Official Title of Study:

A Phase 3, Multicenter, Multinational, Open-Label Extension Study to Evaluate the Long-Term Safety of CC-93538 in Adult And Adolescent Subjects with Eosinophilic Esophagitis

NCT Number: NCT04991935

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A PHASE 3, MULTICENTER, MULTINATIONAL, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY OF CC-93538 IN ADULT AND ADOLESCENT SUBJECTS WITH EOSINOPHILIC ESOPHAGITIS

PROTOCOL NUMBER:	**CC-93538-EE-002**
COMPOUND NUMBER:	**CC-93538 (BMS-986355)**
DATE FINAL:	**26 Feb 2021**
AMENDMENT No. 0.1 DE DATE:	**01 Dec 2021**
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IND NUMBER:	**119240**
SPONSOR NAME/ADDRESS:	Celgene International II Sàrl Route de Perreux 1 2017 Boudry Switzerland

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

24/7 PPD Medical Monitor Safety Hotline

North American Regional Contact	EMEA & APAC Regional Contact
Phone: +1-888-483-7729	**Phone:** +44-122-337-4240
Fax: +1-888-529-3580	**Fax:** +44-122-337-4102

Sponsor Clinical Trial Physician

Contact Information:
Name: [redacted]
Title: [redacted]
Address: Bristol-Myers Squibb 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: +1-877-501-7738

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

[redacted]	
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]	4th July 2023 **Date**
[redacted]	
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 2:

Protocol Amendment 2 is being implemented to support the introduction of a new autoinjector (AI) presentation for administration of CC-93538 (BMS-986355) as a weekly subcutaneous (SC) dose by a [redacted] injection at a concentration of [redacted] mg/mL. The details on the transition of current and new subjects to the new AI presentation, timing of visits, and the inclusion of the AI Administration Questionnaire are incorporated in the body of the protocol. This amendment also includes the preliminary results from Study IM042-003, a single dose pharmacokinetic study comparing the AI and pre-filled syringe (PFS) presentations.

The following summary of changes outlines the revisions to the various sections of Protocol Amendment 2.

This amendment includes changes from approved Administrative Letter 01, and those changes are not listed in the table below. The Protocol Summary was updated to reflect changes made in the body of the protocol.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout	Pre-filled syringe (PFS) has been replaced with autoinjector (AI) in multiple places throughout the protocol.	Upon the implementation of this amendment, the CC-93538 360 mg SC dose will be administered via a new AI presentation.
Section 1.1, Disease Background: Eosinophilic Esophagitis	Deleted part of a sentence that is no longer accurate and included a new statement for Food and Drug Administration and European Medicines Agency approval of dupilumab as new treatment for eosinophilic esophagitis (EoE).	Updated the background information to include new available treatments for EoE.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.2, Clinical Studies	Updated the list of CC-93538 clinical studies with results available.	Study CC-93538-CP-002 was completed with the results available in the clinical study report. These changes include the preliminary results of Phase 1 Study IM042003, which provides the pharmacokinetic (PK) comparability, safety, tolerability, and immunogenicity of [redacted] subcutaneous (SC) injections of CC-93538 administered using an AI versus PFS.
Section 1.2.2.6, Phase 1 Study, IM042-003 Section 1.3.3, Rationale for Dose, Schedule and Regimen Selection	A new section was added providing background information and data regarding Study IM042-003. Section updated to include the rationale for the introduction of the [redacted] AI presentation.	To include the preliminary results of Phase 1 Study IM042-003 Part 1, which provides PK comparability, safety, tolerability, and immunogenicity of [redacted] SC injections of CC-93538 administered using an AI versus PFS. The results of Study IM042-003 support the introduction of the [redacted] AI presentation in Protocol Amendment 2.
Section 1.2.2.2, Phase 2 Study, CC-93538-AD-001	A new section was added to provide information on 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.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.3.2, Rationale for the Study Design	Advisory panel of patients, caregivers, and feedback from the members of the EoE community was consulted for input on protocol design and development of patient-facing materials and recruitment initiation.	To provide information on the involvement of patients, caregivers, and patient advocacy groups in the study design/implementation process.
Table 1, Study Objectives Table 2, Study Endpoints	A new exploratory objective and endpoint has been added to estimate the frequency of successful self-administration of CC-93538 by AI under supervised (in-clinic) and unsupervised (at home) conditions.	To account for the change in the presentation of administration of CC-93538 from PFS to AI.
Table 2, Study Endpoints	A new exploratory endpoint has been added to estimate the proportion of subjects previously treated with CC-93538 in Study CC-93538-EE-001 and with peak esophageal eosinophil count ≤ 6/high power field (hpf) at open label extension (OLE) baseline who continue to have a peak esophageal eosinophil count ≤ 6/hpf throughout the OLE study.	To analyze the trend of peak eosinophil count in subjects previously treated with CC-93538 in Study CC-93538-EE-001 with histologic response at OLE baseline who continue to demonstrate response in the OLE study, as an assessment of durability of response.
Table 2, Study Endpoints	Added the time point of Week 104 for evaluation of clinical response endpoints [redacted].	To enable further evaluation of EoE symptoms with the mDSD at the end of Year 2.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 3.2.1, Open-label Treatment Period Table 3, Table of Events for the Open-label Extension Study Section 6.2, Open-label Extension Treatment Period	Increased the maximum acceptable interval between the last dose of investigational product (IP) in Study CC-93538-EE-001/CC-93538-DDI-001 to the first dose in the OLE study (increased from 14 to 21 days). Subjects will not be allowed to be enrolled in the study if there will be a delay of > 21 days from CC-93538 dosing in Study CC-93538-EE-001 or in Study CC-93538-DDI-001, unless discussed with the Medical Monitor.	Accounting for unavoidable situations that may cause delays in the first dose in OLE (eg. coronavirus disease 2019 restrictions, unavailability of IP supplies, scheduling issues) and for increased flexibility for sites to enroll subjects on this study and receive CC-93538.
Section 3.2.3, Worsening of EoE Symptoms or Lack of Improvement	Removed the requirement to discontinue study treatment for subjects who demonstrate persistent lack of improvement or worsening of EoE symptoms. The text has been updated to state that these subjects should be evaluated to determine if the continuation of study treatment is appropriate.	For clarification purposes.
Section 3.2.4, Planned Database Locks	New section added for planned database locks.	Section added to provide information on the multiple database locks planned throughout the study.
Section 3.3, Study Duration in Subjects	In Japan, subjects may continue in the study until marketing launch is obtained in the country or the Sponsor discontinues the study, whichever comes first. In Japan, the term “this study” in this protocol will automatically be replaced with “post-marketing clinical study” on and after the date of marketing approval.	To incorporate country-specific requirements.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.2, Inclusion Criteria 4)	The definition of female of childbearing potential was updated to include those who have not undergone a bilateral salpingectomy.	For clarification purposes.
Section 4.3, Exclusion Criteria 1) and 4) Section 8.2, Prohibited Concomitant Medications and Procedures	• Added Schatzki's rings and a history of fundoplication as exclusion criteria, and updated nomenclature for eosinophilic gastroenteritis to eosinophilic gastritis and/or duodenitis. • Included JAK inhibitors and phosphodiesterase-4 inhibitors as examples of immunomodulating drugs and as prohibited concomitant medications on study.	For clarification purposes.
Table 3, Table of Events for the Open-label Extension Study	• Included an additional AI Administration Visit for switching to the new IP presentation. • Footnote y added to provide the window for the First AI Administration Visit. • AI Administration Questionnaire updated with additional time points. • Footnote w has been updated to include the time points for the AI Administration Questionnaire collection (as applicable).	• This First AI Administration Visit is being added to expedite the switch to the new AI presentation for subjects whose next scheduled visit is not within 4 weeks of the Protocol Amendment 2 implementation and IP availability at the site. • To denote the time points when the AI Administration Questionnaire is performed.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 3, Table of Events for the Open-label Extension Study Section 6.2, Open-label Extension Treatment Period Section 6.4.2.1, Modified Daily Symptom Diary (mDSD)	• Additional time points added for mDSD collection on the 28 days prior to the Quarterly (Q)4 Visit at the end of Year 2 (Week 104). • Phone call reminders added within a couple days prior to Week 100 and prior to Week 102. • Modified 2 footnotes (l and m) regarding timing for phone call reminders to complete the mDSD and the time points for collection of mDSD at the end of Year 2 for consistency with Table 3.	To continue collection of the mDSD at the end of Year 2 to assess the effects of CC-93538 on clinical response longer term.
Table 3, Table of Events for the Open-label Extension Study	• Additional time points added for serum CC-93538 PK assessment at Q1 and Q3 Visits. • Additional time points added for serum antibodies to CC-93538 assessment at Week 16 and 36 of Year 1 and at the Q1 and Q3 Visits at Year 2 and beyond.	To acquire more data on the drug product presentations.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.2, Open-label Extension Treatment Period	• Discussion with Medical Monitor was added if there is a delay of > 21 days from CC-93538 dosing in Study CC-93538-EE-001 or in Study CC-93538-DDI-001 to enrollment in this study. • Revised and provided additional guidance on the baseline esophagogastroduodenoscopy (EGD) at Day 1. • Time points for the AI Administration Questionnaire were removed from this section for simplification and replaced with reference to the Table of Events.	• Change in the number of days to align with the longest window allowed between dosing in the CC-93538-EE-001/CC-93538-DDI-001 studies. • To provide further clarification on the timing of the baseline EGD procedure in the OLE study. • Overall simplification of text and consolidation of information to the Table of Events.
Section 6.2.2, First Autoinjector Administration Visit	A new section for the First AI Administration Visit and the required evaluations has been added.	To include the assessments that will be conducted in the First AI Administration Visit.
Section 6.4.2.1, Modified Daily Symptom Diary (mDSD)	[redacted]	[redacted]
Section 6.4.2.7, Worsening of EoE Symptoms, EoE Flare, the EoE Flare Assessment Visit, and Lack of Improvement	Removed the requirement to discontinue study treatment for subjects who demonstrate persistent lack of improvement or worsening of EoE symptoms. The text has been updated to state that these subjects should be evaluated to determine if the continuation of study treatment is appropriate.	For clarification purposes.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.9.2, Autoinjector (AI) Administration Questionnaire/PFS Administration Questionnaire	This section has been revised to align with the introduction of the AI presentation and a switch to the AI Administration Questionnaire going forward.	The introduction of a new AI presentation requires an AI Administration Questionnaire to evaluate the successful self-administration of CC-93538 by the AI.
Section 6.6.1, Serum CC-93538 Assessments	Statement added, " in the event dosing occurs during a non-clinic visit day, it is still acceptable to obtain the serum samples".	For clarification purposes.
Section 7.1, Description of Investigational Product(s)	CC-93538 AI information has been provided.	Treatment information for the AI has been added.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2, Treatment Administration and Schedule	• AI implementation details have been added for subjects beginning the OLE study with the AI and for ongoing subjects switching to the AI, with requirements for the first dose of the AI and completion of the AI Administration Questionnaire. Further, requirements for a First AI Administration Visit are noted. • Additionally, text is included to clarify that if IP is not available on site at the time of Protocol Amendment 2 site approval, then subjects should continue receiving the [redacted] weekly SC injection using the [redacted] PFS presentation, until the availability of the new IP (AI) presentation. Subjects who self-administer with the PFS presentation should continue to complete the PFS Administration Questionnaire until the switch to the new AI presentation.	• To provide clarification as to which assessments will be conducted in the First AI Administration Visit. • To provide clarification on which IP presentation should be provided to subjects and the questionnaire that should be completed in the event the IP (AI) is not available on site at the time of Protocol Amendment 2 site approval.
Section 9.7, Safety Analysis	Updated information based on the AI administration has been added.	Updated per changes in Protocol Amendment 2.
Section 9.9.1, Pharmacokinetics, Pharmacodynamics and Exposure-Response	Additional text added to describe how Serum trough concentrations (C_{trough}) of CC-93538 will be summarized for subjects in the OLE Study, CC-93538-EE-002 and subjects transitioning from the Phase 1 Study, CC-93538-DDI-001.	For clarification purposes.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 2		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.6, Adverse Events of Special Interest	Adverse events of special interest (AESIs) will be reported to the electronic data capture and identified by the Sponsor programmatically.	Updates made to include Sponsor capture and review of AESIs in addition to the Investigator.
Section 11.1, Treatment Discontinuation Section 11.2, Study Discontinuation	Clarified that protocol deviation that may impact subject safety is a sufficient reason for permanent discontinuation from CC-93538.	For clarification purposes.

