Proportion of Subjects with Event	The proportion of subjects with an EoE flare during the Induction Phase	Through Week 24
	Proportion of Subjects with Event	The proportion of subjects with use of rescue therapy during the Induction Phase	Through Week 24
	Safety and Tolerability	Safety and tolerability evaluated by the incidence, severity, and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities, and the presence of anti-drug antibodies	Through Week 24
	Pharmacokinetics	Measurements of trough concentrations of CC-93538 in subjects with EoE during the Induction Phase	Through Week 24

Table 2: Study Endpoints: Induction Phase Endpoints at Week 24

For endpoints listed below with statistical comparisons, the CC-93538 360 mg SC once weekly treatment arm (2 active arms combined) will be compared to the placebo arm.

Induction Phase Endpoints at Week 24			
Endpoint	**Name**	**Description**	**Timeframe**
[redacted]			

Table 2: Study Endpoints: Induction Phase Endpoints at Week 24

For endpoints listed below with statistical comparisons, the CC-93538 360 mg SC once weekly treatment arm (2 active arms combined) will be compared to the placebo arm.

Induction Phase Endpoints at Week 24
[redacted]

Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48

For endpoints listed below with statistical comparisons, the 2 CC-93538 dosing regimens (360 mg SC once weekly and 360 mg SC once every other week) will be compared to placebo separately.

Maintenance Phase Endpoints at Week 48			
Endpoint	**Name**	**Description**	**Timeframe**
Secondary	Change in DD Clinical Response	The mean change in dysphagia days (DD), evaluated over the prior 14-day period using the modified Daily Symptom Diary (mDSD), from baseline to Week 48	Week 48
	Eosinophil Histologic Response (≤ 6/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/high-power field (hpf) at Week 48	Week 48
	Eosinophil Histologic Response (< 15/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf at Week 48	Week 48
	EREFS	The mean change in the endoscopic features of eosinophilic esophagitis (EoE) as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to Week 48	Week 48
	EoEHSS Grade Score	The mean change in the mean adjusted histology grade score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 48	Week 48
	EoEHSS Stage Score	The mean change in the mean adjusted histology stage score as measured by the EoE histology scoring system (EoEHSS) from baseline to Week 48	Week 48
	mDSD Composite Score	The mean change in the modified Daily Symptom Diary (mDSD) composite score from baseline to Week 48	Week 48
	Eosinophil Histologic Response (≤ 6/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/high-power field (hpf) at Week 48 among subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 24	Week 48
	Time to Event	The time to event of EoE flare during the study (Induction and Maintenance Phases)	Through Week 48
	Time to Event	The time to event of use of rescue therapy during the study (Induction and Maintenance Phases)	Through Week 48
	Proportion of Subjects with Event	The proportion of subjects with an EoE flare during the study (Induction and Maintenance Phases)	Through Week 48
	Proportion of Subjects with Event	The proportion of subjects with use of rescue therapy during the study (Induction and Maintenance Phases)	Through Week 48

Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48

For endpoints listed below with statistical comparisons, the 2 CC-93538 dosing regimens (360 mg SC once weekly and 360 mg SC once every other week) will be compared to placebo separately.

Maintenance Phase Endpoints at Week 48			
Endpoint	**Name**	**Description**	**Timeframe**
	Safety and Tolerability	Safety and tolerability evaluated by the incidence, severity, and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities, and the presence of anti-drug antibodies	Through Week 48
	Pharmacokinetics	Measurements of trough concentrations of CC-93538 in subjects with EoE during the Maintenance Phase	Through Week 48
[redacted]			

Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48

For endpoints listed below with statistical comparisons, the 2 CC-93538 dosing regimens (360 mg SC once weekly and 360 mg SC once every other week) will be compared to placebo separately.

Maintenance Phase Endpoints at Week 48			
Endpoint	**Name**	**Description**	**Timeframe**
[redacted]			

Table 3: Study Endpoints: Maintenance Phase Endpoints at Week 48

For endpoints listed below with statistical comparisons, the 2 CC-93538 dosing regimens (360 mg SC once weekly and 360 mg SC once every other week) will be compared to placebo separately.

Maintenance Phase Endpoints at Week 48			
Endpoint	**Name**	**Description**	**Timeframe**
[redacted]			

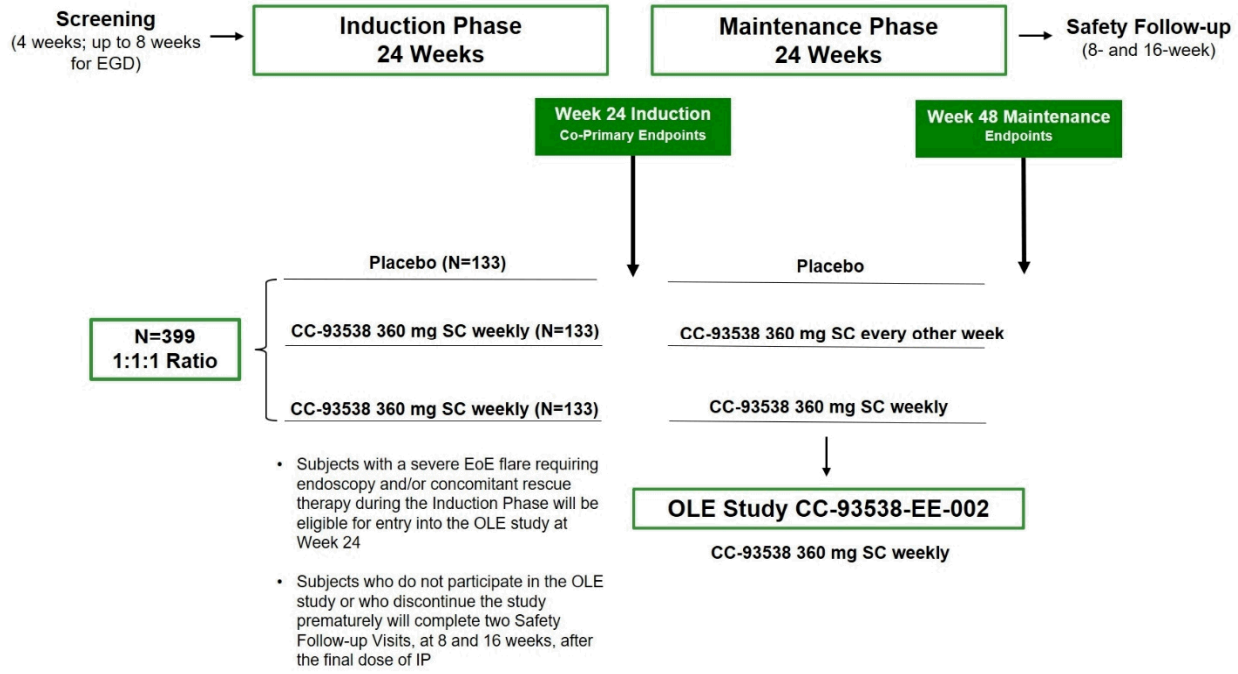
3 OVERALL STUDY DESIGN

3.1 Study Design

The Phase 3 program includes a multicenter, multinational, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EoE (Study CC-93538-EE-001) with a separate, optional Open-Label Extension Study (OLE; Study CC-93538-EE-002). Globally, the study includes both subjects who have had an inadequate response to or are intolerant to corticosteroid therapy (Steroid Inadequate Responders/Intolerant; approximately 70% of the study population) as well as subjects who are naïve or have had an adequate response to corticosteroid therapy (Steroid Responders/Naïve; approximately 30% of the study population). However, in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy will be enrolled in the studies. Also, in Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled. The study will include a 24-week Induction Phase followed by a 24-week Maintenance Phase. Subjects will be randomized at the beginning of the study into 3 treatment arms: placebo for Induction and Maintenance, CC-93538 360 mg SC once weekly for Induction followed by 360 mg SC once every other week for Maintenance, or CC-93538 360 mg SC once weekly for Induction and Maintenance. All subjects will receive CC-93538 360 mg SC once weekly in the optional OLE

study; the dosing regimen may be revised through an amendment to the OLE study protocol once results from Study CC-93538-EE-001 are available and the most effective and safest dosing regimen is confirmed. An overview of the study design is presented in Figure 1.

Figure 1: Overall Study Schema



Abbreviations: EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; IP = investigational product; N = sample size; OLE = Open-Label Extension; SC = subcutaneous injection

This study will empanel a steering committee (Section 9.9.5), and safety monitoring will be performed by an external, independent Data Monitoring Committee (Section 9.9.4) in addition to routine internal review by the Safety Management Team (Section 9.9.3).

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1.1 Screening Period

Prospective subjects will be assessed during a Screening Period of up to 4 weeks to confirm initial eligibility for the study via medical history, physical examination, review of prior therapy, clinical laboratory tests, and esophagogastroduodenoscopy (EGD), for evaluation of histologic and endoscopic findings. For the EGD and informed consent only, an extension of the screening window of up to 8 weeks total may be allowed to accommodate the scheduling of this procedure after informed consent has been obtained. The screening EGD must be performed within 8 weeks (56 days) of the planned Day 1 Visit for subjects to be eligible to participate in the study, but the EGD may not be performed during the last 2 weeks of screening when the mDSD will be evaluated

for the baseline time point. All other screening procedures should be performed during the 4-week Screening Period prior to Day 1. Symptoms of EoE will be assessed with the mDSD, which will be completed daily for at least the last 3 consecutive weeks (21 days) but may be completed for up to 28 days prior to Day 1. Refer to Section 6.1 for further details.

3.1.2 Induction Phase

Following a 4-week Screening Period, subjects meeting all inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the Induction Phase. Approximately 399 subjects 12 to 75 years of age, inclusive, with a diagnosis of EoE and with symptoms of dysphagia will be randomized 1:1:1 (N ≈ 133 per treatment arm) to receive CC-93538 360 mg subcutaneously (SC) once weekly (2 of the 3 treatment arms) or matching placebo, in a double-blind fashion for 24 weeks. Subjects will be required to have symptoms of dysphagia of at least 4 DD as assessed with the mDSD over the prior 2 consecutive weeks (14 days) before baseline and histologic evidence of EoE defined as a peak count of ≥ 15 eosinophils per hpf at any 2 levels of the esophagus (proximal, mid, distal); both assessments will be conducted when not receiving anti-inflammatory therapy. Peak esophageal eosinophil count will be confirmed by the central reader. Additionally, subject eligibility also includes a previous PPI trial without a complete response as described in Section 4.2, Inclusion Criterion 4. Treatment assignment at baseline will be stratified based on steroid responder status to ensure an equal balance in the treatment arms. Baseline assessments and procedures will be completed prior to randomization and administration of IP on Day 1.

Of the approximately 399 subjects to be enrolled, approximately 30 adolescent subjects will be included and approximately 70% will be Steroid Inadequate Responders/Intolerant (see Section 7.3). Subjects weighing ≥ 40 kg will be enrolled as this aligns with the eligibility criteria used in the Phase 2 program.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests (female of childbearing potential [FCBP] subjects only), EGD, clinical symptom assessment, [redacted] serum CC-93538 PK concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and AE/SAE assessments will be performed according to the Table of Events presented in Table 4. [redacted]

3.1.3 Maintenance Phase

After completion of Week 24 of the Induction Phase, eligible subjects will continue participation and enter the Maintenance Phase if none of the conditions disqualifying subjects from eligibility have been met as described in Section 6.4.2.8. For example, subjects with a severe EoE flare, as defined in Section 6.4.2.7, requiring endoscopic intervention and/or concomitant use of rescue therapy, including but not limited to corticosteroid therapy or dilation procedure, will not be eligible for participation in the Maintenance Phase. A placebo-controlled Maintenance Phase will allow for a determination of persistence of treatment effect and the overall long-term efficacy of CC-93538.

The Maintenance Phase treatment arms include 360 mg SC once every week, 360 mg SC once every other week, and matching placebo. As assigned upon randomization to the Induction Phase, approximately half of the subjects receiving CC-93538 360 mg SC once weekly during Induction will continue on the same dosing regimen for the Maintenance Phase and the remaining subjects will continue on the less frequent regimen of 360 mg SC once every other week. Subjects originally randomized to placebo will remain on placebo.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests (FCBP subjects only), EGD, clinical symptom assessment, [redacted] serum CC-93538 PK concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and AE/SAE assessments will be performed according to the Table of Events presented in Table 5. [redacted]

The study blind should be maintained for persons responsible for the ongoing conduct of the study (after all subjects have completed the Week 48 assessments for endpoint analysis). Blinded persons may include but are not limited to: Clinical Research Physician (also referred to as Clinical Trial Physician), Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, and Clinical Research Associates.

3.1.4 Safety Follow-up Visits

Subjects who complete Week 48 of the Maintenance Phase and do not participate in the OLE study will be required to return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively, after the last dose of IP (at Week 55 and Week 63 for study completers). Subjects may discontinue from the study at any time. For subjects who discontinue the study prematurely for any reason, the Early Termination (ET) Visit will be conducted (Section 6.2.2). In addition to the ET Visit procedures, subjects exiting the study early will also return for the Interim and the Final Safety Follow-up Visits (Section 6.3.1). However, subjects who are permanently discontinued from IP and continue study participation in order to complete safety and efficacy assessments will return for the Interim and Final Safety Follow-up Visits after their last study visit (refer to Section 6.3.1).

3.1.5 Worsening of EoE Symptoms

Subjects with a worsening of EoE symptoms during the study, either in the Induction Phase or Maintenance Phase will be required to complete the EoE Flare Assessment Visit per the Table of Events (Table 4 and Table 5). For subjects with a worsening of EoE symptoms, an EGD will be required to determine if rescue therapy is clinically indicated. Subjects with increased signs and symptoms of EoE are instructed to contact the Investigator and/or study staff to determine if an EoE Flare Assessment Visit is warranted.

Any worsening of EoE symptoms during study participation will be documented as an EoE flare. See Sections 6.4.2.7 and 6.2.1 for the protocol definition of EoE flare and EoE Flare Assessment Visit details, respectively.

Subjects experiencing a severe EoE flare in the Induction or Maintenance Phase may continue to participate with concomitant rescue therapy as needed and will be eligible to enter the OLE study only following completion of Week 24 of the Induction Phase or Week 48 of the Maintenance Phase, respectively (refer to Section 6.4.2.7 for details). Subjects with a severe EoE flare in the Induction Phase will not qualify for entry into the Maintenance Phase.

Subjects experiencing a mild to moderate EoE flare in Induction will continue on into the Maintenance Phase of the study and will be eligible to enter the OLE study following the completion of the Week 48 Visit.

3.2 Study Duration for Subjects

The maximum duration of subject participation in this study is approximately 72 weeks. Subjects will participate up to 4 weeks in the Screening Period (the screening EGD may be completed up to 8 weeks prior to Day 1), 24 weeks in the Induction Phase Treatment Period, and 24 weeks in the Maintenance Phase Treatment Period of the study. Following Induction, subjects not entering the Maintenance Phase or OLE study will return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively after final IP administration for the assessment of safety and clinical status. Similarly, subjects completing the Maintenance Phase who do not continue to participate in the OLE study will complete the Interim and the Final Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration; for these subjects, the maximum duration is approximately 71 weeks. However, as an exception, the maximum duration of participation will be approximately 72 weeks for subjects permanently discontinuing IP during the Maintenance Phase but who continue study participation through Week 48, as the Interim and Final Safety Follow-up Visits will occur 8 and 16 weeks after the last study visit instead of the last dose of IP.

3.3 End of Study

The End of Study is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as pre-specified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

Globally, the study population will consist of males and females aged 12 to 75 years (inclusive) with EoE who have had an inadequate response to corticosteroid therapy (as defined in Section 4.2, Inclusion Criterion 5a) or are intolerant to corticosteroid therapy (Steroid Inadequate Responders/Intolerant; approximately 70% of the study population) as well as subjects who are naïve or have had an adequate response to corticosteroid therapy (Steroid Responders/Naïve; approximately 30% of the study population). A total of approximately 369 adults (aged 18 to 75 years) and 30 adolescents (aged 12 to 17 years) will be enrolled in the study.

However, in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy will be enrolled in the study. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

4.2 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1) Subject must be ≥ 12 years and ≤ 75 years of age and have a body weight of ≥ 40 kg (88.2 lb) at the time of signing the informed consent form (ICF)/assent form.

   Note: Countries or sites with local restrictions that prohibit enrollment of adolescents (aged 12 to 17 years inclusive) will only enroll subjects who are 18 years of age or older. Enrollment of adolescent subjects will begin only after the applicable regulatory requirements for enrolling subjects in that age group have been satisfied and the necessary health authority approvals have been granted. Where national or regional guidelines for the definition of adolescence differ from the definition stated above, the national or regional guidelines may be used to determine eligibility. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

2) Subject has histologic evidence of EoE, defined as a peak count of ≥ 15 eosinophils per high-power field (hpf) at any 2 levels of the esophagus (proximal, mid, and/or distal) when off anti-inflammatory therapy (eg, corticosteroids, see Exclusion Criterion 7) for EoE. The histologic criterion for diagnosis of EoE must be confirmed by a centrally read histological assessment of an EGD specimen during the Screening Period prior to randomization.
3) Subject has symptoms of dysphagia of at least 4 DD, as assessed with the mDSD instrument, over the last 2 consecutive weeks (14 days) prior to Day 1 when off anti-inflammatory therapy (eg, corticosteroids, see Exclusion Criterion 7) for EoE. Subjects are required to have at least 11 days of diary data out of the final 14-day period of screening mDSD collection in order to be enrolled in the study. During these 11 days, responses to questions 2 through 5 of the mDSD instrument must be complete.
4) Subject must have previously received an adequate trial of proton-pump inhibitor (PPI) medication (8 weeks per guidance, Dellon, 2013) that did not provide complete response to EoE, or the subject remains symptomatic with continued use (Dellon, 2018b; Lucendo, 2017). Prospective subjects who discontinued use of a PPI must not have received a PPI for at least 4 weeks before their first Screening Visit and must agree not to restart a PPI during the study. If a prospective subject is receiving a PPI medication at screening, he or she must have been receiving a stable dose for at least 4 weeks prior to the first Screening Visit and agree to continue the same dose throughout the study.
5) Subject must either (1) be naïve or have had an adequate response to corticosteroid therapy (ie, classified as Steroid Responders/Naïve) or (2) have had an inadequate response to corticosteroid therapy and is not considered to be a candidate for continued corticosteroid therapy, or is intolerant to corticosteroid therapy. For subjects who have previously received systemic or swallowed topical corticosteroids for EoE, designation of the status of Steroid Inadequate Responders/Intolerant will include either of the following definitions. Note that if any of the below criteria are met, a subject will be deemed Steroid Inadequate Responders/Intolerant (approximately 70% of the study population) and cannot be classified as Steroid Responders/Naïve (approximately 30% of the study population).
   a) Inadequate response to corticosteroid therapy (failed to respond or lost response) and not considered a candidate for continued corticosteroid therapy: subjects who have had a trial of at least 6 weeks of swallowed topical corticosteroid treatment or 4 weeks of systemic

corticosteroids at doses in accordance to published guidelines for the management of EoE (Lucendo, 2017), or a trial for the treatment duration specified in the prescribing information for approved products and judged by the treating physician as not achieving clinical improvement or having clinical improvement initially but lost response while on therapy.

b) Intolerant to corticosteroid therapy: subjects who initiated systemic or swallowed topical corticosteroid treatment but were unable to achieve treatment durations or dose levels due to intolerance because of side effects, including intolerance from use of corticosteroids for conditions other than EoE, or subjects with underlying conditions in which corticosteroid use is not recommended or contraindicated.