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Multinational, Open-label Extension Study to Evaluate the Long-term 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.

The Phase 3 program will include a multicenter, multinational, randomized, double-blind, placebo-controlled 24-week induction and 24-week maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with eosinophilic esophagitis (EoE; Study CC-93538-EE-001) with a separate, optional Open-label Extension study (OLE; Study CC-93538-EE-002).

Additionally, a Phase 1, open-label, single-sequence study will be employed to evaluate potential disease-mediated drug-drug interactions with selected cytochrome P450 (CYP) substrates and to assess the safety of CC-93538 with or without CYP substrates in adult subjects with active eosinophilic esophagitis receiving CC-93538 (Study CC-93538-DDI-001).

Subjects participating in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will be offered the opportunity to enroll in the OLE Study CC-93538-EE-002. Globally, the Phase 3 studies will include subjects who have had an inadequate response to corticosteroid therapy or are intolerant to corticosteroid therapy as well as subjects who are naïve or have had an adequate response to corticosteroid therapy. 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 (as defined in Protocol CC-93538-EE-001) will be enrolled in the studies.

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 CC-93538 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 who were 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 in Study RPC02-201 (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, and the OLE study will continue to investigate the long-term safety profile of CC-93538 in adult and adolescent subjects with EoE.

Objectives (Primary and Secondary)

Primary Objective

- To evaluate the long-term safety and tolerability of CC-93538 in subjects with EoE

Secondary Objective

- To characterize the immunogenicity profile of CC-93538 following long-term treatment

See Section 2 for a complete list of study objectives, including all exploratory objectives.

Study Endpoints (Primary and Secondary)

Primary Endpoint

- Safety and tolerability of long-term treatment with CC-93538 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, and physical examination abnormalities.

Secondary Endpoint

- Immunogenicity of CC-93538 assessed through the incidence of anti-drug antibodies to CC-93538 including neutralizing antibodies when warranted.

See Section 2 for a complete list of study endpoints including all exploratory endpoints.

Study Design

The OLE study is a Phase 3, open-label, uncontrolled study to explore the long-term effects of treatment with CC-93538 360 mg SC once weekly in adult and adolescent subjects with EoE who had previously participated in the Induction and Maintenance Study, CC-93538-EE-001. Approximately, 259 of the 399 subjects aged 12 to 75 years and weighing ≥ 40 kg at the time of screening and initially randomized in Study CC-93538-EE-001 are expected to participate in the OLE study assuming an overall drop-out rate of 35% in Study CC-93538-EE-001. Of these, approximately 239 adults and approximately [redacted] adolescents aged 12 to 17 years at the time of screening in Study CC-93538-EE-001 are anticipated to enroll.

In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled. Subjects participating in Study CC-93538-EE-001 who do not qualify for entry into the Maintenance Phase, including subjects who experience a severe EoE flare requiring endoscopic intervention and/or rescue therapy during the Induction Phase or subjects who complete Week 48 of the Maintenance

Phase may be eligible. In addition, subjects must have demonstrated sufficient investigational product (IP) compliance and must not have been permanently discontinued from IP in Study CC-93538-EE-001 and, in the opinion of the Investigator, must have experienced no clinically significant AEs related to IP that would preclude further dosing. Additionally, approximately [redacted] subjects aged 18 to 75 years initially enrolled in Study CC-93538-DDI-001 and who completed Period 2 of Study CC-93538-DDI-001 will be offered an opportunity to enroll in the OLE Study CC-93538-EE-002.

During the Open-label Treatment Period, all subjects will be administered CC-93538 at a dose of 360 mg SC once weekly. 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 monitor for immunogenicity), concomitant medications, AE assessments, and relevant biomarker measurements in tissue biopsy and blood samples will be performed in accordance with the Table of Events (Table 3).

Subjects may discontinue from the study at any time. Furthermore, subjects who demonstrate a persistent lack of improvement or worsening of EoE symptoms during the course of the study should be discontinued. Subjects who discontinue the study at or after 2 years of participation (ie, the Quarterly 4 Visit in Year 2 [Week 104]) will complete an End of Treatment Visit within 2 weeks after the final dose of CC-93538 and 2 Safety Follow-up Visits at 8 and 16 weeks, respectively, after the final dose of CC-93538 for the assessment of safety and clinical status. Subjects who discontinue the study before Week 104 will complete an Early Termination Visit.

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:

- Male and female adult and adolescent subjects with EoE aged 12 to 75 years (inclusive, at the time of screening in Study CC-93538-EE-001) who have participated in the core Phase 3 Induction and Maintenance Study, CC-93538-EE-001. Subjects who have completed Study CC-93538-EE-001 and subjects who do not meet entry criteria to the Maintenance Phase in Study CC-93538-EE-001, including subjects who have a severe EoE flare requiring endoscopic intervention and/or rescue therapy during Study CC-93538-EE-001 may be eligible to participate in the OLE study.
- Male and female adult subjects with EoE aged 18 to 75 years (inclusive, at the time of screening in Study CC-93538-DDI-001) who have participated in Study CC-93538-DDI-001. Subjects who have completed Week 18/End of Study Treatment Visit of Period 2 may be eligible to participate in the OLE study.

Note: In Study CC-93538-EE-001, 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 and Ethics Committee 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.

Length of Study

Subjects will begin participation in the OLE study on OLE Day 1 and following completion of all baseline assessments (including those obtained from either the Study CC-93538-EE-001 Induction Phase Week 24 or Maintenance Phase Week 48 Visit, as applicable, or the Study CC-93538-DDI-001 Week 18/End of Treatment Visit, as applicable) will receive the first OLE dose of CC-93538. Subjects will receive weekly doses of CC-93538 during the Open-label Treatment Period for a minimum of 2 years or as long as they are participating in the study, will complete an End of Treatment Visit within 2 weeks after the final dose, and will complete the 2 Safety Follow-up Visits at 8 and 16 weeks after the final dose. Subjects may participate in the Open-label Treatment Period as early as 24 weeks after beginning enrollment in the Induction Phase of the core Phase 3 Study CC-93538-EE-001 or as late as following Week 48 of the core study.

Additionally, subjects who complete Period 2 in Study CC-93538-DDI-001 may be eligible to participate in the Open-label Extension (OLE) study.

Individual subject participation in the OLE study will be for a minimum of 2 years but may extend for a longer duration. Where applicable per local or national regulations, subjects may continue in the study until marketing approval (or marketing launch in Japan) is obtained in the country or the Sponsor discontinues the study, whichever comes first. In Japan, the term “this study” in this protocol will automatically be replaced with “post-marketing clinical study” on and after the date of marketing approval.

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 (the Final 16-week Safety Follow-up Visit), or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

All subjects in the OLE study will receive CC-93538 360 mg SC once weekly. The dosing regimen for the OLE may be revised after results from the Induction and Maintenance Study, CC-93538-EE-001, are available and the optimal dosing regimen is confirmed. The CC-93538 360 mg SC dose will be administered by a [redacted] provided in a [redacted] autoinjector (AI) at a concentration of [redacted] mg/mL.

The original protocol required CC-93538 weekly SC dosing to be administered by [redacted] of [redacted] mL each at a concentration of [redacted] mg/mL. With the implementation of Protocol Amendment 1 (dated 10 May 2022), all subjects in the study and any subjects newly entering the study began receiving a [redacted] pre-filled syringe (PFS) presentation. As

of Protocol Amendment 2, all subjects currently in the study and any new subjects entering the study will start receiving a [redacted] AI once Protocol Amendment 2 is implemented, informed consent is obtained, and IP is available on-site. For currently enrolled subjects, a switch to the new AI presentation will occur at the next regularly scheduled study visit or at a First AI Administration Visit in case the next scheduled protocol visit is not within 4 weeks of Protocol Amendment 2 site approval, once the IP is available on site. This First AI Administration Visit is added to expedite the switch to the new AI presentation.

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) including assessment of neutralizing antibodies if warranted

For additional details about key safety assessments, please refer to the Table of Events (Table 3).

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 3).

Statistical Methods

Analysis Population

The analysis population that will be used in the statistical analysis is the OLE population which consists of all subjects receiving at least one dose of IP during the OLE.

The OLE population consists of subjects who are originally randomized to the 3 arms in CC-93538-EE-001: placebo in both the Induction Phase and the Maintenance Phase, CC-93538 360 mg SC once weekly in the Induction Phase and CC-93538 360 mg SC once every other week in the Maintenance Phase, and CC-93538 360 mg SC once weekly in both the Induction Phase and the Maintenance Phase. These subjects can enter the OLE either: after completing Week 24 of the Induction Phase or after completing Week 48 of the Maintenance Phase.

Subjects will be analyzed based on the treatments received during the core Induction and Maintenance Study, CC-93538-EE-001, defined as:

- For subjects who enter OLE after completing Week 24 of the Induction Phase, based on the treatment(s) the subjects received in CC-93538-EE-001 before they enter OLE, there are 2 different cohorts:
  - Cohort A: Subjects receiving placebo in the Induction Phase but did not enter the Maintenance Phase (denoted as "PBO/-")
  - Cohort B: Subjects receiving CC-93538 360 mg SC once weekly in the Induction Phase but did not enter the Maintenance Phase (denoted as "360 mg QW/-")
- For subjects who enter after completing Week 48 of the Maintenance Phase, based on the treatment(s) the subjects received in CC-93538-EE-001 before they entered OLE, there are 3 different cohorts:
  - Cohort C: Subjects receiving placebo in both the Induction Phase and the Maintenance Phase (denoted as "PBO/PBO")
  - Cohort D: Subjects receiving CC-93538 360 mg SC once weekly in the Induction Phase and CC-93538 360 mg SC once every other week in the Maintenance Phase (denoted as "360 mg QW/360 mg Q2W")
  - Cohort E: Subjects receiving CC-93538 360 mg SC once weekly in both the Induction Phase and the Maintenance Phase (denoted as "360 mg QW/360 mg QW").

The OLE population will also consist of subjects who completed Period 2 of the Phase 1 open-label drug-drug interaction study and met the eligibility criteria for Study CC-93538-EE-002.

Safety Analysis (Primary Endpoint):

The assessment 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. All safety endpoints will be summarized by cohort (subjects from Study CC-93538-DDI-001 will be summarized separately) using descriptive statistics. No statistical hypothesis testing will be performed on any safety results.

Overall safety and tolerability will be summarized for each drug presentation: the 360-mg dose of CC-93538 administered by [redacted] at a concentration of [redacted] mg/mL CC-93538, or by [redacted] at a concentration of [redacted] mg/mL CC-93538 administered with the PFS device, or by [redacted] at a concentration of [redacted] mg/mL CC-93538 administered with the AI device utilizing descriptive statistics.