Documentation of type of therapy, treatment duration, and outcome details will be collected when possible.

In Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy will be enrolled.

6) Subjects must agree to maintain a stable diet (including any food elimination diet for the treatment of food allergy or EoE) from the first Screening Visit and throughout the duration of the study, and subjects must have maintained a stable diet for at least 4 weeks prior to the first Screening Visit. Subjects must agree not to introduce any changes in their diet while participating in the study.
7) Subjects currently receiving inhaled corticosteroids, leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for indications other than EoE, or medium potency topical corticosteroids (eg, mometasone furoate cream or lotion) for dermatologic conditions, must maintain stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens must remain stable throughout the duration of the study. If recently discontinued, the medication must have been discontinued at least 4 weeks prior to the first Screening Visit.
8) Female subjects of childbearing potential must agree to practice a highly effective method of contraception. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly.

   A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, and 2) has not undergone a hysterectomy or bilateral oophorectomy or bilateral salpingectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months. A FCBP must:

   a) Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study and through the Final 16-week Safety Follow-up Visit. This applies even if the subject practices true abstinence* from heterosexual contact.

* True abstinence is acceptable when this is the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), and lactational amenorrhea method are not acceptable methods of contraception.

b) Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, highly effective contraception without interruption throughout the study and for 5 months after the last dose of IP. Acceptable methods of birth control in this study are the following (birth control must be effective by the time the FCBP subject is randomized into the study [eg, hormonal contraception should be initiated at least 28 days before randomization]):

- combined hormonal (estrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal

  Note: Intravaginal and transdermal combined hormonal contraception are not approved in Japan and would therefore not be an acceptable method of contraception for subjects enrolled in this region
- progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable

  Note: progestogen-only hormonal contraception is not approved in Japan and would therefore not be an acceptable method of contraception for subjects enrolled in this region
- placement of an intrauterine device (IUD)
- placement of an intrauterine hormone-releasing system (IUS)
- bilateral tubal ligation; or bilateral tubal occlusion (if an implantable device was recently placed, the subject must use an additional effective method of birth control until full occlusion has been confirmed and documented)
- vasectomized partner (vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the FCBP and has received medical assessment of the surgical success)
- sexual abstinence

9) Subject is willing to receive weekly SC injections throughout the study.
10) Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted. For subjects less than 18 years of age, subject assent must be obtained, and parental/legal representative consent is required.
11) Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1) Subject has clinical or endoscopic evidence of the presence of any other disease that may interfere with or affect the histologic, endoscopic, and clinical symptom endpoints for this study (eg, erosive esophagitis Los Angeles [LA] classification Grade B or above, Barrett's esophagus, esophageal lichen planus, upper gastrointestinal bleed, achalasia, inflammatory bowel disease, diagnosed eosinophilic gastroenteritis [clinical symptoms and/or EGD findings and confirmatory eosinophilia in gastric and/or duodenal mucosa], or significant hiatal hernia [> 3 cm], etc.).
2) Subject demonstrates presence of esophageal varices.

3) Subject has a known active Helicobacter pylori infection and/or is currently being treated for this condition.
4) Subject has evidence of a severe endoscopic structural abnormality in the esophagus (eg, high-grade stenosis where an 8- to 10-mm endoscope could not pass through the stricture without dilation at the time of the screening EGD).
5) Subject had esophageal dilation for symptom relief during the Screening Period or within 8 weeks prior to the first Screening Visit, or esophageal dilation is anticipated to be performed within 48 weeks of dosing during the study.
6) Subject demonstrates evidence of immunosuppression or is receiving systemic immunosuppressive or immunomodulating drugs (eg, anti-IL-13 antibodies [except IP in this study], IL-4 receptor alpha antagonist antibodies [eg, dupilumab], anti-IL-5 antibodies, anti-IL-17 antibodies, anti-immunoglobulin E [IgE] antibodies, α4β7 integrin inhibitor antibodies, or any other monoclonal antibody, methotrexate, cyclosporine, azathioprine, mercaptopurine, interferon alpha [IFNα], tumor necrosis factor alpha [TNFα] inhibitors, etc.) within 5 drug half-lives prior to the first Screening Visit. Any use of these medications will be prohibited during the study.
7) Subject is currently receiving systemic or swallowed topical corticosteroid medication. Prospective subjects with EoE previously treated with a corticosteroid must not have received a systemic corticosteroid within 8 weeks or swallowed topical corticosteroid within 4 weeks of the first Screening Visit.
8) Subject is currently receiving a high potency topical corticosteroid (eg, augmented betamethasone dipropionate, clobetasol propionate, etc.) for dermatologic use. Prospective subjects must not have received a high potency topical corticosteroid for dermatologic use within 8 weeks of the first Screening Visit. Any use will be prohibited during the study.
9) Subject is currently receiving a leukotriene receptor antagonist (eg, montelukast) or mast cell stabilizer (eg, cromolyn sodium) for the indication of EoE. Subjects must not have received a leukotriene receptor antagonist or mast cell stabilizer for EoE within 4 weeks of the first Screening Visit. Any use for the treatment of EoE during the study will be prohibited.
10) Subject is currently successfully treated for EoE with dietary modifications (eg, food elimination diet) and is able to fully adhere to the diet resulting in a complete response to EoE (ie, the subject does not meet the symptoms of dysphagia requirement of at least 4 DD and histologic criterion for diagnosis of EoE per Section 4.2, Inclusion Criteria 2 and 3).
11) Subject has received oral or sublingual immunotherapy within 6 months of the first Screening Visit; any use will be prohibited during the study. Subjects receiving SC immunotherapy may participate but must be on stable doses for at least 3 months prior to the first Screening Visit and during the study.
12) Subject is receiving concurrent treatment with another IP, including through participation in an interventional trial for COVID-19. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to signing the ICF/assent for this study. Further, for subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.

13) Subject has received a live attenuated vaccine within one month prior to the first Screening Visit or anticipates the need to be vaccinated with a live attenuated vaccine during the course of the study. Administration of any live attenuated vaccine will be prohibited during the study through the Final 16-week Safety Follow-up Visit.
14) Subject has previously received CC-93538 treatment (formerly known as RPC4046 and ABT-308) through participation in the Phase 2 Study, RPC02-201, or any Phase 1 clinical study.
15) Subject has any other disease that would make conduct of the protocol or interpretation of the study results difficult or that would put the prospective subject at risk by participating in the study (eg, severe uncontrolled asthma, infection causing eosinophilia, hypereosinophilic syndrome, gastritis, colitis, celiac disease, Mendelian disorder associated with EoE, or cardiovascular condition, or neurologic or psychiatric illness that compromises the prospective subject's ability to accurately document symptoms of EoE).
16) Subject has liver function impairment or persisting elevations of aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) that are 2 times the upper limit of normal (ULN), or total bilirubin 1.5 times the ULN. Subjects with elevations that are not clinically significant in total bilirubin associated with Gilbert's syndrome may participate.
17) Subject has an active parasitic/helminthic infection or a suspected parasitic/helminthic infection. Subjects with suspected infections may participate if clinical and laboratory assessments, if needed, rule out active infection prior to randomization.
18) Subject has an ongoing infection (eg, hepatitis B or C, human immunodeficiency virus [HIV], or tuberculosis as defined by standard medical guidelines and as outlined in Section 6.1).
19) Subject had a previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within 4 weeks prior to screening. Symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment.
20) Subject has known hereditary fructose intolerance (HFI).
21) Subject is pregnant or lactating.
22) Subject has a history of idiopathic anaphylaxis or a major immunologic reaction (such as anaphylactic reaction, anaphylactoid reaction, or serum sickness) to an immunoglobulin G (IgG) containing agent. In Japan, a known hypersensitivity to any ingredient in the IP is also exclusionary.
23) Subject has a history of cancer or lymphoproliferative disease, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or adequately treated cervical carcinoma in situ, within 5 years of screening.
24) Subject has a history of alcohol or drug abuse within 5 years prior to initiation of screening.
25) Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
26) Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
27) Subject has any condition that confounds the ability to interpret data from the study.

5 TABLE OF EVENTS

Table 4: Table of Events for the Induction Phase

Study Procedures		Induction Phase Treatment Period								EoE Flare Visit[e]	ET Visit[f]	Interim 8-week Safety Follow-up Visit[g]	Final 16-week Safety Follow-up Visit[g]
Visit Label	**Screening[a]**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[c,d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 2 (Day 15±3d)**	**Week 4 (Day 29±3d)**	**Week 8 (Day 57±3d)**	**Week 12 (Day 85±3d)**	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**			**Week 31 (Day 218±7d)**	**Week 39 (Day 274±7d)**
Informed consent/assent	X												
Inclusion/ exclusion criteria	X	X											
Demographics/baseline characteristics	X												
Medical history	X												
Prior therapy	X												
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[h,i]	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation panel	X												
Urinalysis[h]	X	X		X					X	X	X	X	X
Testing for hepatitis B and C and HIV	X												
TB assessment	X												

Table 4: Table of Events for the Induction Phase

Study Procedures		Induction Phase Treatment Period								EoE Flare Visit[e]	ET Visit[f]	Interim 8-week Safety Follow-up Visit[g]	Final 16-week Safety Follow-up Visit[g]
Visit Label	**Screening[a]**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[c,d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 2 (Day 15±3d)**	**Week 4 (Day 29±3d)**	**Week 8 (Day 57±3d)**	**Week 12 (Day 85±3d)**	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**			**Week 31 (Day 218±7d)**	**Week 39 (Day 274±7d)**
Pregnancy test (FCBP only)[j]	X	X		X	X	X	X	X	X		X	X	X
Physical examination[k]	X	X		X	X	X	X	X	X		X	X	X
Height (cm)	X								X		X		
Weight (kg)	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X												
Serum antibodies to CC-93538[h]		X		X	X				X		X	X	X
Serum CC-93538 PK assessment[h]		X	X	X	X	X	X		X		X	X	X
[redacted]													
SARS-CoV-2 serology[m]		X							X		X		
[redacted]													
Phone call reminder[o]	X							X[o]	X[o]			X[o]	

Table 4: Table of Events for the Induction Phase

Study Procedures		Induction Phase Treatment Period								EoE Flare Visit[e]	ET Visit[f]	Interim 8-week Safety Follow-up Visit[g]	Final 16-week Safety Follow-up Visit[g]
Visit Label	**Screening[a]**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[c,d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 2 (Day 15±3d)**	**Week 4 (Day 29±3d)**	**Week 8 (Day 57±3d)**	**Week 12 (Day 85±3d)**	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**			**Week 31 (Day 218±7d)**	**Week 39 (Day 274±7d)**
Modified Daily Symptom Diary (mDSD)[p]	X	X	X	X	X	X	X	X	X		X	X	X
[redacted]													

Table 4: Table of Events for the Induction Phase

Study Procedures		Induction Phase Treatment Period								EoE Flare Visit[e]	ET Visit[f]	Interim 8-week Safety Follow-up Visit[g]	Final 16-week Safety Follow-up Visit[g]
Visit Label	**Screening[a]**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[c,d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 2 (Day 15±3d)**	**Week 4 (Day 29±3d)**	**Week 8 (Day 57±3d)**	**Week 12 (Day 85±3d)**	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**			**Week 31 (Day 218±7d)**	**Week 39 (Day 274±7d)**
[redacted]													
EGD with tissue biopsies[r]	X								X	X[s]	X[t]		
EoE Endoscopic Reference Score (EREFS)	X								X	X[s]	X[t]		
[redacted]													

Table 4: Table of Events for the Induction Phase

Study Procedures		Induction Phase Treatment Period								EoE Flare Visit[e]	ET Visit[f]	Interim 8-week Safety Follow-up Visit[g]	Final 16-week Safety Follow-up Visit[g]
Visit Label	**Screening[a]**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8[c,d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 2 (Day 15±3d)**	**Week 4 (Day 29±3d)**	**Week 8 (Day 57±3d)**	**Week 12 (Day 85±3d)**	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**			**Week 31 (Day 218±7d)**	**Week 39 (Day 274±7d)**
Entry to Maintenance Phase[u]									X				
Randomization via IWRS		X											
IP administration[v]		X	X	X	X	X	X	X					

Abbreviations: AE = adverse event; [redacted]; d = day; ECG = electrocardiogram; [redacted] EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; ePRO = electronic patient-reported outcome; [redacted] EREFS = EoE Endoscopic Reference Score; ET = Early Termination; FCBP = female of childbearing potential; [redacted] HIV = human immunodeficiency virus; [redacted] IP = investigational product; IWRS = Interactive Web Response System; mDSD = modified Daily Symptom Diary; OLE = Open-Label Extension; [redacted] PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]; TB = tuberculosis; [redacted].

[a] All assessments must be completed within 4 weeks prior to Day 1, except for EGD with tissue biopsies and informed consent, which must be completed within 8 weeks prior to Day 1.

[b] The Day 1 assessments will serve as baseline measurements and will be conducted before dose administration.

[c] For subjects continuing in the Maintenance Phase, Visit 8 (Week 24) of the Induction Phase will also be the first visit in the Maintenance Phase. See Table 5 for the Table of Events for the Maintenance Phase.

[d] In the event of scheduling challenges, EGD may be performed with a +7 days visit window. All assessments are to be performed prior to IP administration for the first day of dosing in the Maintenance Phase.

[e] An EoE Flare Assessment Visit should be scheduled as close as possible to the time that an EoE flare is suspected. Note that laboratory samples do not need to be a pre-dose draw unless the subject is expected to dose later that day.

[f] Subjects who discontinue the study prior to completing the 24-week Induction Phase will be asked to complete an ET Visit and an Interim and a Final Safety Follow-up Visit at 8 weeks and at 16 weeks, respectively, after final IP administration for the assessment of safety and clinical status. Early Termination procedures performed at the EoE Flare Assessment Visit do not need to be repeated for subjects discontinuing the study prematurely due to an EoE flare.

[g] Subjects who complete the Induction Phase and do not enter either the Maintenance Phase or OLE study will be asked to complete the Interim 8-week Safety Follow-up Visit (8 weeks after final IP administration; at Week 31 for subjects that complete the Induction Phase) and the Final 16-week Safety Follow-up Visit (16 weeks after final IP administration; at Week 39 for subjects that complete the Induction Phase) for the assessment of safety and clinical status. For subjects exiting the study before completing the Induction Phase, these visits should occur at 8 and 16 weeks following the last dose of IP (ie, visits may occur before Week 31 and 39). However, subjects who are permanently discontinued from IP and continue study participation will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 24 or the ET Visit).

[h] Pre-dose collection, except for Safety Follow-up Visits (if applicable), the ET Visit (if applicable), and the EoE Flare Assessment Visit (if applicable; unless dose is taken that day).

[i] Fasting Lipid Panel and fasting glucose (instead of random glucose) will only be conducted at Day 1, Week 24, and the ET Visit (if applicable).

[j] For females of childbearing potential (FCBP), a serum pregnancy test at screening, urine (or serum) pregnancy test at Day 1, and urine pregnancy tests at subsequent visits are required. In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At each study visit, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study. Additional pregnancy tests may be required per local guidelines.

[k] Complete physical examination will be conducted at screening, Day 1, Week 24, both Safety Follow-up Visits (if applicable), and at the ET Visit (if applicable). Abbreviated physical examination will be conducted at Weeks 4, 8, 12, 16, and 20.

[redacted]

[m] Serum will be collected at Day 1 (baseline), Week 24, and the ET Visit (if applicable) as well as approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, for possible measurements of [redacted] per national and local requirements [redacted].

[redacted]

[o] A phone call will be made to subjects as a reminder to complete the mDSD. The Table of Events X's are noted in the visit before the start of the collection period in order to alert sites to the upcoming interim visit activity. Phone calls will take place just prior to the beginning of the final 14-day mDSD data collection period for screening (just prior to Day -14) and for the Week 24 (just prior to Week 22) endpoint analyses. For subjects who are required to complete the Safety Follow-up Visits, a phone call will take place before the 14-day mDSD data collection period just prior to the Interim Safety Follow-up Visit and the Final Safety Follow-up Visit, if applicable. During this call, subjects will also be reminded to complete the [redacted] at Day -14.

[p] The mDSD will be completed daily after the last meal of the day for at least the last 3 consecutive weeks (at least 21 days [up to 28 days]) during the Screening Period and daily from Day 1 through Week 24 using an electronic diary (eDiary) on a handheld device (ePRO instrument). For subjects who are required to complete the Safety Follow-up Visits, the mDSD will also be completed daily for the 14-day period before each of the 2 Safety Follow-up Visits. The ePRO

instrument will be distributed to subjects at the Screening Visit. Subjects are instructed to continue daily completion of the mDSD in the time interval between the transition from Induction Phase to Maintenance Phase or Study CC-93538-EE-001 to the OLE Study, CC-93538-EE-002.

[q] The screening [redacted] will be conducted at Day -14.

[r] Esophagogastroduodenoscopy (EGD) biopsies will be measured for relevant [redacted] when possible. The screening EGD must be completed within 8 weeks prior to Day 1 but should not be performed during the last 2 weeks of screening just prior to Day 1.

[s] EGD is required at EoE Flare Assessment Visits to determine if use of rescue therapy is clinically indicated. Alternatively, if endoscopy is conducted as part of an emergency department visit or hospitalization for the EoE flare, data should be collected for the EoE Flare Assessment Visit EGD requirement. All attempts should be made to collect biopsy samples, and these samples should be sent to the central reader for histologic analysis.

[t] EGD is not required at Early Termination Visits that occur before Week 8 of the study.

[u] The Investigator will confirm the subject's suitability for entry to the Maintenance Phase according to protocol requirements detailed in Section 6.4.2.8.

[v] Once weekly IP administration (CC-93538 or placebo: subcutaneous [SC] doses on Day 1 followed by SC doses weekly from Week 1 through Week 23 [ie, a total of 24 weekly SC doses inclusive of the Day 1 dose]). The first 3 weekly SC doses will be required to be given in the clinic, and subjects will remain in the clinic for at least 30 minutes following dosing for observation. Additionally, the Investigator will review the importance of IP compliance and evaluate compliance for each subject in accordance with the protocol.

[redacted]

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period							EoE Flare Visit[b]	ET Visit[c]	Interim 8-week Safety Follow-up Visit[d]	Final 16-week Safety Follow-up Visit[d]
Visit Label	Visit 8[a]	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14				
Visit Week (Window)	Week 24 (Day 169±3d)	Week 28 (Day 197±3d)	Week 32 (Day 225±3d)	Week 36 (Day 253±3d)	Week 40 (Day 281±3d)	Week 44 (Day 309±3d)	Week 48 (Day 337±5d)			Week 55 (Day 386±7d)	Week 63 (Day 442±7d)
Confirm eligibility	X										
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Hematology[e]	X	X	X	X	X	X	X	X	X	X	X
Chemistry[e,f]	X		X		X		X	X	X	X	X
Urinalysis[e]	X						X	X	X	X	X
Urine pregnancy test (FCBP only)[g]	X	X	X	X	X	X	X		X	X	X
Physical examination[h]	X			X			X		X	X	X
Height (cm)	X						X		X		
Weight (kg)	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Serum antibodies to CC-93538[e]	X	X		X			X		X	X	X
Serum CC-93538 PK assessment[e]	X	X	X	X	X		X		X	X	X

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period							EoE Flare Visit[b]	ET Visit[c]	Interim 8-week Safety Follow-up Visit[d]	Final 16-week Safety Follow-up Visit[d]
Visit Label	Visit 8[a]	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14				
Visit Week (Window)	Week 24 (Day 169±3d)	Week 28 (Day 197±3d)	Week 32 (Day 225±3d)	Week 36 (Day 253±3d)	Week 40 (Day 281±3d)	Week 44 (Day 309±3d)	Week 48 (Day 337±5d)			Week 55 (Day 386±7d)	Week 63 (Day 442±7d)
[redacted]											
SARS-CoV-2 serology[j]	X						X		X		
Phone call reminder[k]						X[k]	X[k]			X[k]	
Modified Daily Symptom Diary (mDSD)[l]	X	X	X	X	X	X	X		X	X	X
[redacted]											

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period							EoE Flare Visit[b]	ET Visit[c]	Interim 8-week Safety Follow-up Visit[d]	Final 16-week Safety Follow-up Visit[d]
Visit Label	Visit 8[a]	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14				
Visit Week (Window)	Week 24 (Day 169±3d)	Week 28 (Day 197±3d)	Week 32 (Day 225±3d)	Week 36 (Day 253±3d)	Week 40 (Day 281±3d)	Week 44 (Day 309±3d)	Week 48 (Day 337±5d)			Week 55 (Day 386±7d)	Week 63 (Day 442±7d)
[redacted]											
EGD with tissue biopsies[m]	X						X	X[n]	X[o]		

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period							EoE Flare Visit[b]	ET Visit[c]	Interim 8-week Safety Follow-up Visit[d]	Final 16-week Safety Follow-up Visit[d]
Visit Label	**Visit 8[a]**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**				
Visit Week (Window)	**Week 24 (Day 169±3d)**	**Week 28 (Day 197±3d)**	**Week 32 (Day 225±3d)**	**Week 36 (Day 253±3d)**	**Week 40 (Day 281±3d)**	**Week 44 (Day 309±3d)**	**Week 48 (Day 337±5d)**			**Week 55 (Day 386±7d)**	**Week 63 (Day 442±7d)**
EoE Endoscopic Reference Score (EREFS)	X						X	X[n]	X[o]		
[redacted]											
IP administration[p]	X	X	X	X	X	X					

Abbreviations: AE = adverse event; [redacted] EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; ePRO = electronic patient-reported outcome; [redacted] EREFS = EoE Endoscopic Reference Score; ET = Early Termination; FCBP = female of childbearing potential; [redacted] IP = investigational product; mDSD = modified Daily Symptom Diary; OLE = Open-Label Extension; PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]

[a] The assessments performed at the Induction Phase Week 24 Visit will also serve as the data for the first visit of the Maintenance Phase (Maintenance Phase Week 24 is equivalent to Induction Phase Week 24) and do not need to be repeated specifically for the Maintenance Phase. If the first visit of the Maintenance Phase does not occur at the Induction Week 24 Visit, an assessment of concomitant medications and AEs/SAEs will be performed, and a urine pregnancy test (FCBP only) will be performed only if it has been more than 30 days since the last test. A +4 day allowance (in addition to the Visit 8 window of ±3 days) for the scheduling of the EGD and Investigator assessment of subject suitability for entry to Maintenance may be used if needed. All assessments are to be performed prior to IP administration.

[b] An EoE Flare Assessment Visit should be scheduled as close as possible to the time that an EoE flare is suspected. Note that laboratory samples do not need to be a pre-dose draw unless the subject is expected to dose later that day.

[c] Subjects who prematurely discontinue the study during the Maintenance Phase will be asked to complete an Early Termination Visit and then an Interim and a Final Safety Follow-up Visit at 8 weeks and at 16 weeks, respectively after final IP administration for the assessment of safety and clinical status. Early Termination procedures performed at the EoE Flare Assessment Visit do not need to be repeated for subjects who are discontinuing the study prematurely due to an EoE flare.

[d] Subjects who complete the Maintenance Phase and do not enter the OLE study will be asked to complete the Interim 8-week Safety Follow-up Visit (8 weeks after final IP administration; at Week 55 for subjects that complete the Maintenance Phase) and the Final 16-week Safety Follow-up Visit (16 weeks following final IP administration; at Week 63 for subjects that complete the Maintenance Phase) for assessment of safety and clinical status. For subjects exiting the study before completing the Maintenance Phase, these visits should occur at 8 and 16 weeks following the last dose of IP (ie, visits may occur before Week 55 and 63). However, subjects who are permanently discontinued from IP and continue study participation will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 48 or the ET Visit).

[e] Pre-dose collection except for Safety Follow-up Visits (if applicable), the ET Visit (if applicable), and the EoE Flare Visit (if applicable; unless a dose is taken that day).

[f] Fasting Lipid Panel and fasting glucose (instead of random glucose) will only be conducted at Week 24, Week 48, and the ET Visit (if applicable).

[g] For females of childbearing potential (FCBP), urine pregnancy tests are required. In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At each study visit, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study. Additional pregnancy test may be required per local guidelines.

[h] Complete physical examination to be performed at Maintenance Phase Week 24, Week 48, both Safety Follow-up Visits (if applicable) and at the ET Visit (if applicable). Abbreviated physical examination to be conducted at Week 36.

[redacted]

[j] Serum will be collected at Week 24, Week 48 and the ET Visit (if applicable) as well as approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, for possible measurements of [redacted] per national and local requirements [redacted]

[k] A phone call will be made to subjects as a reminder to complete the mDSD. The Table of Events X's are noted in the visit before the start of the collection period in order to alert sites to the upcoming interim visit activity. Phone calls will take place just prior to the beginning of the 14-day mDSD data collection period for the Week 48 (just prior to Week 46) endpoint analysis. For subjects who are required to complete the Safety Follow-up Visits, a phone call will take place before the 14-day mDSD data collection period just prior to the Interim Safety Follow-up Visit and the Final Safety Follow-up Visit, if applicable.

[l] The mDSD will be completed daily after the last meal of the day from Week 24 through Week 48 using an electronic diary (eDiary) on a handheld device (ePRO instrument). For subjects who are required to complete the Safety Follow-up Visits, the mDSD will also be completed daily for the 14-day period before each of the 2 Safety Follow-up Visits. Subjects are instructed to continue daily completion of the mDSD in the time interval between the transition from Induction Phase to Maintenance Phase or Study CC-93538-EE-001 to the OLE Study, CC-93538-EE-002.

[m] Esophagogastroduodenoscopy (EGD) biopsies will be measured for relevant [redacted] when possible.

[n] EGD is required at EoE Flare Assessment Visits to determine if use of rescue therapy is clinically indicated. Alternatively, if endoscopy is conducted as part of an emergency department visit or hospitalization for the EoE flare, data should be collected for the EoE Flare Assessment Visit EGD requirement. All attempts should be made to collect biopsy samples, and these samples should be sent to the central reader for histologic analysis.

[o] EGD is not required at Early Termination Visits that occur before Week 32 of the Maintenance Phase.

[p] Subjects continuing participation in the Maintenance Phase will be given their first dose of IP at the first visit of the Maintenance Phase (ie, the Week 24 Induction Visit for most subjects). Subjects will then receive weekly doses through Week 47 (ie, a total of 24 doses of IP). Additionally, the Investigator will review the importance of IP compliance and evaluate compliance for each subject in accordance with the protocol.

[redacted]

6 PROCEDURES

Assessments and procedures for the Screening Period and the Induction Phase Treatment Period are outlined in Table 4. Assessments and procedures for the Maintenance Phase Treatment Period are outlined in Table 5. For the Follow-up Period (Safety Follow-up Visits), assessments and procedures are included in both Table 4 and. Table 5. Study assessments and procedures are also described in Section 6.1, Section 6.2, and Section 6.3. The day of administration of the first dose of IP is defined as Day 1 (pre-dose/baseline).

It is recommended that the study visits are scheduled in the morning. Whenever possible, the assessment order sequence should remain constant and should be conducted at approximately the same time of day throughout the study.

The following order for performing assessments and procedures is recommended (note that not all assessments and procedures are performed at every visit):

- EoE clinical symptom assessment instruments [redacted]
- Spontaneous or solicited AE reporting
- Vital signs
- Physical examination
- Clinical laboratory tests, including blood sampling for the assessment of serum CC-93538 levels, anti-drug antibodies (ADAs), [redacted]
- Esophagogastroduodenoscopy (EGD) (if applicable)
- IP administration

Throughout the study, IP administration should occur on the same day each week. For administration on study visit days, dosing should occur in the clinic. In the event a study visit can only be scheduled on a different day of the week than the usual dosing day, subjects should maintain their usual dosing schedule when possible.

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

6.1 Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days (4 weeks) prior to receiving the first dose of IP unless noted otherwise below. Waivers to the protocol will not be granted during the conduct of this study, under any circumstances.

Screening procedures, as specified in the Table of Events detailed in Table 4, will be performed for all subjects to determine study eligibility. All screening procedures must be completed within 4 weeks prior to receiving the first dose of IP. If there are issues with scheduling the screening EGD procedure, the screening window for informed consent and the EGD procedure may be extended up to 8 weeks prior to the first dose of IP. However, the EGD may not be performed during the last 2 weeks of screening at the same time the mDSD will be evaluated for the baseline

time point. In addition, a preliminary assessment of inclusion/exclusion criteria, including the frequency of dysphagia symptoms, should be performed by the Investigator before scheduling the EGD procedure for subjects. For FCBP subjects who initiate treatment with birth control during screening, birth control must be effective by the time the FCBP subject is randomized into the study (eg, hormonal contraception should be initiated at least 28 days before randomization). If necessary, the randomization/Day 1 Visit may be delayed up to a maximum of 28 days to achieve the minimum treatment duration. If the Day 1 Visit is delayed, the Medical Monitor should be contacted to confirm if any screening assessments (eg, safety labs, etc.) need to be repeated prior to randomization. All other screening assessments and procedures are to be performed by the Principal Investigator or a qualified designee. The electronic patient-reported outcome (ePRO) instruments including the electronic diary (eDiary [the mDSD]) on a handheld device will be distributed to subjects at the Screening Visit.

After completion of a training module, the mDSD will be completed daily for at least the last 3 consecutive weeks (21 days) during the Screening Period (prior to Day 1) but may be collected for up to 28 consecutive days during screening. Subjects are required to have completed at least 11 days of mDSD data collection out of the final 14 days of screening (ie, the final 14-day period preceding Day 1) in order to be enrolled in the study. A phone call will be made to subjects as a reminder to complete the mDSD. Phone calls will take place just prior to the beginning of the final 14-day mDSD data collection period for screening (prior to Day -14) which serves as the study baseline. The mDSD will be completed daily during the Induction and Maintenance Phases, and for those subjects who are required to complete the Safety Follow-up Visits (Section 6.3.1), the mDSD will be completed daily for the 14-day period before each of the 2 Safety Follow-up Visits. During the study, additional phone call reminders will take place before the 14-day collection period preceding the Week 24 and Week 48 endpoint assessment (ie, just prior to Weeks 22 and 46), before the collection period preceding the 2 Safety Follow-up Visits, if applicable, and a phone contact may be made at other time points as part of ongoing surveillance.

Safety laboratory analyses and all assessments will be performed. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

Written, signed, and dated informed consent/assent from the subject prior to the performance of any study related procedures must be obtained by the Principal Investigator or designee (refer to Section 12.3 for further details regarding obtaining subjects informed consent/assent). A copy of the signed informed consent/assent must be given to the subject for his/her records.

The following evaluations will be performed at screening as specified in the Table of Events, after informed consent/assent has been obtained:

- Assessment of inclusion/exclusion criteria
- Demographics and baseline characteristics
- Medical history including atopy status (documentation of atopic conditions and pharmacotherapy) and details of any prior dilation procedures

- Prior therapy and concomitant therapy including details of the determination of steroid responder status. The use of concomitant medication and procedures will be monitored throughout the study. Refer to Section 8 for prohibited concomitant therapies and permitted concomitant therapies including stable dose requirements and other restrictions.
- Adverse event assessment begins when the subject signs the informed consent/assent form. Throughout the course of the study, every effort must be made to remain alert to possible AEs or serious AEs (SAEs). Once subjects consent, AEs/SAEs will be recorded at each study visit. Refer to Section 10 for definitions of AEs/SAEs, monitoring, and reporting. In addition, device (ie, pre-filled syringe) failures or malfunctions should be captured, and device related AEs should also be collected.
- Hematology, chemistry, coagulation panel, and urinalysis (central laboratory). The following safety laboratory tests will be performed to assess the safety profile of CC-93538:
  - Hematology: red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)
  - Blood chemistry: indices included at all required chemistry time points are sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose (random, at time points not requiring fasting), albumin, alkaline phosphatase, creatinine, creatine phosphokinase (CPK), ALT/SGPT, AST/SGOT, gamma glutamyltransferase (GGT), amylase, total bilirubin, direct bilirubin and C-reactive protein (CRP); in addition, fasting lipid panel (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) and fasting glucose (instead of random glucose) will be performed only at Day 1, Week 24, Week 48, and the ET Visit (if applicable)
  - Coagulation: Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - The coagulation panel will only be conducted at screening. The hematology, chemistry, and urinalysis will be performed pre-dose (except for the Safety Follow-up Visit and ET Visit, if applicable) at screening and the additional time points outlined in the Table of Events (Table 4 and Table 5).
- Testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV (central laboratory) will be performed at screening only.
  - HBV: Hepatitis B surface antigen (HBsAg) screening test and hepatitis B core antibody (HBcAb) test will be performed. Subjects who test positive for HBsAg will be excluded from the study. For subjects who test positive only for HBcAb, an HBV deoxyribonucleic acid (DNA) test must be performed. If the HBV DNA test is positive, the subject will be excluded from the study. If the HBV DNA test is negative (without antiviral therapy) and ALT and AST are ≤ ULN, the subject will be eligible for this study.
  - HCV: HCV antibody (anti-HCV IgG) test will be performed. Subjects testing positive for HCV antibody and have a positive confirmatory test (HCV ribonucleic acid [RNA]) will be excluded from the study. Subjects with evidence of cleared HCV infection (eg, HCV

antibody positive subjects who are negative for HCV RNA) and who have not received anti-HCV therapy for at least 12 weeks will be eligible for participation.

  - HIV: An HIV antibody test will be performed. Subjects testing positive for HIV (enzyme-linked immunosorbent assay [ELISA] test result, confirmed by western blot) will be excluded from the study.

- Testing for tuberculosis (TB) will be performed at screening only. Active TB must be ruled out according to local medical practices. Latent TB must be assessed with a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (IGRA) (eg, T-SPOT). Subjects with latent TB must have documentation of completed prophylactic treatment by local standard of care. Subjects with an indeterminate test result using any IGRA test, must be discussed for eligibility on a case by case basis by the Sponsor's Medical Monitor or designee. Subjects with latent TB who were only partially treated or who are currently receiving prophylactic treatment will not be eligible for randomization.
- Serum pregnancy test (only for FCBP). A test for the β-subunit of serum human chorionic gonadotropin (β-hCG) must be performed at screening in females of childbearing potential. Urine (or serum) β-hCG will be performed at Day 1 and at the time points outlined in the Table of Events (Table 4 and Table 5). In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At screening and at each subsequent study visit, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.
- Physical examination: A complete physical examination (including evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities) or an abbreviated (interim/brief) physical examination (including areas with previously noted abnormalities and/or that are associated with any new complaints from the subject) will be performed according to the Table of Events (Table 4 and Table 5).
- Height (in centimeters) and weight (in kilograms)
- Vital signs: Heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be assessed at each visit. Blood pressure and pulse will be assessed in a sitting position and once the subject is at rest. An automated validated device may be used, if available. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
- Electrocardiogram (ECG): Single 12-lead ECG will be conducted only at the Screening Visit when the subject is at rest and may be repeated to confirm any abnormal findings.
- Modified Daily Symptom Diary (mDSD) (Section 6.4.2.1)
- Phone call reminder for mDSD completion (just prior to Day -14)

- EGD with tissue biopsies (Section 6.4.1)
- EoE Endoscopic Reference Score (EREFS) (Section 6.4.1)

[redacted]

6.1.1 Additional Information Regarding Safety Laboratory Assessments

Analysis of samples will be conducted by a central laboratory. Details regarding collection of samples, shipment of samples, reporting of results, laboratory reference ranges, and alerting abnormal values will be supplied to the site before site initiation in a Study Laboratory Manual. The results of the analysis will be made available to each site by the central laboratory.