Efficacy Analysis (Exploratory Endpoints):

Efficacy analyses will be descriptive for each of the Study CC-93538-EE-001 pre-defined cohorts and will include the exploratory endpoints except for pharmacokinetic (PK) and biomarker endpoints. The analyses of the PK endpoints and the immunogenicity secondary endpoint will be described separately in the PK Analysis Plan. The biomarker endpoints and the related analyses will be described separately in the Biomarker Analysis Plan. Subjects from Study CC-93538-DDI-001 will be summarized separately.

For continuous endpoints (ie, mean change over time), descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum will be provided by cohort at each time point. In addition, the 95% confidence interval (CI) for the mean estimates will be presented for the following endpoints: [redacted] the mean change over time in the endoscopic features of EoE as measured by the EREFS from baseline, the mean change over time in the histologic features of EoE as measured by the EoE histology scoring system (EoEHSS) from baseline, and the mean change over time in mDSD composite score from baseline.

For categorical endpoints (ie, proportions), descriptive statistics including counts and percentages will be provided by cohort at each time point. In addition, the 95% CI for the mean estimates will be presented for the following endpoints: the proportion of subjects with histologic response defined as a peak esophageal eosinophil count ≤ 6/high-power field (hpf) and the proportion of subjects with histologic response defined as a peak esophageal eosinophil count < 15/hpf.

For subjects who enter the OLE study with clinical, histologic, or clinical and histologic response after completing the Maintenance Phase in Study CC-93538-EE-001, the durability of response will be reported as proportion of subjects who continue having their clinical, histologic, or clinical and histologic response at each time point, and will be reported by subjects' original treatment in the Maintenance Phase.

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 the duration of DMC implementation during the OLE study, 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 to10.88) 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 biomarkers, 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 (PPIs) 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 included 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 dispersible 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 Food and Drug Administration, 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 co-signaling through a shared receptor component, decreasing type 2 inflammation. Weekly treatment with dupilumab for 24 weeks in the pivotal study demonstrated histologic remission in approximately 60% of patients and improvements in symptomatic scores (Dellon, 2022; Straumann, 2022). Dupilumab's approval marks the introduction of 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 6-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. [redacted]

[redacted] of CC-93538 is mutated at [redacted] 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). [redacted] 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 subcutaneous (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 (C_{max}), increased in a dose-dependent manner and were similar in healthy subjects and subjects with asthma. The median time to the observed maximum concentration (t_{max}) 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 ($t_{½}$) 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 protocol finalization.

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 t_{max} of approximately [redacted] hours (approximately [redacted] days). CC-93538 showed a long elimination $t_{½}$ of approximately [redacted] to [redacted] hours (approximately [redacted] to [redacted] days) and a small volume of distribution of approximately [redacted] L. The SC bioavailability of CC-93538 was estimated to be approximately [redacted]. Anti-CC-93538 antibodies were detected in [redacted] of 24 subjects. Of those [redacted] subjects, [redacted] had pre-existing antibodies and there was no indication that the response increased after treatment. Thus, in [redacted] out of 24 ([redacted]) subjects, treatment-induced ADAs were detected. Of those [redacted] subjects for which treatment-induced ADAs were detected, the ADA titers were low for [redacted] of them. However, [redacted] subject had titers that were higher than the others ([redacted]). 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 [redacted]. 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. Following SC administration of either 180 mg or 360 mg, the absorption of CC-93538 was slow with a median t_{max} of 5.4 to 7.5 days. A long elimination $t_{½}$ 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 C_{max} 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 [redacted]. 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.

During the CC-93538-CP-002 study, 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 bio-comparable. The nonparametric analysis of serum CC-93538 t_{max} using Hodges-Lehmann showed the median difference between these treatments was not statistically significant.

The two concentrations 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. The two concentrations had similar PK profiles and were biocomparable. 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 patient. 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 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 1 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 1 event of moderate TEAE (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 [1 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.

For subjects that received active treatment in the DB Treatment Period, long-term treatment (52 weeks) with CC-93538 360 mg in the OLE showed sustained improvements in esophageal eosinophil count and other inflammatory features of EoE. 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 (C_{trough}) values for subjects in the 360 mg dose group were approximately 2-fold of mean CC-93538 C_{trough} 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 C_{trough} 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 $t_{½}$.

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 (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event 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. The Phase 2 data results therefore support the continued development of CC-93538 as a novel treatment for EoE. The single pivotal Phase 3 Study, CC-93538-EE-001, is designed to

confirm and extend the findings obtained from the positive Phase 2 study with CC-93538, and the OLE Study, CC-93538-EE-002, will continue to investigate the long-term safety profile and durability of response of CC-93538 in adult and adolescent subjects with EoE.

Study CC-93538-DDI-001 is a Phase 1, open-label, single-sequence study designed to evaluate potential disease-mediated drug-drug interaction with selected cytochrome P450 substrates and to evaluate the safety of CC-93538 with or without CYP substrates in adult subjects with active eosinophilic esophagitis receiving CC-93538. Subjects participating in the parent Study CC-93538-DDI-001 will be offered the opportunity to transition to OLE Study CC-93538-EE-002, allowing for continued access to 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 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) provides 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 assessment, 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 [redacted] permanently discontinuing IP ([redacted] and Section 7.2.5), and [redacted]. In order 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 supplementary safety report forms, which will allow the Sponsor to further evaluate these events.

While the global 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 current OLE Study CC-93538-EE-002 is an open-label, uncontrolled study design to evaluate the longer-term safety profile as well as durability of response of administration of a [redacted] level of CC-93538. The study will enroll subjects who participated in and complete the Induction and Maintenance Study, CC-93538-EE-001, as well as subjects who do not qualify for entry into the Maintenance Phase of the study. Subjects who experience a severe EoE flare requiring endoscopic intervention and/or rescue therapy during the Induction or Maintenance Phase and complete the Induction or Maintenance Phase, respectively will also have the opportunity to participate. In addition, subjects participating in the parent Study CC-93538-DDI-001 who complete assessments in Period 2 through the End of Treatment Visit (Week 18) and who meet all eligible criteria will be offered the opportunity to transition to the OLE Study CC-93538-EE-002. See Section 3.2 for details. Rationale for the CC-93538 dose selection is discussed in Section 1.3.3.

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.

1.3.3 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 [redacted] mg dose once weekly and the [redacted] mg dose once every other week is very similar. The fluctuation between C_{max} and C_{trough} is larger in the [redacted] mg dose administered every other week compared to the [redacted] 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 [redacted] mg SC once weekly is not expected to provide additional therapeutic benefit, as trough concentrations observed in the [redacted] 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 [redacted] 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 [redacted] mg with the IV loading dose. These subjects also showed a mean C_{trough} 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 [redacted] mg once weekly regimen has shown a relevant histological but not clinical effect in the same study, and (3) the CC-93538 [redacted] mg once every other week regimen is not expected to achieve average concentrations different than the [redacted] mg once weekly regimen, the [redacted] mg once weekly dose was selected for the Induction Phase and the [redacted] mg once weekly and [redacted] mg once every other week doses were selected for the Maintenance Phase in Study CC-93538-EE-001. Furthermore, population PK analysis indicated that age is not a significant covariate for CC-93538 PK parameters suggesting adolescents with a body weight of at least 40 kg will display similar CC-93538 exposures to adults.