Additional and repeat laboratory safety testing may be performed locally at the discretion of the Investigator. As local laboratory data will not be collected in the electronic case report form (eCRF), if feasible, a sample should also be sent to the central laboratory.

Investigators will be asked to comment on those abnormalities on the respective laboratory result page, including a notation of the clinical significance of each abnormal finding in the subject's source documents. The laboratory sheets will be filed with the subject's source documents. Reporting of laboratory AEs is described in Section 10.3.

6.1.2 Screening Failures and Rescreening of Potential Subjects

A screen failure is defined as a subject who has given informed consent/assent and failed to meet the inclusion and/or exclusion criteria. Subjects who initially fail to meet the inclusion/exclusion criteria may be re-screened as per the assessment of the Investigator. Subjects who are re-screened will be required to be re-consented and have all required Screening Visit procedures performed.

6.1.2.1 Rescreening of Subjects Who Develop COVID-19 During the Screening Period

Although molecular testing for asymptomatic COVID-19 infection is not required in this study, some subjects may develop suspected or confirmed symptomatic COVID-19 infection, or it is discovered that subjects have asymptomatic COVID-19 infection during the Screening Period. In such cases, subjects may be considered eligible for the study after meeting all Inclusion/Exclusion Criteria related to active infection, and after meeting the following criteria:

- At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
- At least 24 hours have passed since last fever without the use of fever-reducing medications, and
- Symptoms (eg, cough and shortness of breath) have resolved and
- In the opinion of the Investigator, there are no COVID-19 sequelae that may place the subject at a higher risk of receiving investigational treatment, and
- Negative follow-up molecular test for COVID-19 based on institutional, local or regional guidelines

6.2 Induction Phase and Maintenance Phase Treatment Period

On Day 1, prior to randomization in the Induction Phase, the baseline assessments (including laboratory assessments), as shown in Table 4, will be completed. The Investigator will review all available information to confirm subject eligibility.

- Screening laboratory tests will be used to determine eligibility for randomization with the exception of pregnancy tests, which will need to be confirmed by the Day 1 test results.
- A urine (or serum) pregnancy test must be performed for all females of childbearing potential on Day 1 and the results reviewed prior to randomization. A negative pregnancy test result must be obtained prior to randomization. If the urine pregnancy test result is positive but this is believed to be a false positive, the site may perform a stat serum pregnancy test at the local laboratory to confirm pregnancy status.
- Baseline laboratory tests will be performed on Day 1 for comparison with follow-up tests. However, the results of these tests will not be available prior to randomization on Day 1.

After eligibility has been confirmed and baseline assessments have been completed, eligible subjects will be randomized to treatment on Day 1. The first 3 weekly SC doses will be administered in the clinic. Subjects will remain in the clinic for at least 30 minutes following dosing for observation. Subsequent visits, assessments and procedures will be performed as per the Table of Events (Table 4 for the Induction Phase and Table 5 for the Maintenance Phase).

For the Maintenance Phase, the assessments performed at the Week 24 Visit (Visit 8) of the Induction Phase will also serve as the data for the Maintenance Phase Week 24 Visit (Visit 8) and

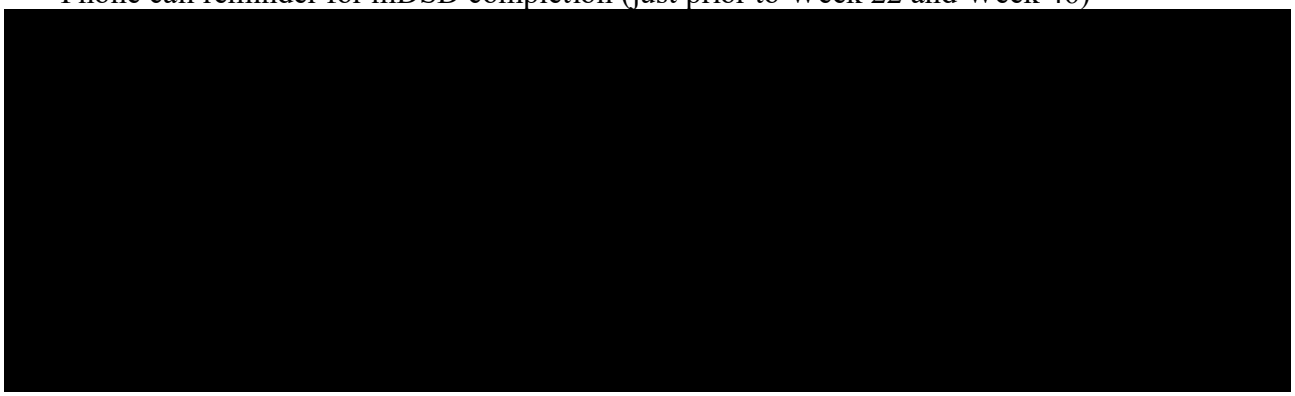
do not need to be repeated specifically for the Maintenance Phase. If the Maintenance Phase Week 24 Visit, the first day of the Maintenance Phase, does not occur at the Induction Phase Week 24 Visit (Visit 8), an assessment of concomitant medications and AEs/SAEs will be performed, and a urine pregnancy test (in FCBP only) will be conducted if it has been more than 30 days since the last test. The Investigator will confirm subjects meet the criteria to enter the Maintenance Phase according to Section 6.4.2.8. A +4 day allowance (in addition to the Visit 8 window of +/-3 days) for the scheduling of the EGD and Investigator assessment of subject suitability for entry to Maintenance is available if needed.

If subjects are out of window for their Week 24 dose due to use of the additional +4 day window for the EGD, subjects should skip the Week 24 dose and take the Week 25 dose which will be their first Maintenance Phase dose.

The following will be performed during the Induction Phase and Maintenance Phase Treatment Periods as specified in the Table of Events detailed in Table 4 and Table 5:

- Assessment of inclusion/exclusion criteria to confirm eligibility (Day 1 only)
- Concomitant therapy
- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis
- Urine pregnancy test (only for FCBP)
- Physical examination
- Height and weight
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment

- Modified Daily Symptom Diary (mDSD)
- Phone call reminder for mDSD completion (just prior to Week 22 and Week 46)



[redacted]

- EGD with tissue biopsies
- EoE Endoscopic Reference Score (EREFS)

[redacted]

- Entry to the Maintenance Phase assessment (only at Induction Phase Week 24)
- IP administration

Refer to Section 6.4 for a description of the efficacy assessments conducted throughout the study.

6.2.1 EoE Flare Assessment Visit

Subjects with a worsening of EoE symptoms during the study, either in the Induction Phase or Maintenance Phase will be required to complete the EoE Flare Assessment Visit as shown in the Table of Events (Table 4 and Table 5). Subjects with increased signs and symptoms of EoE are instructed to contact the Investigator and/or study staff to determine if an EoE Flare Assessment Visit is warranted. An EoE Flare Assessment Visit should be scheduled as close as possible to the time that an EoE flare is suspected.

Any worsening of EoE symptoms during study participation will be documented as an EoE flare. See Section 6.4.2.7 for the protocol definition of EoE flare and EoE Flare Assessment Visit details.

In the event that subjects discontinue the study prematurely due to an EoE flare, the ET Visit will also be completed, but procedures performed at the EoE Flare Assessment Visit do not need to be repeated for the ET Visit.

If subjects had an EGD performed for an EoE flare assessment during the Induction (prior to Week 24) or Maintenance (prior to Week 48) Phases, an EGD will also be performed at Week 24 or 48, respectively. However, an exception will be made if in the Investigator's judgement the EoE flare assessment occurred too close to Week 24 or Week 48 such that it is considered unsafe to perform another EGD within this short interval. In these cases, a discussion with the Medical Monitor will take place well in advance of the Week 24 or Week 48 Visit.

The following evaluations will be performed as specified in Table 4 and Table 5:

- Concomitant therapy
- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis*
- Weight
- Vital signs

[redacted]

* Note that these samples do not need to be a pre-dose draw unless the subject is expected to dose later that day.

[redacted]

- EGD with tissue biopsies[**]
- EoE Endoscopic Reference Score (EREFS)[**]

Refer to Section 6.4 for a description of the efficacy assessments conducted throughout the study.

6.2.2 End of Treatment/ Early Termination (ET) Visit

For subjects who discontinue the study prematurely for any reason (ie, subjects that do not complete Week 48), every attempt should be made to complete the assessments detailed in the ET Visit conducted as close as possible to the time of study discontinuation. If study discontinuation occurs at the regularly scheduled visit (eg, Induction Phase Week 12 or Maintenance Phase Week 36), the ET Visit and all corresponding ET Visit procedures should be conducted (Table 4 and Table 5). In addition, these subjects should return for the Safety Follow-up Visit (Section 6.3.1). Subjects who complete the Induction Phase Week 24 Visit but do not continue in the Maintenance Phase or OLE study should complete the Week 24/ET Visit and return for the Interim 8-week and Final 16-week Safety Follow-up Visits at Week 31 and Week 39, respectively (Section 6.3.1). Subjects who complete the Induction Phase and enter the OLE study should complete the Week 24/ET Visit; these subjects do not need to return for the 2 Safety Follow-up Visits. Assessments conducted at the Week 24 Visit do not need to be repeated. Subjects who complete the Maintenance Phase Week 48 but do not continue in the OLE study should return for the Interim 8-week and Final 16-week Safety Follow-up Visits at Week 55 and Week 63, respectively. For subjects who are discontinuing the study prematurely due to an EoE flare, ET procedures performed at the EoE Flare Assessment Visit do not need to be repeated.

The following evaluations will be performed as specified in Table 4 and Table 5:

- Concomitant therapy
- Assessment of AEs/SAEs (monitored through 16 weeks after the last dose of IP or the Final Safety Follow-up Visit, whichever is longer)
- Hematology, chemistry, and urinalysis
- Pregnancy test (only for FCBP)
- Physical examination
- Height and weight

[**] Note that EGD is required at EoE Flare Assessment Visits to determine if use of rescue therapy is clinically indicated. Alternatively, if endoscopy is conducted as part of an emergency department visit or hospitalization for the EoE flare, medical record source data should be collected for the EoE Flare Assessment Visit EGD requirement. In addition, all attempts should be made to collect biopsy samples, and these samples should be sent to the central reader for histologic analysis.

- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment

[redacted]

- Modified Daily Symptom Diary (mDSD)

[redacted]

- EGD with tissue biopsies*
- EoE Endoscopic Reference Score (EREFS)*

Refer to Section 6.4 for a description of the efficacy assessments conducted throughout the study.

6.3 Follow-up Period

6.3.1 Safety Follow-up Visits (Interim 8-week and Final 16-week)

All subjects will be followed for 16 weeks after the last dose of IP or until the Final Safety Follow-up Visit, whichever is longer, for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP, as described in Section 10.2.3.

In the Induction Phase, subjects who discontinue from the study prior to completing Week 24, or subjects who complete Week 24 and do not enter the Maintenance Phase or the OLE study will return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively after final IP administration (at Week 31 and Week 39 for subjects completing the Induction Phase) for the assessment of safety and clinical status after exiting the study. However, subjects who are permanently discontinued from IP and continue study participation in order to complete safety and efficacy assessments in the phase of the study that permanent discontinuation from IP occurs (according to Section 11.1) will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 24 or the ET Visit). Assessments should be performed in accordance with the Table of Events (Table 4). Subjects who

* Note that EGD is not required for ET Visits occurring before Week 8 in the Induction Phase or before Week 32 in the Maintenance Phase.

continue participation in the Maintenance Phase or OLE study will not return for the 2 Safety Follow-up Visits.

In the Maintenance Phase, subjects who discontinue from the study prior to completing Week 48 or complete Week 48 but do not enroll in the OLE study will also return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively after final IP administration (at Week 55 and Week 63 for completers of the Maintenance Phase) for the assessment of safety and clinical status after exiting the study. However, subjects who are permanently discontinued from IP and continue study participation in order to complete safety and efficacy assessments in the phase of the study that permanent discontinuation from IP occurs (according to Section 11.1) will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 48 or the ET Visit). Assessments to be performed are presented in the Table of Events (Table 5). Subjects who continue participation in the OLE study will not return for the 2 Safety Follow-up Visits.

The following evaluations will be performed as specified in Table 4 and Table 5:

- Concomitant therapy
- Assessment of AEs/SAEs (monitored through 16 weeks after the last dose of IP or the Final Safety Follow-up Visit, whichever is longer)
- Hematology, chemistry, and urinalysis
- Pregnancy test (only for FCBP)
- Physical examination
- Weight
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- [redacted]
- Modified Daily Symptom Diary (mDSD) only for the 14-day period preceding each of the 2 Safety Follow-up Visits
- Phone call reminder for mDSD completion just prior to the 14-day collection period preceding each of the 2 Safety Follow-up Visits

[redacted]

6.4 Efficacy Assessment

6.4.1 Esophagogastroduodenoscopy (EGD)

To ensure quality data and standardization, the same person should perform endoscopic procedures at a study site at each study visit.

The EGD biopsy results for eosinophil counts will be read blinded to treatment allocation at a centralized reading facility. Biopsy specimens will be sent to the centralized reading facility, and with the exception of screening, results of the centrally read eosinophil counts will be blinded to

investigative sites. After randomization, a local histologic assessment of EGD biopsy samples should not be performed, unless required for safety reasons (eg, severe EoE flare, AEs, or incidental findings, etc.). Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the study should be evaluated and handled by the Investigator per the site's standard of care and clinical judgement. More detailed instructions for specimen processing, storage, and shipping will be provided in a separate Study Laboratory Manual.

Endoscopic procedures will be performed as follows:

- EGD will be performed at the time points specified in the Table of Events (Table 4 and Table 5).
- Biopsies should be obtained from 3 levels, the proximal, mid, and distal esophagus, to maximize the likelihood of meeting histologic eligibility criteria for this study as follows:
  - Distal esophagus (3 to 5 cm above the Z-line [squamo-columnar junction])
  - Proximal esophagus (≈ 15 cm above the Z-line and within 10 cm of the esophageal inlet)
  - Mid esophagus (dependent on subject anatomy as described in the Study Laboratory Manual)
- All subsequent biopsies should be obtained from the same levels as the screening biopsies (ie, all 3 levels) maintaining consistency throughout the study.
- Biopsy samples must be obtained from 2 to 4 separate areas at each level, ideally from the areas with the most prominent visible abnormalities. For example, if 2-bite biopsies are being obtained, a minimum total of 4 biopsy fragments (from 2 separate 2-bite biopsies) would be obtained from each esophageal level.
- The screening EGD must be performed within 8 weeks prior to Day 1. The Investigator must document all treatments received at the time of the EGD and biopsy (for any indication) through Day 1, and the subject must not have received any new treatment that might affect EoE since the time of EGD according to protocol requirements (see Section 8). Subjects should not undergo the screening EGD during the 14-day period just prior to baseline when the final 14 days of the screening mDSD is collected.
- Histologic analysis of the esophageal biopsy samples for any study-specific assessments will be performed by a central laboratory including enumeration of eosinophil count (peak eosinophil count) by analysis of hematoxylin and eosin (H&E) stained biopsies and EoE histology scoring system (EoEHSS) assessment (histology grade and stage score).
- Endoscopic findings will be assessed by each Investigator using the EoE EREFS (Hirano, 2013) in 5 classification categories at the time points specified in the Table of Events (Table 4 and Table 5). The classification features include edema, fixed rings, exudates, furrows, and stricture. Assessments will be conducted at all 3 levels of the esophagus (the proximal, mid, and distal).
- In addition to obtaining the eosinophil counts required for inclusion in the study and primary endpoint determination, the esophageal biopsies will be used for evaluation of potential diagnostic [redacted] using appropriate laboratory methodology, including histopathology, immunohistochemistry, and transcript profiling.

6.4.2 Clinical Symptoms of EoE

6.4.2.1 Modified Daily Symptom Diary (mDSD)

The mDSD is a patient-reported diary to assess the daily experience of dysphagia symptoms (APPENDIX B). The original 4-item version of the DSD utilized in Phase 2 was modified to reflect the findings from the concept elicitation and cognitive interviews conducted with adolescent and adult EoE subjects in the mDSD validation study, EVA-20655. The mDSD includes 6 primary questions and 2 sub-questions, including an assessment of solid food consumption that day (item 1), experience with trouble swallowing (item 2), food going down slowly (item 3), food getting stuck in the throat or chest (item 4), actions taken by subjects to obtain relief (item 5), and any pain associated with swallowing (item 6). The recall period is "today," as the diary is meant to be completed daily.

The mDSD questions 2, 3, and 4 represent the primary symptoms to determine if a subject is experiencing dysphagia on any given day. Specifically, a DD is defined as a "yes" response to any or all of mDSD questions 2, 3, and 4. The mDSD composite score utilizes participant responses to mDSD questions 2, 3, 4, and 5. Subjects will receive a single score of "1" for any or all "yes" response(s) to questions 2, 3, or 4 in order to capture an episode of dysphasia experienced during the day and will receive a score of 0 to 4 for the response to question 5 depending on the action taken to seek relief for the dysphagia episode. Scores range from 0 to 70, with higher scores indicating more frequent and/or severe dysphagia.

Subjects will complete the mDSD daily via an eDiary on a handheld device for at least the last 3 consecutive weeks during the Screening Period. Subjects are required to have completed at least 11 days of mDSD data collection out of the final 14 days of screening (ie, the final 14-day period preceding Day 1) in order to be enrolled in the study. A number of measures will be employed in order to enhance subject adherence to eDairy completion and limit the amount of missing data, which is critical to ensure interpretability of mDSD assessment in this study. First, eDiary reminder alarms will allow subjects to select the timing for their alarm within a standardized window every evening such that completion occurs after the subject's last meal of the day. Second, ongoing surveillance of diary completion data will occur in order to correct any issues as close to real time as possible. Third, subjects will receive reminder calls from site staff in advance of the 14-day collection period preceding the screening (baseline) assessment and the Week 24 and 48 assessments (as well as additional times as needed based on ongoing surveillance) to help ensure compliance with the daily diary completion requirements at critical assessment points during the study. In addition, for subjects who are required to complete the Safety Follow-up Visits (Section 6.3.1), a phone contact will be made ahead of the 14-day period before each of the 2 Safety Follow-up Visits.

The mDSD will be administered daily in the evening or at bedtime after the subject's last meal of the day via an eDiary for at least the last 3 consecutive weeks (at least 21 days, but up to 28 days) in screening, from Day 1 through Week 48 (through the duration of the Induction and Maintenance Phases) of the study, through the ET Visit (if applicable), and for the 14-day period just prior to each of the 2 Safety Follow-up Visits (if applicable) according to the Table of Events (Table 4 and

Table 5). Subjects are instructed to continue daily completion of the mDSD in the time interval between the transition from Induction Phase to Maintenance Phase or Study CC-93538-EE-001 to the OLE study.

Further assessment of the psychometric properties of the mDSD in a Phase 3 study will include a preliminary blinded analysis after the first one-third of subjects complete 24 weeks of treatment in the Induction Phase as well as a final analysis, in all subjects completing Week 24, at the end of the study. These analyses will focus on the reproducibility, validity, and responsiveness of the DD and mDSD composite score endpoints as well as confirmation of the clinically meaningful response definition for the clinical co-primary endpoint, mean change in DD from baseline to Week 24, as described in a separate Psychometric Analysis Plan. The reproducibility of the mDSD will be assessed among "stable" subjects (ie, those reporting no change in [redacted] rating at Week 2) using 2 consecutive 14-day periods, the final 14-days of screening (baseline) and Weeks 1 to 2.

[redacted]

6.4.2.7 *Worsening of EoE Symptoms, EoE Flare, and the EoE Flare Assessment Visit*

Subjects with a worsening of EoE symptoms during the study, either in the Induction Phase or Maintenance Phase will be required to complete the EoE Flare Assessment Visit as shown in the Table of Events (Table 4 and Table 5). Subjects with increased signs and symptoms of EoE are instructed to contact the Investigator and/or study staff to determine if an EoE Flare Assessment Visit is warranted.

An EoE Flare Assessment Visit including safety and efficacy evaluations can occur at any time during the study. An EGD is required at EoE Flare Assessment Visits to determine if use of rescue therapy is clinically indicated. Alternatively, if endoscopy is conducted as an intervention during an emergency department visit or hospitalization for a worsening of EoE symptoms or flare, medical record source data including details of the endoscopic procedure should be collected for the EoE Flare Assessment Visit EGD requirement. In addition, all attempts should be made to collect biopsy samples, and these samples should be sent to the central reader for histologic analysis.

The Investigator will confirm if the worsening of EoE symptoms requires rescue therapy and, thus, is deemed a severe EoE flare according to the following protocol definitions.

Any worsening of EoE symptoms during study participation will be documented as an EoE flare.

- A severe EoE flare is defined as any worsening of EoE symptoms including a high intensity episode resulting in emergency department visit or hospitalization, with the need for endoscopic intervention (eg, for prolonged food impaction) and/or need for rescue therapy (eg, including but not limited to corticosteroid therapy or dilation), or a worsening of EoE symptoms resulting in the need for rescue therapy only without endoscopic intervention.
- A mild to moderate EoE flare is defined as any worsening of EoE symptoms without the need for rescue therapy or endoscopic intervention.

ET procedures performed at the EoE Flare Assessment Visit do not need to be repeated for subjects who discontinue the study prematurely due to an EoE flare.

Induction Phase

In the Induction Phase, if a subject experiences a severe EoE flare requiring intervention with endoscopy and/or treatment with any rescue therapy (eg, including but not limited to systemic or swallowed topical corticosteroid therapy or dilation), the subject may continue participation in the Induction Phase with concomitant rescue therapy as needed until completion of the Induction Phase at Week 24. The subject will not meet the entry criteria for the Maintenance Phase. The subject will be eligible to enroll in the OLE Study, CC-93538-EE-002, based on the judgement of the Investigator after completing Week 24 of the Induction Phase.

Subjects participating in the Induction Phase who require pharmacotherapy or dietary modifications prohibited by the protocol that may affect CC-93538 efficacy assessment or a dilation procedure will not be eligible for entry into the Maintenance Phase. Refer to Maintenance entry criteria in Section 6.4.2.8.

Maintenance Phase

In the Maintenance Phase, if a subject experiences a severe EoE flare requiring intervention with endoscopy and/or treatment with any rescue therapy (eg, including but not limited to systemic or swallowed topical corticosteroid therapy or dilation), the subject may continue participation in the Maintenance Phase with concomitant rescue therapy as needed until completion of the Maintenance Phase at Week 48. The subject will be eligible to enroll in the OLE Study, CC-93538-EE-002, based on the judgement of the Investigator after completing the study (Week 48).

6.4.2.8 Entry to Maintenance Phase

Following completion of Week 24 of the Induction Phase, subjects will be eligible for entry into the Maintenance Phase if none of the conditions listed below are met, and based on Investigator clinical judgement, it is in the best interest of the subject to continue study participation. Subjects who do not qualify for entry to the Maintenance Phase will be eligible for participation in the OLE Study, CC-93538-EE-002, unless permanent discontinuation from IP has occurred. The following are conditions that will exclude subjects from entry to the Maintenance Phase:

- Subjects with a severe EoE flare as described in Section 6.4.2.7
- Subjects who demonstrate a significant worsening upon endoscopic assessment at Week 24 compared to baseline as evidenced by the development of severe rings (EREFS Grade 3), a stricture < 10 mm, or a stricture that requires dilation, as evaluated by the Investigator; any other significant findings that, in the opinion of the Investigator, could potentially disqualify a subject from entering the Maintenance Phase must be assessed in conjunction with the Medical Monitor to determine if the subject is eligible for participation in the OLE Study, CC-93538-EE-002
- Subjects who are permanently discontinued from IP during the Induction Phase (before or at Week 24), and these subjects will not be eligible for participation in the OLE Study, CC-93538-EE-002 (see Section 11.1)
- In addition, for subjects who meet the following condition during the first 24 weeks of treatment (and without a severe EoE flare), a discussion with the Medical Monitor will be required before entry into Maintenance:
  - Subjects with any protocol-prohibited use of or change to diet (eg, food elimination) or medication which will impact efficacy assessment for CC-93538 (as determined through consultation with the Medical Monitor) will be excluded from entry to the Maintenance Phase

By contrast, subjects requiring concomitant systemic corticosteroids for an indication other than EoE may be eligible for entry to the Maintenance Phase if the duration of therapy is no more than 10 days and use does not occur within the 6 weeks preceding Induction Phase Week 24.

Note that subjects with use of systemic immunosuppressive or immunomodulating drugs prohibited per protocol (see Section 8.2) will be permanently discontinued from IP and will not be eligible for the OLE study (refer to Section 11.1).

For any subject in which there are no disqualifying criteria but the Investigator does not believe it is in the best interest of the subject to continue on into the Maintenance Phase, a discussion with the Medical Monitor will be required prior to decision to transition to the OLE study.

6.5 Anti-drug Antibody Assessments

Serum samples to assess blood levels of antibodies to CC-93538 will be obtained pre-dose (except for the ET Visit and 2 Safety Follow-up Visits, if applicable) at the time points outlined in the Table of Events (Table 4 and Table 5).

Details of the procedures to be followed for sample collection, processing, storage, shipment, and testing will be documented in a separate Study Laboratory Manual.

The development of anti-CC-93538 antibodies will be monitored to assess the impact of immunogenicity on safety, PK, and efficacy of CC-93538. The impact of immunogenicity will be evaluated by considering the results of PK, [redacted] and immunogenicity data taken together. Samples will be stored for additional analysis if necessary.

Further analysis on samples that are positive for ADA may be performed, including assessment of neutralizing antibodies when warranted. Samples will be stored for up to 5 years after study completion.

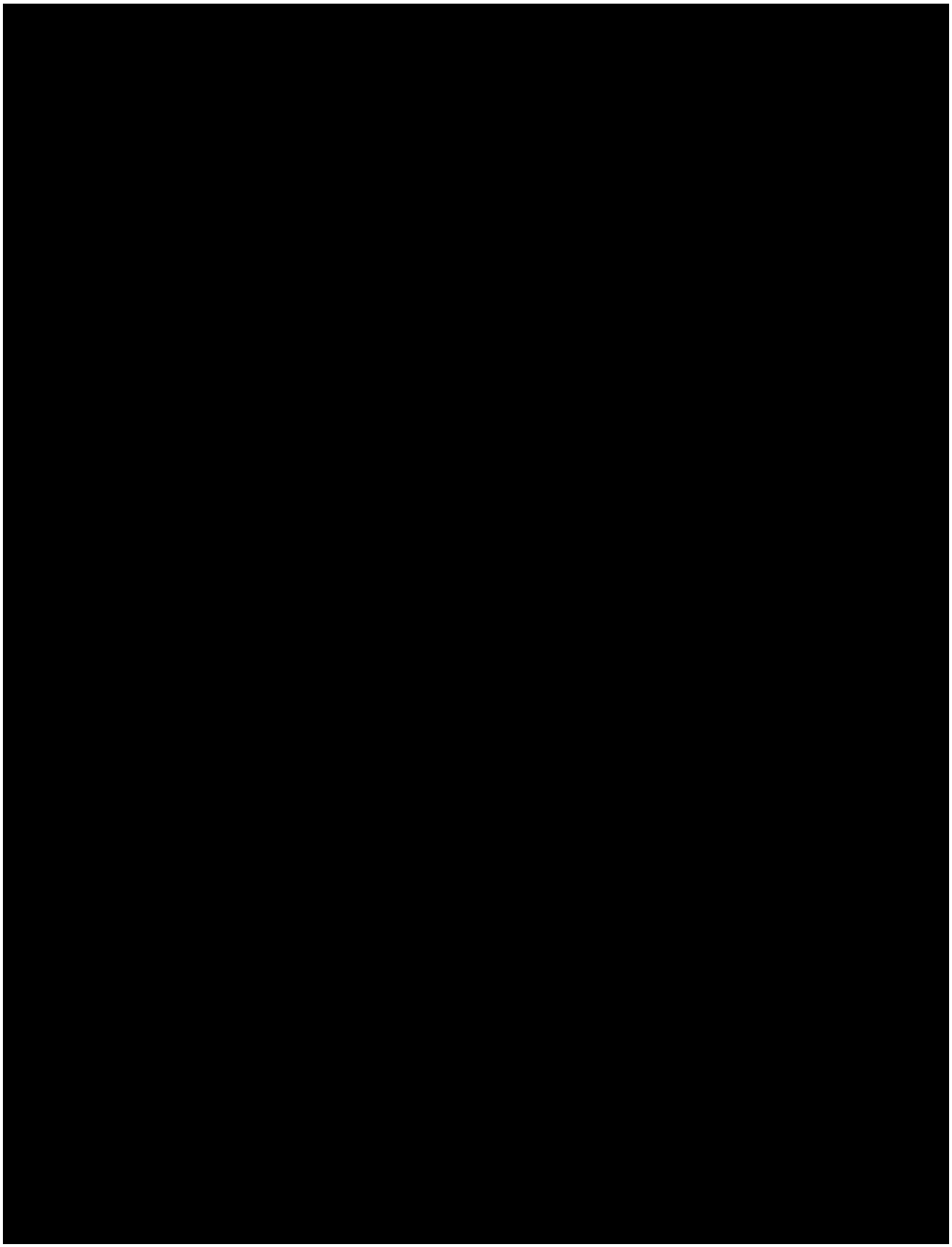
6.6 Pharmacokinetics

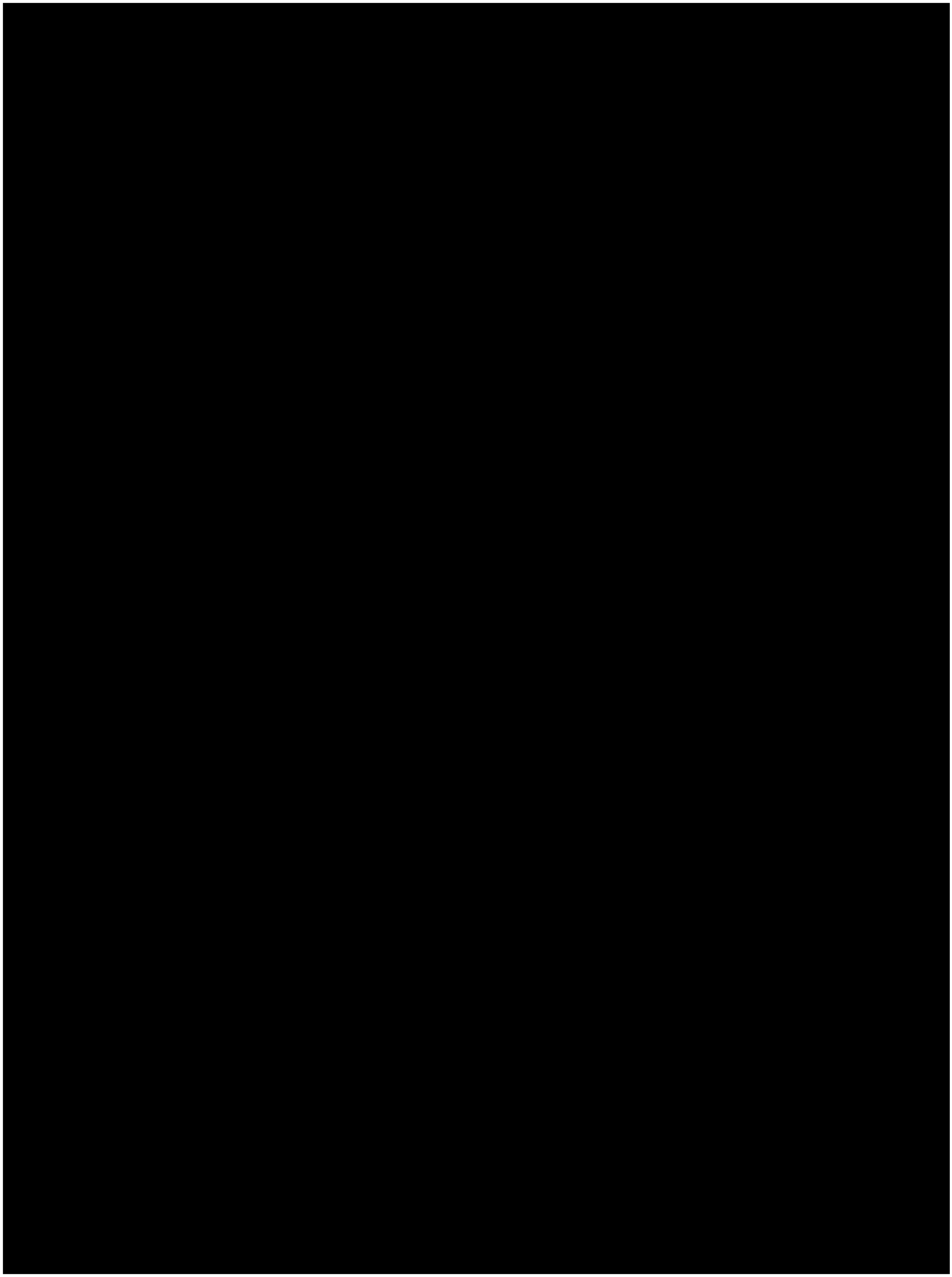
6.6.1 Serum CC-93538 Assessments

Serum samples to assess CC-93538 concentrations will be obtained pre-dose (except for the ET Visit and 2 Safety Follow-up Visits, if applicable) at the time points described in the Table of Events (Table 4 and Table 5). In the event that dosing occurs during a non-clinic visit day, it is still acceptable to obtain the serum samples.

Details of the procedures to be followed for sample collection, processing, storage, shipment, and testing will be documented in a separate Study Laboratory Manual.

[redacted]





[redacted]

7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Product(s)

The active ingredient of CC-93538 is a recombinant humanized IgG1 monoclonal antibody directed against human IL-13. Investigational products (CC-93538 and placebo solutions for injection) are to be stored at 2° to 8°C. The IP should not be frozen. The labeling will be in accordance with GCP and any other local regulatory requirements. During the study, IP will be dispensed in pre-filled syringes (PFS) provided by the Sponsor.

The 360 mg dose of CC-93538 (or placebo) will be administered by 2 injections of 1.2 mL each at a concentration of 150 mg/mL CC-93538.

Specific handling and dispensing instructions associated with each presentation of IP are provided below.

IP in PFS

A PFS presentation containing drug product at a concentration of 150 mg/mL CC-93538 (or placebo) in a 1.2 mL fill will be utilized in the study. CC-93538 solution for injection (or placebo) will be provided as a sterile liquid in PFS at a concentration of 150 mg/mL (or placebo) packaged in cartons (2 PFS per carton). CC-93538 and placebo solutions differ slightly in physical appearance and when presented in vials, the slight color difference in IP cannot be fully blinded. Therefore, for the PFS a label cover on the active and placebo syringes (to be applied during packaging/labeling) will be used to maintain the blind. As the PFS packaging will sufficiently blind the syringe contents, an unblinded pharmacist will not be required to dispense IP in the PFS. At home self-administration (as outlined in Section 7.2.1) or administration of IP through a home health nurse (as outlined in Section 7.2) will be available IP administration options with the PFS.

Additional instructions related to IP handling, preparation, and dispensation will be provided in a separate Study Pharmacy Manual (including an Instructions for Use document).

7.2 Treatment Administration and Schedule

The dosing schedule in the Induction and Maintenance Phases are as follows.