For the OLE Study, CC-93538-EE-002, all subjects will receive CC-93538 360 mg SC once weekly. The dosing regimen for the OLE (ie, a change to an every other week dosing regimen) may be revised after results from the Induction and Maintenance Study, CC-93538-EE-001, are available and the optimal dosing regimen is confirmed. A PFS presentation of [redacted] administered as a [redacted] instead of [redacted] of [redacted] each for the full dose of 360 mg was introduced in Protocol Amendment 1. In Protocol Amendment 2, the CC-93538 360 mg SC dose will be administered by a [redacted] provided in a [redacted] AI. The Study CC-93538-CP-002 results demonstrated that a [redacted] of [redacted] mg CC-93538, when administered as either a [redacted] at a concentration of [redacted] mg/mL or [redacted] at a higher concentration of [redacted] mg/mL, were both safe and well tolerated in healthy adults. The two formulations had similar PK profiles and were biocomparable. No differences were observed in safety, tolerability, or immunogenicity. The ADA profiles were similar between subjects receiving [redacted] mg/mL and [redacted] mg/mL. There was no indication that the ADA response impacted the safety and PK of CC-93538 following [redacted] SC dose of [redacted] mg using either [redacted]

mg/mL or [redacted] mg/mL. ADAs were not associated with differences in safety, tolerability, or PK. Overall, the results of Study CC-93538-CP-002 support the introduction of the [redacted] PFS presentation administered as a [redacted] in Protocol Amendment 1. Further, Study IM042-003 Part 1 preliminary results demonstrated that the [redacted]. The two presentations of CC-93538, given by PFS or AI, administered as a [redacted] dose of [redacted] mg, were well tolerated and had an acceptable safety profile in healthy adults. [redacted] The results of Study IM042-003 support the introduction of the [redacted] AI presentation in Protocol Amendment 2.

1.3.4 Rationale for Pharmacodynamics and Potential Predictive Biomarkers

EoE is characterized by eosinophil-predominant inflammation and additional pathogenesis including esophageal tissue remodeling and over-expression of cytokines. Biomarkers that are thought to play a role in EoE disease pathogenesis, such as circulating periostin, eotaxin-3, and IL-13, and markers of epithelial mesenchymal transition (EMT), eotaxin-3, and periostin in esophageal biopsy tissue as well as Endolumenal Functional Lumen Imaging Probe (EndoFLIP™) assessment will be evaluated for potential diagnostic or prognostic importance.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is: • To evaluate the long-term safety and tolerability of CC-93538 in subjects with eosinophilic esophagitis (EoE)
Secondary Objective
The secondary objective is: • To characterize the immunogenicity profile of CC-93538 following long-term treatment
Exploratory Objectives
The exploratory objectives are: • To estimate the long-term efficacy of CC-93538 in reducing dysphagia symptoms and esophageal eosinophil counts • To estimate the long-term efficacy of CC-93538 in improving the endoscopic and histologic features of EoE • To assess trough concentrations of CC-93538 in subjects with EoE • To conduct a population pharmacokinetic (PK) analysis to characterize the population PK of CC-93538 and to evaluate the exposure-response or pharmacodynamic relationships between dose (or concentration) and efficacy, safety, and biomarkers • To estimate improvements in subject and clinician rating of disease severity and subject impression of change in EoE symptoms • To estimate improvements in patient-reported outcome measures of EoE symptoms • To estimate improvements in additional EoE symptoms reported by subjects • To estimate health-related quality of life and work productivity • To estimate the frequency of successful self-administration of CC-93538 by PFS under supervised (in-clinic) and unsupervised (at home) conditions • To estimate the frequency of successful self-administration of CC-93538 by AI under supervised (in-clinic) and unsupervised (at home) conditions • To estimate the utilization of health care resources • To explore the clinical profile of CC-93538 as a function of EoE biomarker expression • To explore the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serologic status on subjects receiving CC-93538, on EoE, and to support health authority requests • To estimate improvements in esophageal distensibility in subjects participating in the EndoFLIP sub-study, if applicable

Table 2: Study Endpoints

For OLE study endpoints, OLE baseline will be used. In the Statistical Analysis Plan, baseline comparisons will be defined and additional subgroup analyses will be described.

Endpoint	Name	Description	Timeframe
Primary	Safety and Tolerability	Safety and tolerability of long-term treatment with CC-93538 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, and physical examination abnormalities	Baseline through Safety Follow-up Visit
Secondary	Immuno-genicity	Immunogenicity of CC-93538 assessed through the incidence of anti-drug antibodies, including neutralizing antibodies when warranted	Baseline through Safety Follow-up Visit
Exploratory	Change in DD Clinical Response	[redacted]	Baseline through OLE Week 24, Week 48, and Week 104
	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)	OLE Weeks 24, 48, and 104
	Durability of Histologic Response (≤ 6/hpf)	The proportion of subjects previously treated with CC-93538 in CC-93538-EE-001 and with peak esophageal eosinophil count ≤ 6/hpf at OLE baseline who continue to have a peak esophageal eosinophil count ≤ 6/hpf	OLE Weeks 24, 48, and 104
	Eosinophil Histologic Response (<15/hpf)	The proportion of subjects with eosinophilic histologic response defined as a peak esophageal eosinophil count < 15/hpf	OLE Weeks 24, 48, and 104
	EREFS	The mean change over time in the endoscopic features of eosinophilic esophagitis (EoE) as measured by the EoE Endoscopic Reference Score (EREFS) from baseline	OLE Weeks 24, 48 and 104
	EoEHSS	The mean change over time in the histologic features of EoE as measured by the EoE histology scoring system (EoEHSS) from baseline	OLE Weeks 24, 48, and 104
	DD Clinical Responder Definition	The proportion of subjects with a ≥ 50% decrease in dysphagia days (DD) from baseline	Baseline through OLE Week 24, Week 48, and Week 104
	Clinical and Histologic Response Composite	The proportion of subjects with histologic response defined as a peak esophageal eosinophil count < 15/hpf and dysphagia symptom response defined as the proportion of subjects with ≥ 50% decrease in dysphagia days (DD) from baseline	OLE Weeks 24, 48, and 104

Table 2: Study Endpoints

For OLE study endpoints, OLE baseline will be used. In the Statistical Analysis Plan, baseline comparisons will be defined and additional subgroup analyses will be described.

Endpoint	Name	Description	Timeframe
	Clinical and Histologic Response Composite	The proportion of subjects with histologic response defined as a peak esophageal eosinophil count ≤ 6/hpf and dysphagia symptom response defined as the proportion of subjects with ≥ 50% decrease in dysphagia days (DD) from baseline	OLE Weeks 24, 48, and 104
	Durability of Response	For subjects entering the OLE with clinical, histologic, or clinical and histologic response after completing the Maintenance Phase in Study CC-93538-EE-001, the proportion of subjects with response (clinical, histologic, or clinical and histologic)	Baseline through OLE Week 24, at Week 48, and Week 104 for clinical; Weeks 24, 48, and 104 for histologic
	mDSD Composite Score	The mean change over time in modified Daily Symptom Diary (mDSD) composite score from baseline	Baseline through OLE Week 24, Week 48, and Week 104
	Pharmaco-kinetics	Measurements of trough concentrations of CC-93538 in subjects with EoE	Through OLE Treatment Period
	Population Pharmaco-kinetics	CC-93538 population pharmacokinetic parameters and covariates	Through Safety Follow-up Visit
	Exposure-response, Pharmaco-dynamic Relationship	Exposure-response or pharmacodynamic relationships between dose (or concentration) and efficacy, safety, and biomarkers	Through Safety Follow-up Visit
	PGI-S	The proportion of subjects demonstrating improvements in Patient Global Impression of Severity (PGI-S) rating of EoE symptoms from baseline	OLE Weeks 24, 48, and beyond
	CGI-S	The proportion of subjects demonstrating improvements in Clinician Global Impression of Severity (CGI-S) rating of EoE symptoms from baseline	OLE Weeks 24, 48, and beyond
	GIC-EoE	The proportion of subjects demonstrating improvements in Global Impression of Change in EoE symptoms (GIC-EoE) from baseline	OLE Weeks 24 and 48
	EEsAI	The mean change in dysphagia clinical symptom frequency and severity as assessed by the Eosinophilic Esophagitis Activity Index (EEsAI) total score from baseline and proportion of subjects that meet various response thresholds (including but not limited to EEsAI score ≤ 20)	OLE Weeks 24, 48, and beyond

Table 2: Study Endpoints

For OLE study endpoints, OLE baseline will be used. In the Statistical Analysis Plan, baseline comparisons will be defined and additional subgroup analyses will be described.