Subjects will be randomized 1:1:1 to the following treatment arms:

- CC-93538 360 mg SC once weekly for 24 weeks followed by CC-93538 360 mg SC once weekly for 24 weeks
- CC-93538 360 mg SC once weekly for 24 weeks followed by CC-93538 360 mg SC once every other week for 24 weeks. During the Maintenance Phase, matching placebo will be administered once every other week on alternate weeks to maintain the blind.
- Matching placebo SC once weekly for 24 weeks followed by matching placebo SC once weekly for 24 weeks

For the Induction Phase, subjects assigned to the CC-93538 360 mg SC arm will be administered two 1.2 mL CC-93538 SC injections once weekly for 24 weeks (1.2 mL x 2 = 2.4 mL at 150 mg/mL CC-93538 = 360 mg CC-93538/week). Subjects assigned to the placebo arm will receive matching placebo SC doses.

For the Maintenance Phase, subjects assigned to one of the CC-93538 360 mg arms will be administered two 1.2 mL CC-93538 SC injections once weekly for 24 weeks or once every other week for 24 weeks. Subjects assigned to the CC-93538 360 mg SC once every other week arm will receive a matching placebo SC dose every other week to maintain blinding. Subjects assigned to the placebo arm will receive matching placebo SC doses.

During the study, weekly SC doses should be administered on the same day each week at approximately the same time of day. The first 3 weekly SC doses will be administered in the clinic. Subjects will remain in the clinic for at least 30 minutes following dosing for observation. The number of injections to be administered in the clinic and/or the post injection observation time may be extended per Investigator discretion or to comply with local requirements. In Germany, subjects will be required to remain for observation for at least 60 minutes following the first 3 weekly SC doses.

The SC doses should be administered into the abdomen or other appropriate location including the thigh or back of the upper arm (rotating the injection site each time), avoiding any blood vessels, thickened or tender skin, scars, fibrous tissue, stretch marks, bruises, redness, nevi, or other skin imperfections.

An overdose is any dose of IP given to a subject or taken by a subject that exceeds the dose described in the protocol. There is no information regarding overdose with CC-93538. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor. See Section 10.1.

Doses that do not align with required study visits may be administered either in the clinic by study personnel or at the subject's home through self or caregiver administration or by a visiting home health nurse (once the subject has completed the first 3 required in-clinic doses).

7.2.1 Self-Administration

Self-administration (defined as either by subject or by caregiver, applicable per local regulations) will be an option for dose administration of IP by the PFS presentation. For subjects enrolled in

Japan, self-administration should be performed by the subject himself/herself in principle; however, in the event that it is not feasible for the subject to self-administer CC-93538, IP-administration may be performed by a family member. Subjects will be provided with an Instructions for Use document outlining steps for proper dose administration.

Self-administration will be dependent on the subject's (or caregiver's) ability to perform it and is independent of the subject's age. Subjects who plan to self-administer IP will be required to perform at least the first 3 weekly injections using the PFS presentation onsite in the presence of site personnel. The number of onsite injections may be increased based on Investigator judgement or other local requirements. This will allow for additional onsite training and a skill assessment to be done by the site personnel to ensure the subject (or subject's caregiver) is proficient with self-injection. In addition, continued injection compliance checks will occur during the course of the study, when the subject doses onsite at the monthly scheduled study visits. To help promote consistency within the data, subjects will not be allowed to "switch" their injection method during the study, unless there is a reasonable rationale for doing so (eg, change in injection proficiency, treatment compliance issue, etc.). For subjects who have difficulty self-administering IP, all weekly dosing will need to be conducted on-site or may be coordinated through a visiting home nurse (where locally feasible) to administer the IP to the subject.

7.2.2 Missed Dose(s)

If a subject is unable to take a dose on the usually scheduled day:

- The subject may take the dose within ±3 days of the normal dosing day and then continue dosing on the regular day the next week
- If the dose cannot be taken within ±3 days of the normal dosing day, the subject should wait to take the next dose on the regular dosing day the following week

See Section 7.2.4 for temporary interruption of dosing, and Section 7.2.5 for criteria for discontinuation of dosing.

7.2.3 Dose Adjustments

There is no provision for dose adjustments in this study. Subjects who cannot tolerate their assigned dose of IP, as determined by the Investigator, will be permanently discontinued from IP (see Section 11.1).

7.2.4 Guidelines for Temporary Interruption of Dosing

Dosing should be interrupted (temporary discontinuation of IP) if any of the following events occur:

- Severe laboratory abnormalities in which a causal relationship to IP is not suspected of being related (ie, a causal relationship is unlikely or remote, or another medication, therapeutic intervention or underlying condition provides a sufficient explanation)
- An infection requiring parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal medications; for an infection requiring oral treatment with these medications

for longer than 2 weeks, the Investigator should determine if an interruption of dosing is in the best interest of the subject

- Any AE, intercurrent medical condition, or major surgery that could present an unreasonable risk to the subject due to continued study participation, as determined by the Investigator
- For subjects who develop suspected or confirmed symptomatic COVID-19 infection, or it is discovered that subjects have asymptomatic COVID-19 infection during the Treatment Period, CC-93538 should be temporarily interrupted until the following conditions are met:
  - For symptomatic subjects:
    - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
    - At least 24 hours have passed since last fever without the use of fever-reducing medications, and
    - Symptoms (eg, cough and shortness of breath) have resolved, and
    - In the opinion of the Investigator, there are no COVID-19 sequelae that may place the subject at a higher risk of receiving investigational treatment, and
    - Negative follow-up molecular test for COVID-19 as required by most current institutional, local or regional COVID-19 guidelines and/or requirements.
  - For asymptomatic subjects:
    - At least 7 days have passed since positive test result (based on date of collection, not date of test result availability), and
    - Negative follow-up molecular test for COVID-19 as required by most current institutional, local or regional COVID-19 guidelines and/or requirements.

The decision to interrupt dosing of IP remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to interruption of dosing, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. Once the laboratory abnormality stabilizes (and is not suspected of being related to IP) or the condition resolves, IP dosing may be resumed at the discretion of the Investigator in consultation with the Medical Monitor if 3 or more consecutive doses have not been missed (3 or more consecutive missed doses requires permanent discontinuation of IP). If dosing is interrupted for any reason (AE, non-compliance, etc.), the Investigator should contact the Medical Monitor to discuss when/if IP dosing should be resumed.

7.2.5 Criteria for Discontinuation of Dosing

Dosing will be permanently discontinued (treatment discontinuation) for a subject if the subject experiences any of the events listed in Section 11.1 following initiation of IP. These subjects will be encouraged to remain in the study and complete all required study assessments in the phase of the study that permanent discontinuation of IP occurs with the exception of IP dosing and will not be allowed to participate in the OLE study. In order to prevent missing data, the site staff will ensure attempts are made to reach subjects by phone or email that do not maintain contact with the

Investigator. Any subject discontinuing the study prematurely will be asked to complete the ET Visit and the Interim and the Final Safety Follow-up Visits.

7.2.6 Rescue Therapy

Subjects with a worsening of EoE symptoms requiring rescue therapy (defined as a severe EoE flare; refer to Section 6.4.2.7) during the Induction or Maintenance Phase may continue to participate in the phase of the study in which the EoE flare occurs. Rescue therapy includes EoE standard of care pharmacotherapy, dietary modification (eg, food elimination diet), and/or dilation procedure.

7.3 Method of Treatment Assignment

Subjects enrolled in the Induction Phase will be centrally randomized on Day 1 after all screening and baseline assessments have been completed and the Investigator has verified that the subject is eligible per the inclusion (Section 4.2) and exclusion criteria (Section 4.3). Subjects will be randomized 1:1:1 to receive one of 2 active CC-93538 treatment arms (360 mg SC weekly for 48 weeks or 360 mg SC weekly for 24 weeks followed by 360 mg SC every other week for 24 weeks) or matching placebo for 48 weeks. Approximately 70% of the study population will be Steroid Inadequate Responders/Intolerant. Enrollment will be closely monitored, and enrollment of Steroid Responders/Naïve subjects will be limited to approximately 30%, if necessary. Treatment assignment at baseline will be stratified based on steroid responder status to ensure an equal balance in the treatment arms. Randomization will be performed through the Interactive Web Response System (IWRS) system.

Treatment groups are described in Section 7.2. The treatment each subject will receive will not be disclosed to the Investigator, study center personnel, subject, Sponsor or their representatives. The treatment codes will be held according to the IWRS. Further instructions will be provided in a separate IWRS manual.

The study blind should be maintained for persons responsible for the ongoing conduct of the study (after all subjects have completed the Week 48 assessments for endpoint analysis). Blinded persons may include but are not limited to: Clinical Research Physician (also referred to as Clinical Trial Physician), Clinical Research Scientist, Clinical Trial Manager, Study Statistician, Data Manager, Programmers, and Clinical Research Associates (CRAs). For details of the emergency procedure for unblinding of individual subjects, see Section 11.4.

7.4 Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations. For the PFS presentation, a label cover on the active and placebo syringes will be used to maintain the blind.

7.5 Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

All supplies of IP and placebo will be accounted for in accordance with GCP. There will be an individual IP accountability record for each subject and the Investigator should maintain accurate records relating to IP supplies received during the study. These records should include the amount of and dates clinical drug supplies were received, dispensed and administered to the subject by the investigative site or by a home healthcare nurse, or returned by the designated investigative site staff or by a home healthcare nurse and returned to the Sponsor. If errors or damages in the clinical drug supply shipments occur, the Investigator should contact the IP supplier and the Study Monitor immediately. Copies of the IP accountability records will be provided by each Investigator for inclusion in the Trial Master File after database lock. The Study Monitor will periodically check the supplies of IP held by the Investigator or pharmacist to verify accountability of all IP used.

The Investigator will provide IP only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, the Study Monitor will ensure that all unused IP and all medication containers, as applicable, can be destroyed on-site as long as proper documentation is supplied. If destruction on-site is not possible then any unused medication and containers, as applicable, will be returned to the Sponsor or designee. The Study Monitor will perform final accountability, package, seal and prepare for shipment. The clinical research organization (CRO) will verify that a final report of drug accountability is prepared and maintained in the Investigator Trial Master File.

7.6 Investigational Product Compliance

The Investigator must ensure that the IP will be used only in accordance with the protocol and that subjects are correctly instructed on how to take their IP and that each subject is fully compliant with their assigned dosage regimen. Investigational product non-compliance is defined as taking less than 80% or more than 120% of IP doses during the study. Records of IP used and intervals between visits will be kept during the study. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The IP should be dispensed by the Investigator, or by a qualified individual under the Investigator's supervision. An up-to-date treatment inventory/dispensing record must be maintained.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

All treatments (including prescription and over the counter [OTC] medications, herbal and dietary supplements, dietary modifications, vaccines, and procedures) used by subjects within the 4 weeks (28 days) prior to the first Screening Visit or at any time during the study in addition to the IP are regarded as prior or concomitant treatments and must be documented on the appropriate section of the eCRF. In addition, a history of previous treatments for EoE will be documented. The Investigator must document all treatments received at the time of the EGD (for any indication) through Day 1.

All concomitant treatments, including blood and blood products, used from 28 days prior to the first Screening Visit until 16 weeks after the last dose of IP or until the Final Safety Follow-up Visit, whichever is longer, must be reported on the eCRF.

8.1 Permitted Concomitant Medications and Procedures

Concomitant medications, dietary modifications, and procedures that are permitted during the study include:

- Subjects must agree to maintain a stable diet from the first Screening Visit and throughout the duration of the study. Subjects must have maintained a stable diet for at least 4 weeks prior to the first Screening Visit and throughout the duration of the study. Subjects on a food elimination diet for the treatment of food allergy or EoE should maintain it without making any changes through the end of the study and should have maintained this diet for at least 4 weeks prior to the first Screening Visit. Subjects must agree to not introduce any changes in their diet while participating in the study. However, following IP administration, subjects experiencing a severe EoE flare requiring a dietary modification for rescue therapy may be eligible to continue in the study according to protocol requirements. See Section 6.4.2.7.
- Subjects may use inhaled corticosteroids, leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for indications other than EoE if on stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens will remain stable throughout the duration of the study. If one of these medications was recently discontinued, it must have been discontinued at least 4 weeks prior to the first Screening Visit.
- Subjects may use medium potency topical corticosteroids (eg, mometasone furoate cream or lotion) for dermatologic conditions if on stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens will remain stable throughout the duration of the study. If the medication was recently discontinued, it must have been discontinued at least 4 weeks prior to the first Screening Visit.
- Subjects may use intranasal corticosteroids, antihistamines, or other medications for seasonal allergies or other conditions as needed.
- Subjects may use low potency topical corticosteroids for dermatological conditions as needed.
- Subjects receiving PPI medication at the first Screening Visit may participate if the PPI has been maintained at a stable dose from at least 4 weeks prior to the first Screening Visit through the end of the study. Subjects who discontinued a PPI must not have received a PPI for at least 4 weeks before the First Screening Visit and must agree not to restart a PPI during the study. However, following IP administration, subjects experiencing a severe EoE flare requiring the addition of a PPI or modification to the PPI regimen for rescue therapy may be eligible to continue in the study according to protocol requirements. See Section 6.4.2.7.
- Subjects receiving SC immunotherapy (treatment to desensitize to an allergen) must have been on stable doses for at least 3 months prior to the first Screening Visit and for the duration of the study.
- Administration of non-live vaccines including COVID-19 vaccine (except for investigational COVID-19 vaccines administered as part of a clinical trial) is allowed and may occur during the study. For COVID-19 vaccine regimens requiring more than one dose, the full series (eg, both doses of a 2-dose series) should be completed prior to enrollment into the study when

feasible, and when a delay in enrollment would not put the study participant at risk. Ideally, adverse events attributable to a vaccine should have resolved prior to enrollment.

Refer to Table 6 for a summary of the timing for stable dosing regimen requirements for certain medications and requirement of stable diet.

8.1.1 Rescue Therapy

During the study, subjects with a worsening of EoE symptoms requiring rescue therapy (defined as a severe EoE flare; refer to Section 6.4.2.7) may be eligible to continue to participate in the study according to protocol requirements. Rescue therapy includes EoE standard of care pharmacotherapy, dietary modification (eg, food elimination diet), and/or dilation procedure. Note that as part of study eligibility criteria and as described below in Section 8.2, in general, use of these treatment modalities is prohibited unless documented as required therapy for an EoE flare following IP administration.

8.2 Prohibited Concomitant Medications and Procedures

Concomitant medications and procedures that are prohibited for a specific time period prior to the first Screening Visit and throughout the duration of the study include the following (the timeframe before the first Screening Visit is specified below); however, exceptions will occur in the event of a severe EoE flare requiring rescue therapy and in such cases, subjects may continue participation with concomitant rescue therapy:

- Subjects may not use systemic immunosuppressive or immunomodulating drugs (including but not limited to, Janus kinase [JAK] inhibitors, phosphodiesterase-4 [PDE-4] inhibitors, anti-IL-13 antibodies other than IP in this study, IL-4 receptor alpha antagonist, anti-IL-5 antibodies, anti-IL-17 antibodies, anti-IgE antibodies, α4β7 integrin inhibitor antibodies, or any other monoclonal antibodies, methotrexate, cyclosporine, azathioprine, mercaptopurine, interferon alpha [IFNα], tumor necrosis factor alpha [TNFα] inhibitors, etc.) for at least 5 drug half-lives prior to the first Screening Visit and during the study. Use of any of the aforementioned medications during study participation will result in the subject's permanent discontinuation from IP; exceptions are if corticosteroids are used as rescue therapy for an EoE flare (see Section 8.1.1) or if required for treatment of an AE upon discussion with the Medical Monitor.
- Subjects may not use systemic or swallowed topical corticosteroid medication from the first Screening Visit through the end of the study. Subjects who have received corticosteroid therapy for EoE or another indication must have not received a systemic corticosteroid within 8 weeks or a swallowed topical corticosteroid within 4 weeks of the first Screening Visit. However, if a subject experiences a severe EoE flare during study participation following IP administration, the subject may continue participating with concomitant corticosteroid rescue therapy according to protocol pre-specified criteria (see Section 6.4.2.7).
- Subjects may not use high potency topical corticosteroids (eg, augmented betamethasone dipropionate, clobetasol propionate, etc.) for dermatologic conditions from the first Screening Visit through the end of the study. Subjects must not have received high potency topical corticosteroids for dermatologic use within 8 weeks of the first Screening Visit.

- Subjects may not use leukotriene receptor antagonists (eg, montelukast) or mast cell stabilizers (eg, cromolyn sodium) for the indication of EoE from the first Screening Visit through the end of the study. Subjects must not have received leukotriene receptor antagonists or mast cell stabilizers for EoE within 4 weeks of the first Screening Visit.
- Subjects may not receive oral or sublingual immunotherapy (treatment to desensitize to an allergen) from the first Screening Visit through the end of the study. Subjects should not have received oral or sublingual immunotherapy within 6 months prior to the first Screening Visit.
- Subjects may not receive live attenuated vaccines from the first Screening Visit through the end of the study. Subjects must not have received a live attenuated vaccine within 1 month of the first Screening Visit.
- Subjects may not undergo esophageal dilation for EoE symptom relief during the Screening Period or throughout the duration of the study or have had a dilation procedure within 8 weeks of the first Screening Visit. However, if a subject experiences a severe EoE flare following IP administration, the subject may continue participating with a concomitant dilation procedure for rescue therapy according to protocol pre-specified criteria (see Section 6.4.2.7).
- Concurrent treatment with another IP including an investigational treatment or vaccine for COVID-19 is not allowed. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to signing the informed consent/assent form for this study. For subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.

Refer to Table 6 for a summary of the timing of restrictions on medication use as well as for certain procedures or dietary modifications required prior to study enrollment.

Table 6: Medications, Diets, or Procedures Requiring Stable Dosing Regimens or Restricted Use Prior to Study Enrollment

Medication, Diet or Procedure	Restriction Timeframe
Medication (or procedure)	**Subjects must not have received the following medication within the timeframe below before the first Screening Visit**
Systemic immunosuppressive or immunomodulating drugs	5 half-lives
Systemic corticosteroids	8 weeks
Swallowed topical corticosteroids	4 weeks
High potency topical corticosteroids	8 weeks
Leukotriene receptor antagonists or mast cell stabilizers (for the indication of EoE)	4 weeks
Oral or sublingual immunotherapy	6 months
Live attenuated vaccines	1 month
Dilation	8 weeks
Any other investigational product[a]	5 half-lives
Medication (or diet)	**Subjects must be on stable dosing regimens within the timeframe below before the first Screening Visit**
Diet (eg, food elimination diet)	4 weeks
Inhaled corticosteroids, leukotriene receptor antagonists, or mast cell stabilizers (for indications other than EoE)	4 weeks
Proton pump inhibitors	4 weeks
Medium potency topical corticosteroids	4 weeks
Subcutaneous immunotherapy	3 months

[a] For subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the Investigator and the Clinical Trial Physician.