Endpoint	Name	Description	Timeframe
	PEESS	The mean change in adolescent subjects' EoE symptoms using the Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS) total metric score from baseline (adolescent subjects only)	OLE Weeks 24, 48, and beyond
	Additional EoE Symptoms	Additional EoE symptoms reported on the modified Daily Symptom Diary (mDSD) evaluated by the distribution of subject responses regarding solid food avoidance, percentage of days solid food avoidance was due to EoE symptoms, percentage of days pain was associated with swallowing food, and the mean change in pain rating from baseline	Baseline through OLE Week 24, Week 48, and Week 104
	Health-related Quality of Life	Changes in health-related quality of life (HRQoL) assessed by the 12-Item Short Form Health Survey (SF-12v2) in adult subjects and the10-Item Short Form Health Survey for Children (SF-10) in adolescent subjects from baseline	OLE Weeks 24 and 48
	Work Productivity	Changes in Work Productivity as assessed by the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) from baseline (adult subjects only)	OLE Weeks 24 and 48
	PFS Administration	The proportion of subjects who successfully administer CC-93538 by the [redacted] pre-filled syringe (PFS), as assessed by the PFS Administration Questionnaire	Through OLE Week 48
	AI Administration	The proportion of subjects who successfully administer CC-93538 by the [redacted] autoinjector (AI), as assessed by the AI Administration Questionnaire	Through OLE Year 2
	Health Care Resource Utilization	The proportion of subjects with complications of EoE including but not limited to emergency department visits for food impaction, use of rescue therapy, or esophageal dilations	Through Safety Follow-up Visit
	Biomarkers	CC-93538 treatment response as a function of baseline (as collected in Study CC-93538-EE-001) interleukin-13 (IL-13) single nucleotide polymorphism (SNP) characterization	OLE Weeks 24 and 48
	Biomarkers	CC-93538 treatment response as a function of baseline and change from baseline in circulating biomarkers (including but not limited to periostin, eotaxin-3, and IL-13)	OLE Weeks 24 and 48
	Biomarkers	CC-93538 treatment response as a function of baseline and change from baseline in esophageal tissue biomarkers (including but not limited to markers of epithelial mesenchymal transition [EMT], periostin, and eotaxin-3)	OLE Weeks 24, 48, and 104

Table 2: Study Endpoints

For OLE study endpoints, OLE baseline will be used. In the Statistical Analysis Plan, baseline comparisons will be defined and additional subgroup analyses will be described.

Endpoint	Name	Description	Timeframe
	Biomarkers	Exploratory measurements of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serology (anti-SARS-CoV-2 total or immunoglobulin G [IgG]) from serum samples collected at Week 48 and annually thereafter and the potential association between these measurements and selected endpoints related to safety, efficacy, and/or biomarkers	OLE Week 48 and annually thereafter
	Biomarkers	The mean change in esophageal distensibility as measured by EndoFLIP from baseline, if applicable	OLE Weeks 24, 48, and 104

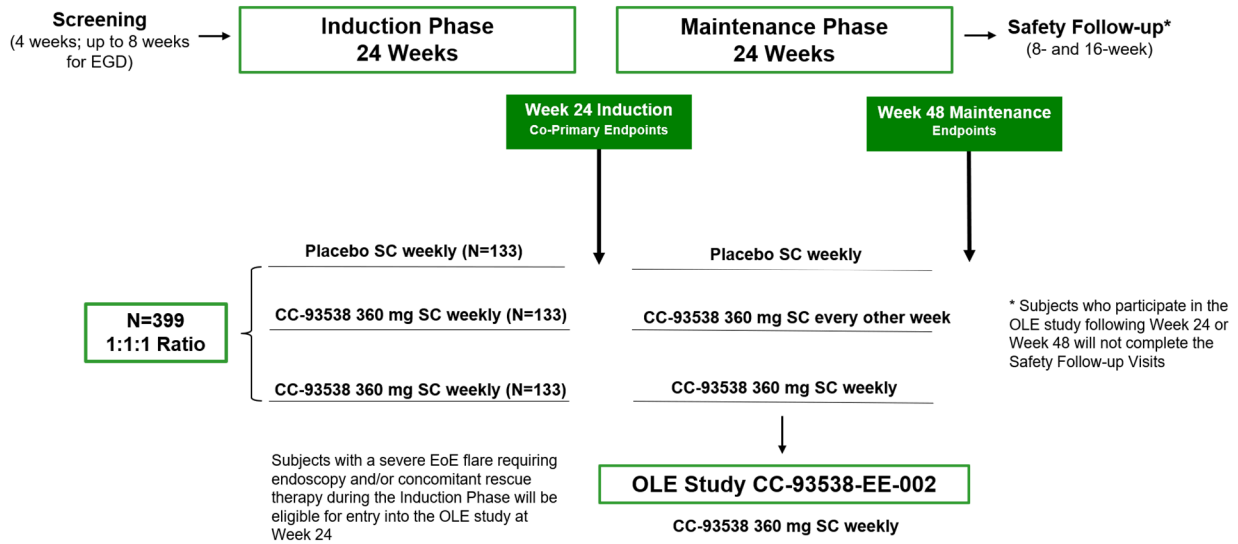
3 OVERALL STUDY DESIGN

3.1 Phase 3 Program 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).

An overview of the overall Phase 3 program 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.

3.2 Open-label Extension Study Design

The OLE study is a Phase 3, open-label, uncontrolled study to explore the long-term effects of treatment with CC-93538 360 mg SC once weekly in adult and adolescent subjects with EoE who had previously participated in the core Induction and Maintenance Study, CC-93538-EE-001. Approximately 259 subjects of the 399 subjects initially randomized in the core study, Study CC-93538-EE-001, are expected to participate in the OLE study assuming an overall drop-out rate of 35% in Study CC-93538-EE-001. Along with approximately 239 adult subjects, approximately [redacted] adolescent subjects aged 12 to 17 years (at the time of screening in Study CC-93538-EE-001) are expected to participate in the OLE study from the approximately [redacted] subjects who are expected to enroll in the Induction Phase of the core study. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled. Globally, subjects aged 12 to 75 years of age with a body weight of ≥ 40 kg (at the time of screening in Study CC-93538-EE-001) who have a diagnosis of EoE and who meet one of the following criteria with respect to participation in Study CC-93538-EE-001 will be given the opportunity to participate in the OLE study.

- Subjects who do not qualify for entry into the Maintenance Phase including:
  - Subjects who experience a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy during the Induction Phase will be eligible for the OLE after completion of Week 24 of the Induction Phase
- Subjects who complete Week 48 of the Maintenance Phase including:
  - Subjects who experience a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy during the Maintenance Phase will be eligible for the OLE after completion of Week 48 of the Maintenance Phase.

In addition, approximately [redacted] adult subjects aged 18 to 75 years old (inclusive, at the time of screening) will be enrolled in Study CC-93538-DDI-001, and up to [redacted] of these subjects who completed Period 2 in Study CC-93538-DDI-001 will also be given the opportunity to participate in the OLE study.

Refer to the Worsening of Symptoms, EoE flare, and the EoE Flare Assessment Visit Section and the Entry to Maintenance Phase Section of the CC-93538-EE-001 protocol for more details. In addition, in order to participate in the OLE, subjects must not have been permanently discontinued from IP and must have demonstrated sufficient IP compliance in Study CC-93538-EE-001 and, in the opinion of the Investigator, must have experienced no clinically significant adverse events (AEs) related to IP that would preclude further dosing. The OLE study includes an Open-label Treatment Period, an End of Treatment Visit at or after a minimum of 2 years of participation, and 2 Safety Follow-up Visits as presented in Figure 2.

Figure 2: Open-label Extension Study Schema

This study will empanel a Steering Committee (Section 9.9.4) and safety monitoring will be performed by an external, independent Data Monitoring Committee (Section 9.9.3) in addition to routine internal review by the Safety Management Team (Section 9.9.2).

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.

3.2.1 Open-label Treatment Period

Because subjects eligible for the OLE study have all participated in Study CC-93538-EE-001 or Study CC-93538-DDI-001, there will be no Screening Visit, and baseline assessments will be obtained from either the Induction Phase Week 24 Visit or the Maintenance Phase Week 48 Visit in Study CC-93538-EE-001 assessments, as applicable. For subjects who are entering the OLE after completion of Study CC-93538-DDI-001, most baseline assessments will be obtained in Study CC-93538-DDI-001 and a few additional assessments will be collected on OLE Day 1. Additional OLE baseline assessments not performed at the final Induction Phase (Week 24) or final Maintenance Phase (Week 48) Visits of Study CC-93538-EE-001 or Week 18/End of Treatment Visit of Study CC-93538-DDI-001 should be conducted at the OLE Day 1 Visit in accordance with the Table of Events (Table 3); it is anticipated that this should occur for most subjects on the same day. Subjects will not be allowed to enroll in the OLE study and receive CC-93538 on OLE Day 1 if there will be a delay of > 21 days from dosing in Study CC-93538-EE-001 or Study CC-93538-DDI-001 unless discussed with the Medical Monitor (refer to Section 6.2). The 2 Safety Follow-up Visits in Study CC-93538-EE-001/Study CC-93538-DDI-001 are not required for subjects enrolling in the OLE study.

The esophagogastroduodenoscopy (EGD) procedure should not be repeated at the OLE Day 1 Visit, as long as this assessment was conducted at the final Induction or Maintenance Phase Visit

of Study CC-93538-EE-001 or prior to the End of Treatment Visit in Study CC-93538-DDI-001 (refer to Section 6.2).

During the Open-label Treatment Period, all subjects will be administered CC-93538 at a dose of 360 mg SC once weekly for as long as they are participating in the study or until the Investigator decides to withdraw the subject or the Sponsor decides to terminate the study.

Clinical laboratory tests, vital signs, physical examinations (including height and weight), pregnancy tests (female of childbearing potential [FCBP] subjects only), EGD, clinical symptom assessment, subject-reported outcomes, serum CC-93538 PK concentrations, serum antibodies to CC-93538 (to monitor for immunogenicity), concomitant medications, AE/SAE assessments, and relevant biomarker measurements in tissue biopsy and blood samples will be performed in accordance with the Table of Events (Table 3).

3.2.2 End of Treatment and Safety Follow-up Visit

The OLE Treatment Period is a minimum of 2 years. While the duration may continue longer as detailed in Section 3.3, the end of the Treatment Period will be individualized for each subject. Subjects may discontinue from the study at any time. Subjects who discontinue the study at or after 2 years of participation (ie, the Quarterly 4 Visit in Year 2 [Week 104]) will complete an End of Treatment (EoT) Visit (Section 6.2.4) within 2 weeks after their final dose of CC-93538 and an Interim 8-week and a Final 16-week Safety Follow-up Visit (Section 6.3.1) at 8 weeks and 16 weeks, respectively, after the final dose of CC-93538 for the assessment of safety and clinical status. End of Treatment and Safety Follow-up assessments should be performed in accordance with the Table of Events (Table 3). Subjects who discontinue the study before Week 104 will instead complete an Early Termination (ET) Visit.

3.2.3 Worsening of EoE Symptoms or Lack of Improvement

Subjects with a worsening of EoE symptoms during the study will be required to complete the EoE Flare Assessment Visit per the Table of Events (Table 3). 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 Section 6.4.2.7 and Section 6.2.3 for the protocol definition of EoE flare and EoE Flare Assessment Visit details, respectively.

During the course of the study, subjects who demonstrate a persistent lack of improvement or worsening of EoE symptoms should be evaluated if continuation of study treatment is appropriate. While subjects will have the opportunity to continue participation in the OLE with use of rescue therapy as needed, based on clinical judgment, the Investigator should discontinue any subject in which study participation no longer is in the best interest of the subject. Subjects who are discontinued from the OLE study will be asked to complete an ET/EoT Visit (Section 6.2.4) and the 2 Safety Follow-up Visits (Section 6.3.1).

3.2.4 Planned Database Locks

There will be multiple planned database locks occurring at different time points of the study as follows:

- The first planned lock will occur in conjunction with the primary lock of one of the parent studies, CC-93538-EE-001, to support the Biologics License Application (BLA) submission. Preliminary findings of the primary and secondary endpoints available up to the data cutoff date will be summarized in a clinical study report (CSR). The safety data collected up to the data cutoff date will also be integrated with other studies to create the integrated summary of safety.
- The second planned database lock will occur approximately when all the subjects in the parent Study CC-93538-EE-001 complete (or discontinue) the safety follow-up period, or approximately 4 months after the first lock. The purpose of the second lock is to support the 4 month safety update during the regulatory review process.
- The last planned lock is also the final database lock of the study. The triggering timing is when all the subjects complete the safety follow-up period or discontinue from the study prematurely.

Additional ad hoc database locks may be considered upon the request of regulatory agencies.

3.3 Study Duration for Subjects

Subjects will begin participation in the OLE study on OLE Day 1 and following completion of all baseline assessments (including those obtained from either the Induction Phase Week 24 or the Maintenance Phase Week 48 Visit in Study CC-93538-EE-001, as applicable) will receive the first OLE dose of CC-93538. Subjects will receive weekly doses of CC-93538 during the Open-label Treatment Period for a minimum duration of 2 years and will complete an EoT Visit within 2 weeks after the final dose and an Interim 8-week Safety Follow-up Visit and a Final 16-week Safety Follow-up Visit at 8 and 16 weeks, respectively, after the final dose. Subjects may participate in the Open-label Treatment Period as early as completion of Week 24 of the Induction Phase of Study CC-93538-EE-001 or as late as following Week 48 of Study CC-93538-EE-001.

Subjects from Study CC-93538-DDI-001 will be offered an opportunity to enroll in the OLE Study CC-93538-EE-002 following completion of assessments in Period 2 through Week 18/End of Treatment Visit.

Individual subject participation in the OLE study will be for a minimum of 2 years but may extend for a longer duration. Where applicable per local or national regulations, subjects may continue in the study until marketing approval (or marketing launch in Japan) is obtained in the country or the Sponsor discontinues the study, whichever comes first.

Subjects may continue participation as long as they tolerate treatment and are receiving benefit from participation in the study. Participation may continue until the subject decides to withdraw from the study, the subject meets any of the discontinuation criteria, the Investigator decides to withdraw the subject from the study, or the Sponsor decides to terminate the study (see Section 12.8).

3.4 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 (the Final 16-week Safety Follow-up Visit), or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date. The OLE study duration is described in Section 3.3 above.

4 STUDY POPULATION

4.1 Number of Subjects

It is anticipated that approximately 259 subjects of the 399 subjects initially randomized in Study CC-93538-EE-001 will participate in the OLE Study, CC-93538-EE-002. Of these subjects, it is estimated that approximately [redacted] adolescent subjects aged 12 to 17 years of the [redacted] that are expected to enroll in the Induction Phase of Study CC-93538-EE-001 will participate in the OLE study. The study population will consist of males and females aged 12 to 75 years (inclusive) with a diagnosis of EoE who have participated in the core Phase 3 Induction and Maintenance Study, CC-93538-EE-001. Subject age and inclusion in the adolescent age group will be based on age at the time of screening in Study CC-93538-EE-001. Subjects who completed Week 48 of the Maintenance Phase and subjects who experienced a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy may be eligible to participate according to Study CC-93538-EE-001 protocol pre-specified criteria and as outlined in Section 4.2, Inclusion Criterion 1.

Approximately [redacted] subjects who were enrolled in Study CC-93538-DDI-001 who completed assessments in Period 2 through Week 18/End of Treatment Visit and who meet all eligibility criteria will also be offered an opportunity to enroll in the OLE Study CC-93538-EE-002.