8.3 Required Concomitant Medications and Procedures

See inclusion criteria (Section 4.2) for a description of PPI medication requirements and corticosteroid treatment requirements for study eligibility. See Section 6.1 for screening EGD requirements.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

This is a Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EoE. The study will incorporate a 24-week Induction Phase followed by

a 24-week Maintenance Phase. Subjects will be randomized according to the following stratification factor: Steroid Inadequate Responders/Intolerant status (yes or no). An independent Data Monitoring Committee (DMC) will be used to review the safety data regularly during the course of the study.

A primary database lock will be performed when all randomized subjects in this study have completed Week 48 of the Maintenance Phase or discontinued the study, including all Safety Follow-up Period data available to date. Analyses in the primary clinical study report (CSR) will be based on this database. The final database lock will be performed at the end of the study including data for any additional subjects who completed the Safety Follow-up Period after the time the last subject completes Week 48 and any updates for adverse events previously ongoing at the time of the primary database lock. The additional data between the primary database lock and last subject completing last visit in this study will be summarized in an addendum to the primary CSR.

Analysis details not explained in the statistical section of the protocol will be provided in the Statistical Analysis Plan (SAP). In addition, the statistical analysis for the EU will be described in the SAP.

9.2 Study Population Definitions

All study populations will be defined and documented prior to database lock. The following analysis populations will be used in the statistical analysis:

Intent-to-treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received IP (CC-93538 or placebo).

The ITT population will be used as the primary population for all efficacy parameters. Subjects who prematurely withdraw from the trial for any reason and for whom an assessment is not performed for any reason will still be included in the ITT analyses. Subjects who received incorrect IP from what was randomized will be included in the treatment group according to the intended randomization. Subjects who were randomized with a misreported stratum will be analyzed according to their original (misreported) stratum.

Safety Population

The Safety population will consist of all subjects who received at least one dose of IP. This population will be used for all summaries of safety data. Subjects randomized to placebo who receive any dose of CC-93538 will be summarized in the CC-93538 group. Subjects randomized to CC-93538 who receive only placebo will be summarized in the placebo group; otherwise, they will be summarized in the CC-93538 group.

9.3 Sample Size and Power Considerations

A total sample size of 399 subjects (266 subjects for CC-93538 and 133 subjects for placebo) with a 20% dropout rate at the end of the Induction Phase (212 subjects for CC-93538 and 106 subjects for placebo) will provide at least 90% power to detect a difference of -2.79 change in DD from

baseline at Week 24 and at least 90% power to detect a difference of 15% at Week 24 in histologic response with a two-sided significance level (alpha) of 0.05. These calculations were based on a 2 sample t-test assuming a pooled standard deviation of 4.76 for change in DD from baseline and the chi-square test to compare the difference in 2 independent proportions for the histologic response assuming that the true placebo response proportion is 0.05.

9.4 Background and Demographic Characteristics

Summaries for the demographics, baseline characteristics, medical history, prior medication, and protocol deviations will be presented for the ITT population by treatment for the Induction Phase and by treatment and in Total CC-93538 for the Maintenance Phase. Concomitant medications will be presented for the Safety population by treatment for the Induction Phase, and by treatment and in Total CC-93538 for the Maintenance Phase. Individual listings will also be provided, including concomitant medical procedures for the Safety population.

9.5 Subject Disposition

The disposition of subjects will be summarized with numbers and percentages by treatment for all randomized subjects. Summaries will include the number and percentage of subjects in the following categories:

- Never dosed, dosed, completed the study, permanently discontinued from IP, and discontinuation from the study
- Time to permanent discontinuation from IP and time to discontinuation from the study
- Primary reasons for discontinuation from the study

Subjects in each analysis population as defined in Section 9.2 will be summarized with number and percentage.

9.6 Efficacy Analysis

9.6.1 Efficacy Analysis of the Co-primary Endpoints

9.6.1.1 Overview of Attributes of the Main Estimand for the Co-primary Endpoints

The main estimand of interest for the co-primary endpoints are provided in Table 7 and Table 8.

For intercurrent event (ICE) number 1, the treatment policy estimand strategy will be used where all observed data will be included in the primary analysis regardless of the occurrence of the ICE according to the respective endpoint definition. For ICE number 2, a composite variable estimand strategy will be used where data after rescue therapy or prohibited medication which may impact the efficacy assessment will be set as non-responders for histologic response and worst possible value for change in DD.

Table 7: Summary of Attributes of the Main Estimand for the Co-primary Endpoint - Change in DD from Baseline at Week 24

Estimand Attribute	**Definition for Co-primary Endpoint Clinical Response**		
Treatment	Randomized treatments with or without use of rescue therapy/prohibited medication		
Population	Adult and adolescent patients with EoE		
Variable	Change in DD from baseline at Week 24		
Intercurrent Events (ICEs)	Event	Strategy	Description/Rationale
	ICE 1: Treatment discontinuation in subjects without the use of concomitant rescue therapy or prohibited medication before the planned 24 weeks	Treatment Policy	Observations post ICE are used to reflect clinical practice
	ICE 2: The use of concomitant rescue therapy or prohibited medication which may impact the efficacy assessment for CC-93538, regardless of treatment discontinuation, before the planned 24 weeks	Composite Variable	Data post ICE will be set as worst possible value to reflect treatment failure
Population-level Summary	Difference in mean changes between treatment groups		

Table 8: Summary of Attributes of the Main Estimand for the Co-primary Endpoint - Histologic Response at Week 24

Estimand Attribute	**Definition for Co-primary Endpoint Histologic Response**		
Treatment	Randomized treatments with or without use of rescue therapy/prohibited medication		
Population	Adult and adolescent patients with EoE		
Variable	Peak esophageal eosinophil count ≤ 6 eos/hpf at Week 24		
Intercurrent Events (ICEs)	Event	Strategy	Description/Rationale
	ICE 1: Treatment discontinuation in subjects without the use of concomitant rescue therapy or prohibited medication before the planned 24 weeks	Treatment Policy	Observations post ICE are used to reflect clinical practice
	ICE 2: The use of concomitant rescue therapy or prohibited medication which may impact the efficacy assessment for CC-93538, regardless of treatment discontinuation, before the planned 24 weeks	Composite Variable	Data post ICE will be set as non-responders to reflect treatment failure
Population-level Summary	Difference in proportions between treatment groups		

9.6.1.2 Change in Dysphagia Days (DD) from Baseline to Week 24 (Induction Phase)

The mean change in dysphagia days (DD), evaluated over the prior 14-day period using the mDSD, from baseline to Week 24 is one of the 2 co-primary endpoints for the Induction Phase.

A DD is defined as a "yes" response to any or all of mDSD questions 2, 3, and 4. In calculating the number of DD for each subject, if the number of measurable diary days (defined as a diary day for which Questions 2 to 4 are answered) over the 14-day period prior to Day 1 is less than 11 or post-Day 1 visits are less than 8, the normalization formula will not be applied and the value of DD will be set to missing. In addition, subjects with at least 8 measurable diary days at post-Day 1 visits that are very unbalanced across the two weeks, defined as less than 3 measurable diary days in either the first or second week, will also have the value of DD set to missing.

The primary analysis will be conducted on the ITT population based on an analysis of covariance (ANCOVA) model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline DD values included in the model. The comparison between CC-93538 360 mg SC once weekly and placebo for change in DD from baseline at Week 24 will be made using the difference in least squares (LS) mean at a 5% 2-sided significance level. Point estimates for the mean difference between the 2 treatment groups using the adjusted LS Mean changes and corresponding 95% Wald CI will be reported. In addition, adjusted LS Means with standard error (SE), arithmetic means with standard deviation (SD), and arithmetic mean changes with SD will be summarized by treatment group.

Missing data will be handled using a multiple imputation (MI) approach (SAS Institute, 2015) under a missing at random (MAR) assumption.

The following sensitivity analyses will be performed to support the main estimand analysis and provide additional insights to understand the treatment effect:

- Robustness due to missing data MI under MAR assumption will be explored using tipping point analysis (Yan, 2009; Campbell, 2011; Yuan, 2014).
- A minimum of 4 measurable diary days per week is required to derive a DD score for the 14-day period. The analysis method will be the same as the primary analysis.

In considering the ICEs of study interest (ie, ICE number 2, use of rescue therapy/prohibited medication), supplementary analyses will be performed using the treatment policy estimand strategy and a hypothetical estimand strategy. In addition to the overall population, change in DD from baseline to Week 24 will be analyzed in the Steroid Inadequate Responders/Intolerant subgroup. This analysis will be similar to the overall population except that the ANCOVA model will not include Steroid Inadequate Responders/Intolerant status. See Section 9.6.4 for details on the hierarchical testing procedure to control the Type I error rate.

9.6.1.3 Eosinophilic Histologic Response at Week 24 (Induction Phase)

The other co-primary endpoint, eosinophilic histologic response, is defined as a peak esophageal eosinophil count ≤ 6/hpf (across all available esophageal levels) at Week 24.

The primary analysis of the eosinophilic histologic response will be conducted on the ITT population using the CMH test at a 2-sided 5% significance level, stratified by Steroid Inadequate Responders/Intolerant status. For treatment comparison between CC-93538 360 mg SC once weekly and placebo, the 2-sided 95% CI for the difference in proportions using the CMH weights and the 2-sided p-value from the CMH test will be provided.

Missing data in subjects without use of rescue therapy/prohibited medication prior to Week 24 will be handled using a multiple imputation (MI) approach (SAS Institute, 2015) under a missing at random (MAR) assumption.

A sensitivity analysis will be performed using tipping point analysis to assess the robustness of the primary efficacy analysis with regards to handling of missing data.

In considering the ICEs of study interest (ie, ICE number 2, use of rescue therapy or prohibited medication which may impact the efficacy assessment), a supplementary analysis using the treatment policy estimand strategy for the histologic endpoint at Week 24 will be conducted.

In addition to the overall population, histologic response at Week 24 will be analyzed in the Steroid Inadequate Responders/Intolerant subgroup. This analysis will be similar to the overall population except that the analysis will be done using the chi-square test. See Section 9.6.4 for details on the hierarchical testing procedure to control the Type I error rate.

9.6.2 Analysis of Key Secondary Efficacy Endpoints

For the first key secondary endpoint, proportion of subjects achieving eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf (across all available esophageal levels) at Week 24, the main analysis will be conducted based on the ITT population using the same type of method as described for the histologic response at Week 24 (the co-primary endpoint). The same summary and inferential statistics will be reported as specified for the primary analysis of the co-primary endpoint of histologic response in Section 9.6.1.3. Missing data and ICEs of interest will be handled via the same strategy as for the primary analysis of the co-primary endpoint of histologic response.

For the second key secondary endpoint, mean change in the endoscopic features of EoE as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to Week 24, the main analysis will be conducted based on the ITT population using an ANCOVA model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline EREFS values included in the model. The same summary and inferential statistics will be reported as specified for the primary analysis of the co-primary endpoint of change in DD in Section 9.6.1.2. Missing data and ICEs of interest will be handled via the same strategy as for the primary analysis of the co-primary endpoint of change in DD.

For the third key secondary endpoint, mean change in the mean adjusted histology grade score as measured by the scoring system (EoEHSS) from baseline to Week 24, the main analysis will be conducted based on the ITT population using an ANCOVA model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline mean adjusted histology grade score values included in the model. The same summary and inferential statistics will be reported

as specified for the primary analysis of the co-primary endpoint of change in DD in Section 9.6.1.2. Missing data and ICEs of interest will be handled via the same strategy as for the primary analysis of the co-primary endpoint of change in DD.

For the fourth key secondary endpoint, mean change in the mean adjusted histology stage score as measured by the scoring system (EoEHSS) from baseline to Week 24, the main analysis will be conducted based on the ITT population using an ANCOVA model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline mean adjusted histology stage score values included in the model. The same summary and inferential statistics will be reported as specified for the primary analysis of the co-primary endpoint of change in DD in Section 9.6.1.2. Missing data and ICEs of interest will be handled via the same strategy as for the primary analysis of the co-primary endpoint of change in DD.

For the fifth key secondary endpoint, mean change in mDSD composite score from baseline to Week 24, the main analysis will be conducted based on the ITT population using an ANCOVA model with treatment group, Steroid Inadequate Responders/Intolerant status (yes or no), and baseline mDSD composite score values included in the model. The same summary and inferential statistics will be reported as specified for the primary analysis of the co-primary endpoint of change in DD in Section 9.6.1.2. Missing data and ICEs of interest will be handled via the same strategy as for the primary analysis of the co-primary endpoint of change in DD.

For the binary endpoint (the first key secondary endpoint), a supplementary analysis using the treatment policy estimand strategy will also be conducted. All observed data will be used regardless of ICE.

For continuous endpoints (second to fifth key secondary endpoints), supplementary analyses using the treatment policy estimand strategy and a hypothetical estimand strategy to handle ICEs of rescue therapy/prohibited medication use will also be conducted. Data will be analyzed using the same ANCOVA model as described in this section.

9.6.3 Analysis of Secondary Efficacy Endpoints

End of Maintenance Phase (Week 48):

Histologic Response: The analysis of the histologic response endpoint will be conducted on the ITT population using the CMH test stratified by Steroid Inadequate Responders/Intolerant status. For treatment comparison between a CC-93538 dose and placebo, the 2-sided 95% CI for the difference in proportions using the CMH weights will be provided. Missing data will be handled via the same strategy as for the primary analysis of the co-primary endpoint of histologic response.

Mean change in DD: For the analysis of change in DD from baseline at Week 48, the baseline is defined as the last visit prior to receiving any dose of CC-93538 360 mg or placebo in the Induction Phase. The analysis of change in DD from baseline at Week 48 will be conducted using an ANCOVA model with treatment group (CC-93538 360 mg SC once weekly, CC-93538 360 mg SC once every other week, and placebo), Steroid Inadequate Responders/Intolerant status (yes or no), and baseline DD values included in the model. Point estimates for the mean difference between the treatment groups using the adjusted LS Mean changes and corresponding 95% Wald

CI will be reported. Missing data will be handled via the same strategy as for the primary analysis of the co-primary endpoint of change in DD.

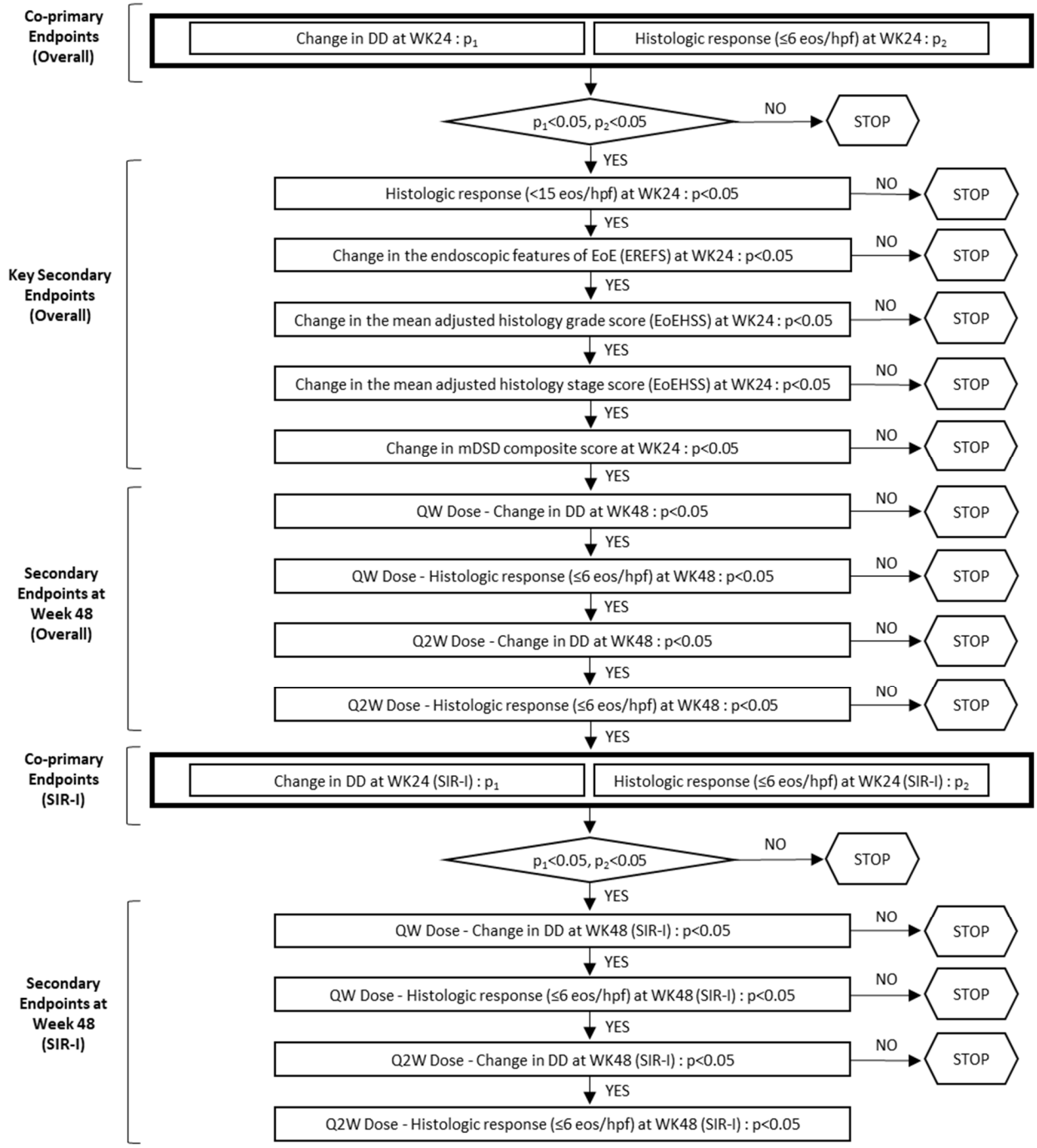
In addition to the overall population, histologic response at Week 48 and change in DD from baseline to Week 48 will be analyzed in the Steroid Inadequate Responders/Intolerant subgroup. These analyses will be similar to the overall population except that the analysis will be done using the chi-square test and the ANCOVA model will not include Steroid Inadequate Responders/Intolerant status. See Section 9.6.4 for details on the hierarchical testing procedure to control the Type I error rate.

9.6.4 Control of the Type I Error Rate

A hierarchical testing procedure will be utilized to permit confirmatory assessment of the co-primary endpoints, 5 key secondary endpoints, and 2 secondary endpoints at Week 48 in the overall population. In addition, the hierarchical testing procedure includes confirmatory assessment of the co-primary endpoints and two secondary endpoints at Week 48 in the Steroid Inadequate Responders/Intolerant subgroup. The Type I error rate is controlled for multiplicity (Dmitrienko, 2013).

Figure 2 presents the schematic for the hierarchical testing procedure for the United States and other non-European Union regions. A fixed sequence test will be applied and each hypothesis will be tested sequentially at an α level of 0.05. For the 2 co-primary endpoints, both p-values need to be less than α to continue to test the next endpoint of the sequence. For this hierarchy, the result(s) will be considered confirmatory if all previously tested hypotheses in the hierarchy are statistically significant at α = 0.05.

Figure 2: Multiplicity Adjustment for the US and Other Non-EU Regions



Abbreviations: DD = dysphagia day(s); EoE = eosinophilic esophagitis; EoEHSS = EoE histology scoring system; eos = eosinophils; EREFS = EoE Endoscopic Reference Score; hpf = high-power field; ITT = intent-to-treat; mDSD = modified daily symptom diary; SIR-I = Steroid Inadequate Responders/Intolerant; WK = week

Note: p_1 and p_2 represent the p-values for the 1st co-primary endpoint of change in DD and 2nd co-primary endpoint of histologic response, respectively.

For the EU, 2 additional endpoints in the Induction Phase will be included in the hierarchy:

- The proportion of subjects with a ≥ 50% decrease in dysphagia days (DD) from baseline at Week 24
- The proportion of subjects who achieve histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf at Week 24 and dysphagia symptom response defined as the proportion of subjects with ≥ 50% decrease in dysphagia days (DD) from baseline at Week 24

Details of the hierarchy for the EU analysis will be discussed in the SAP.

9.6.5 Subgroup Analyses

To assess whether the treatment effect is consistent across various groups, subgroup analyses will be performed for the co-primary endpoints at Week 24. Treatment differences and 2-sided 95% CIs will be provided for each subgroup listed below. Forest plots for the treatment differences by subgroup will also be provided.

1) Steroid Inadequate Responders/Intolerant status as reported in EDC (yes versus no)
2) Prior history of corticosteroid use for the treatment of EoE (yes versus no)
3) Age group (adolescents [< 18 years] versus adults [≥ 18 years], non-elderly adults [18 to < 65 years] versus elderly adults [≥ 65 years])
4) Previous dilation procedure for EoE (yes versus no)
5) Sex (female versus male)
6) Region (North America versus non-North America, European Union versus non-European Union)
7) Presence of atopy (yes versus no)
8) On stable concomitant PPI regimen (yes versus no)
9) On stable dietary modification (eg, elimination diet for the treatment of allergy or EoE [yes versus no])
10) Race (white versus non-white)

9.7 Safety Analysis

All analyses of safety data will be conducted using the Safety population by treatment for the Induction Phase and by treatment and in Total CC-93538 for the Maintenance Phase. The assessment of safety will include AEs, SAEs, AEs leading to discontinuation of study treatment, changes from baseline in laboratory values and vital signs, and incidence and type of laboratory, vital signs, and physical examination abnormalities. Individual data listings will also be provided.

Adverse events will be monitored during the trial, and the data will be analyzed with respect to incidence within each treatment group as well as severity and potential relationship of the AEs to IP.

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the standard International System of Units (SI) provided by the central lab. Each subject's

hematology, blood chemistry, and urinalysis values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

Summary statistics of actual values and changes from baseline in vital signs will be provided by visit.

9.8 Interim Analysis

No formal interim analysis will be conducted for the study.

9.9 Other Topics

9.9.1 Pharmacokinetics, [redacted] and Immunogenicity

Serum trough concentrations (Ctrough) of CC-93538 will be summarized with descriptive statistics by treatment and visit. Additional analysis may be conducted as appropriate (eg, by ADA status).

[redacted] Data from other studies may be included if appropriate. [redacted] will be conducted for efficacy, safety, [redacted] endpoints. Details on the studies and methodology will be outlined in a separate PK Analysis Plan, and results will be issued separately from the clinical study report as a stand-alone report.

Immunogenicity analysis will be described in the SAP.

[redacted]

9.9.3 Internal Safety Management Team

In addition to ongoing safety monitoring conducted by Investigators and individual study personnel, cumulative and interval blinded AEs, SAEs, discontinuations due to AEs, and abnormal laboratory findings will be reviewed internally by the Celgene Safety Management Team (SMT). The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-93538 development program. The scope, conduct, processes, and accountabilities are specified by Celgene Standard Operating Procedure (SOP).

9.9.4 External Data Monitoring Committee

Safety monitoring will also be performed by an external, independent Data Monitoring Committee (DMC). A DMC will be convened that will be comprised of physician experts with experience in treating subjects with EoE and a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified conflict of interest. During the study, the DMC will

review selected data (to be specified in the DMC charter) on a regular basis for the assessment of benefit-risk and determination of study continuation. An independent third party will prepare the reports of aggregate data summaries and individual subject data listings, as appropriate, for the DMC members for each scheduled meeting. Operational details for the DMC, including a blinding plan to assure that all personnel involved in the conduct of the study remain blinded to the results of data reviews, will also be described in the DMC charter.

9.9.5 Steering Committee

A steering committee, which will include the coordinating Principal Investigator, other investigators, and experts in eosinophilic esophagitis will be empaneled and serve in an advisory capacity to the Sponsor. Operational details for the steering committee will be detailed in a separate steering committee charter.

10 ADVERSE EVENTS

10.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE except for symptoms associated with an EoE flare requiring an EoE Flare Assessment, as referenced in Section 6.4.2.7. However, any EoE flare that meets the criteria for serious as detailed in Section 10.2.1, should be documented as an SAE in addition to an EoE flare. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an AE, should be reported as an AE on the AE eCRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the eCRF. The overdose itself should not be reported as an AE.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-93538 overdose. Actual treatment should depend on the severity of the clinical situation and the judgement and experience of the treating physician.

All subjects will be monitored for AEs, including AEs related to SARS-CoV-2 infection, during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures. In addition, device (ie, PFS)

failures or malfunctions should be captured during the study, and any device related AEs should also be documented.

All AEs, including AEs related to SARS-CoV-2 infection, will be recorded by the Investigator from the time the subject signs informed consent/assent until 16 weeks after the last dose of IP or the Final 16-week Safety Follow-up Visit, whichever is longer, as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

The SAE is recorded within the eCRF and the data is transmitted electronically to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the eCRF as well.

10.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to seriousness, severity/intensity, causality, duration, action taken, and outcome.

10.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgement should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

- a procedure for protocol/disease-related investigations (eg, surgery, scans, EGD, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, the AE screen of the eCRF must be completed and ticked "serious".

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2 Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3 Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5 Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, non-serious AEs of special interest (as defined in Section 10.6) and SARS-CoV-2 related AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 11.2).

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4 Pregnancy

All pregnancies or suspected pregnancies occurring in a female subject of childbearing potential are immediately reportable events.

10.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 5 months of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone, or facsimile, or other appropriate method, using the Pregnancy Initial Report Form or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method,

within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of the AE page/screen of the eCRF, and the AE ticked as "serious" in the electronic data capture system (EDC). All SAEs must be reported to Celgene Drug Safety via EDC within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 16 weeks after the last dose of IP or through the Final 16-week Safety Follow-up Visit, whichever is longer) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF/assent) are to be recorded within the eCRF and reported to Celgene Drug Safety.

The SAE report entered into EDC should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and the death certificate are to be provided to Celgene Drug Safety via EDC as soon as these become available. Any follow-up data should be added to the existing SAE case in EDC.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is recorded within the eCRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the eCRF as well.

10.5.1 Safety Queries

Queries pertaining to SAEs will be communicated through EDC.

10.6 Adverse Events of Special Interest

Investigators should identify AEs that meet the following criteria for adverse events of special interest (AESIs). Additionally, AESIs will be identified by the Sponsor programmatically. All AESIs must be entered into EDC within 24 hours of the Investigator's knowledge of the event.

AESIs fall into a number of categories based on the safety observations from dupilumab, lebrikizumab, and CC-93538 clinical studies and the potential pharmacologic effects of IL-4 receptor antagonist and anti-IL-13 antibodies. These include:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Severe injection site reactions (ISR) that last longer than 24 hours
  - A severe ISR is defined as an ISR that manifests with symptoms causing severe discomfort/pain; symptoms requiring medical/surgical attention/intervention; interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest); and/or when drug therapy is required
- Malignancies except in situ carcinoma of the cervix or non-metastatic squamous cell or basal cell carcinoma of the skin
- Helminthic or parasitic infections
- Opportunistic infections
- Any severe infections; or infections requiring treatment with parenteral antibiotic, antiviral, or antifungal medications; or infections requiring treatment with oral antibiotic, antiviral, or antifungal medications for longer than 2 weeks

10.7 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-93538 based on the Investigator's Brochure.

In the US, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 Code of Federal Regulations (CFR) 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information (in Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators):

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Other important safety information and periodic reports according to the local regulations.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 13.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Pregnancy Report Form Completion Guidelines.

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

The following events are considered sufficient reasons for permanently discontinuing a subject from the IP:

- Adverse event
- Physician decision
- Lack of efficacy
- Protocol deviation
- Withdrawal by subject or parent/guardian
- Death
- Lost to follow-up
- Non-compliance with IP
- Other (to be specified on the eCRF)

The following events require permanent discontinuation of IP:

- Pregnancy
- An SAE which is suspected of being related to IP
- Anaphylactic reaction or other severe systemic reaction (eg, hypersensitivity, allergic, or autoimmune) suspected of being related to IP
- Malignancy diagnosis, excluding carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin if it can be successfully treated by local resection
- Presence of an opportunistic infection suggestive of immunocompromise
- The following severe laboratory abnormalities suspected of being related to IP (laboratory indices should be repeated for confirmation prior to permanent IP discontinuation, within 48 to 72 hours the abnormality was first observed):
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values > 3 × ULN with total bilirubin > 2 × ULN or INR > 1.5, excluding confirmed Gilbert's Syndrome or therapeutic anticoagulation
  - ALT and/or AST > 5 × ULN for greater than 2 weeks duration
- 3 or more consecutive missed doses

- Use of systemic immunosuppressive or immunomodulating drugs prohibited per protocol (see Section 8.2)

Note: INR is part of the coagulation panel and may be obtained at the discretion of the investigator via central or local laboratory testing.

Subjects who are permanently discontinued from IP will be encouraged to continue participation in the study without IP administration in order to complete all remaining required study assessments including efficacy evaluation in the phase of the study that permanent discontinuation from IP occurs. If discontinuation from IP occurs during the Induction Phase, subjects will not be eligible to continue into the Maintenance Phase and will be discontinued from the study. Subjects who are permanently discontinued from IP will not be eligible to enter the OLE Study, CC-93538-EE-002. Subjects who continue study participation in the phase that the discontinuation occurs will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit.

The reason for discontinuation of treatment should be recorded in the eCRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject from treatment, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2 Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Withdrawal by subject or parent/guardian
- Lost to follow-up
- Death
- Other (to be specified on the eCRF)

Note that subjects who are permanently discontinued from IP (as detailed in Section 11.1) but are not discontinued from the study will be encouraged to continue participation in order to complete all remaining required study assessments in the phase of the study that permanent discontinuation from IP occurs. In order to prevent missing data, the site staff will ensure attempts are made to reach subjects by phone or email that do not maintain contact with the Investigator.

The reason for study discontinuation should be recorded in the eCRF and in the source documents. Because follow-up of subjects who discontinue from the study prematurely is of particular importance, every attempt should be made to collect all or specific final data on a discontinued subject.

In the Induction Phase, subjects who discontinue from the study for any reason prior to completing Week 24, or who complete Week 24 and do not enter the Maintenance Phase will complete an ET

Visit conducted as close as possible to the time of study discontinuation. If study discontinuation occurs at the regularly scheduled visit (eg, Induction Phase Week 24) the ET Visit/procedures should be performed. These subjects, with the exception of those continuing in the OLE, will also have 2 Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration for the assessment of safety and clinical status after exiting the study. For subjects who are permanently discontinued from IP during the Induction Phase and remain in the study to complete safety and efficacy assessments, the Interim and Final Safety Follow-up Visits will be conducted 8 and 16 weeks, respectively, after their last study visit in the Induction Phase. Assessments should be performed in accordance to the schedule of events (Table 4).

In the Maintenance Phase, subjects who discontinue from the study for any reason prior to completing Week 48 will complete an ET Visit conducted as close as possible to the time of study discontinuation. If study discontinuation occurs at the regularly scheduled visit (eg, Maintenance Phase Week 36) the ET Visit/procedures should be performed. These subjects will also have 2 Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration for the assessment of safety and clinical status after exiting the study. For subjects who are permanently discontinued from IP during the Maintenance Phase and remain in the study to complete safety and efficacy assessments, the Interim and Final Safety Follow-up Visits will be conducted 8 and 16 weeks, respectively, after their last study visit in the Maintenance Phase. Assessments should be performed in accordance to the schedule of events (Table 5).

11.3 Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician (also referred to as Clinical Trial Physician)/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician (also referred to as Clinical Trial Physician)/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s), also referred to as Clinical Trial Physician(s), or Medical Monitor or designee for emergency calls.

11.4 Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator through the IWRS by using an emergency unblinding personal identification number (PIN), and the Investigator should call IWRS for unblinded dose information.

12 REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF/assent) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information.

Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

12.3 Subject Information and Informed Consent

The Investigator must obtain informed consent/assent of a subject and/or a subject's legal representative prior to any study related procedures. Adolescent subjects must agree to participate in the study by signing an assent form. A parent/legal representative of an adolescent subject must sign an informed consent form.

Documentation that informed consent/assent occurred prior to the study subject's entry into the study and of the informed consent/assent process should be recorded in the study subject's source documents including the date. The original ICF/assent signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent/assent, the ICF/assent must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented/assented with the revised version of the ICF/assent. The revised ICF/assent signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

12.4 Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF/assent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

12.5 Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician (also referred to as Clinical Trial Physician)/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically

reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

12.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF/assent, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF/assent should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

12.7 Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

12.8 Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP non-compliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

13 DATA HANDLING AND RECORDKEEPING

13.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of eCRFs/case report forms (CRFs) or CD-ROM.

13.2 Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

13.3 Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the Clinical Trial Agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs/assent for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;

- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

14 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

14.1 Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion

criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

14.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, European Medicines Agency [EMA], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

14.3 Investigational Medicinal Product Quality Issues

Issues that call into question investigational medicinal product (IMP), also referred to as IP, safety, purity, potency, quality and identity (eg, evidence of suspected tampering of product) must be reported as soon as possible to the study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all sponsor supplied IMP, non-investigational medicinal product (NIMP) or auxiliary medicinal product (AxMP), suspected to have occurred before the product was transferred to the responsibility of the investigational site (eg, during manufacturing, packaging and labeling, storage, and/or distribution).

This includes suspected quality issues of components co-packaged with the drug, labeling, and IMP device/drug combination products, and medical devices.

In the event of a suspected product quality issue, the immediate action to be taken by the site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (eg, cytotoxic, risk of injury from broken glass or sharps).

When reporting, provide as much product information as possible. Suspected IMP quality issues will be investigated and a response will be provided back to the investigational site.

15 PUBLICATIONS

As described in Section 12.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical

importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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17 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADL	Activity of daily life
AE	Adverse event
AESI	Adverse event of special interest
AI	Autoinjector
ALT	Alanine aminotransferase
[redacted]	
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BMS	Bristol-Myers Squibb Company
CFR	Code of Federal Regulations
[redacted]	
CI	Confidence interval
Cmax	Observed maximum serum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
DB	Double-blind
Ctrough	Serum trough concentration
DD	Dysphagia day(s)
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSD	Daily Symptom Diary
EC	Ethics Committee

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
eDiary	Electronic diary
EEA	European Economic Area
[redacted]	
EGD	Esophagogastroduodenoscopy
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
[redacted]	
EoE	Eosinophilic esophagitis
EoEHSS	EoE histology scoring system
eos	Eosinophils
ePRO	Electronic patient-reported outcome
[redacted]	
EREFS	EoE Endoscopic Reference Score
ET	Early Termination
EU	European Union
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
GADS-S	Global Assessment of Disease Severity-Subject
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GIC-EoE	Global Impression of Change in EoE Symptoms
H&E	Hematoxylin and eosin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hpf	High-power field
[redacted]	
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IFNα	Interferon alpha
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG1κ	Immunoglobulin G1 kappa
IGRA	Interferon gamma release assay
IMP	Investigational medicinal product
IL-4	Interleukin-4
IL-5	Interleukin-5
IL-13	Interleukin-13
IL-13Rα1	Interleukin-13 receptor alpha 1
IL-13Rα2	Interleukin-13 receptor alpha 2
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous/ly
IWRS	Interactive Web Response System
LS	Least squares
mAb	Monoclonal antibody
MAR	Missing at random
MCH	Mean corpuscular hemoglobin

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mDSD	Modified Daily Symptom Diary
MI	Multiple imputation
OLE	Open-Label Extension
[redacted]	
PFS	Pre-filled syringe(s)
[redacted]	
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
[redacted]	
PT	Prothrombin time
RBC	Red blood cell
RNA	ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneously/Subcutaneous (dose/injection)
SD	Standard deviation
SE	Standard error
[redacted]	
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System of Units
SIR-I	Steroid Inadequate Responders/Intolerant
SMT	Safety Management Team
[redacted]	
SOP	Standard operating procedure
SUSARs	Suspected unexpected serious adverse reactions
t½	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
tmax	Time to the observed maximum concentration
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	United States
[redacted]	[redacted]
WBC	White blood cell
[redacted]	[redacted]

APPENDIX B MODIFIED DAILY SYMPTOM DIARY (MDSD)