Note: In Study CC-93538-EE-001, 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 and Ethics Committee 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.

Subjects will be re-consented/assented for the OLE study. To be eligible for the OLE study, subjects must have qualified for the core Phase 3 Induction and Maintenance Study CC-93538-EE-001 or the Phase 1 Study CC-93538-DDI-001 and must meet the eligibility criteria below.

4.2 Inclusion Criteria

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

1) a. Subject must have participated in Study CC-93538-EE-001, and meets one of the following criteria:

1. Subject experienced a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy during the Induction Phase and has completed Week 24 of the Induction Phase; OR
2. Subject completed the Induction Phase and does not qualify for entry to the Maintenance Phase for reasons other than a severe EoE flare; OR
3. Subject experienced a severe EoE flare requiring endoscopic intervention and/or concomitant rescue therapy during the Maintenance Phase and completed Week 48 of the Maintenance Phase; OR
4. Subject completed Week 48 of the Maintenance Phase;

b. **OR** Subject must have participated in Study CC-93538-DDI-001 and completed assessments in Period 2 through Week 18/End of Treatment Visit.

2) Subject must have had ≥ 80% and ≤ 120% overall compliance of IP use in Study CC-93538-EE-001 or Study CC-93538-DDI-001, and subject must not have been permanently discontinued from IP while participating in Study CC-93538-EE-001 or Study CC-93538-DDI-001.

3) Subject must have, in the opinion of the Investigator, experienced no clinically significant AEs related to IP in Study CC-93538-EE-001 or Study CC-93538-DDI-001 that would preclude further dosing.

4) Female subject 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). An FCBP must:

a. Have 2 negative pregnancy tests as verified by the Investigator prior to starting study therapy in Study CC-93538-EE-001 or Study CC-93538-DDI-001 and an additional negative result prior to continuing study therapy in the OLE. 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.

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 and as applicable per national and local regulations (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]):

* 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.

- 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

5) Subject who is an FCBP must have a negative urine or serum pregnancy test prior to dosing on OLE Day 1.
6) Subject is willing to receive weekly SC injections throughout the study.
7) Subject (18 years of age or older) must understand and voluntarily sign an informed consent form (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. Adolescent subjects who reach the legal age of consent while participating in the study will be asked to sign an ICF (called a Transitional ICF) themselves to acknowledge their willingness to continue in the study. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.
8) 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, Schatzki's rings, inflammatory bowel disease, diagnosed eosinophilic gastritis and/or duodenitis [clinical symptoms and/or EGD findings and confirmatory eosinophilia in gastric and/or duodenal mucosa], or significant hiatal hernia [> 3 cm], etc.); or history of fundoplication.
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 demonstrates evidence of immunosuppression or is receiving systemic immunosuppressive or immunomodulating drugs (including but not limited to, Janus kinase [JAK] inhibitors, phosphodiesterase-4 [PDE-4] inhibitors, anti-interleukin [IL]-13 [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 OLE Day 1. Any use of these medications will be prohibited during the study.
5) Subject has received oral or sublingual immunotherapy within 6 months of OLE Day 1; any use will be prohibited during the study.
6) Subject received an IP, including through participation in an interventional trial for COVID-19, other than the IP administered in Study CC-93538-EE-001 or Study CC-93538-DDI-001 within 5 half-lives prior to OLE Day 1 or plans to receive another IP during the study. Subjects who received an investigational COVID-19 vaccine as part of a clinical trial during the course of Study CC-93538-EE-001 or Study CC-93538-DDI-001 will not be eligible to participate unless it is determined by discussion between Investigator and the Clinical Trial Physician that the biologic impact of the vaccine is stabilized.
7) Subject received a live attenuated vaccine within one month prior to OLE Day 1 or anticipates the need to be vaccinated with a live attenuated vaccine during the course of the study. Administration of any live (including attenuated) vaccine will be prohibited during the study through the Final 16-week Safety Follow-up Visit.
8) 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; a documented medical diagnosis of gastritis, which is clinically significant in the judgment of the Investigator; 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).
9) 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 OLE Day 1.
10) Subject has a chronic infection (eg, hepatitis B or C, human immunodeficiency virus [HIV], or tuberculosis as defined by standard medical guidelines).
11) Subject is pregnant or lactating.
12) Subject has developed idiopathic anaphylaxis or a major immunologic reaction (such as anaphylactic reaction, anaphylactoid reaction, or serum sickness) to an immunoglobulin G (IgG) containing agent. A known hypersensitivity to any ingredient in the IP is also exclusionary.
13) Subject has a newly diagnosed malignancy or lymphoproliferative disease.

14) Subject has a history of alcohol or drug abuse diagnosed within 5 years prior to Study CC-93538-EE-001 or Study CC-93538-DDI-001 participation.
15) Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
16) 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.
17) Subject has any condition that confounds the ability to interpret data from the study.

5 TABLE OF EVENTS

Table 3: Table of Events for the Open-label Extension Study

Study Procedures	Base-line[a]	Open-label Extension Treatment Period Year 1						Open-label Extension Treatment Period Year 2 and Beyond[b]				AI Visit[y]	EoE Flare Visit[c]	ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label (Q = Quarterly)	OLE Visit 1	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6	OLE Visit 7	OLE Q1 Visits	OLE Q2 Visits	OLE Q3 Visits	OLE Q4 Visits					
Visit Week (Window)	OLE Day 1	OLE Week 4 (Day 29 ±3d)	OLE Week 8 (Day 57 ±7d)	OLE Week 16 (Day 113 ±7d)	OLE Week 24 (Day 169 ±7d)	OLE Week 36 (Day 253 ±7d)	OLE Week 48 (Day 337 ±7d)	End of Quarter 1 (Year x + wk 13 [±14d])	Mid-point of Year (Year x + wk 26 [±14d])	End of Quarter 3 (Year x + wk 39 [± 14d])	End of Year (Year x +wk 52 [±14d])			Within 2 weeks After Final Dose	8 Weeks After Final Dose (±7d)	16 Weeks After Final Dose (±7d)
Informed consent/ assent	X															
Inclusion/exclusion criteria and confirm eligibility	X															
Confirm prior therapy	X															
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[f]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Urinalysis[f]	X	X			X		X		X		X		X	X	X	X
Pregnancy test (FCBP only)[g]	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Physical examination[h]	X	X	X	X	X	X	X	X	X	X	X			X	X	X

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Study Procedures	Base-line[a]	Open-label Extension Treatment Period Year 1						Open-label Extension Treatment Period Year 2 and Beyond[b]				AI Visit[y]	EoE Flare Visit[c]	ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label (Q = Quarterly)	OLE Visit 1	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6	OLE Visit 7	OLE Q1 Visits	OLE Q2 Visits	OLE Q3 Visits	OLE Q4 Visits					
Visit Week (Window)	OLE Day 1	OLE Week 4 (Day 29 ±3d)	OLE Week 8 (Day 57 ±7d)	OLE Week 16 (Day 113 ±7d)	OLE Week 24 (Day 169 ±7d)	OLE Week 36 (Day 253 ±7d)	OLE Week 48 (Day 337 ±7d)	End of Quarter 1 (Year x + wk 13 [±14d])	Mid-point of Year (Year x + wk 26 [±14d])	End of Quarter 3 (Year x + wk 39 [± 14d])	End of Year (Year x +wk 52 [±14d])			Within 2 weeks After Final Dose	8 Weeks After Final Dose (±7d)	16 Weeks After Final Dose (±7d)
Height (adolescents only after OLE Day 1)	X				X		X				X			X		
Weight	X	X	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	X	X
Serum antibodies to CC-93538[f,i]	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Serum CC-93538 PK assessment[f]	X	X	X	X	X	X	X	X	X	X	X			X	X	X
Circulating biomarkers assessment[f,j]	X				X		X							X	X	X
SARS-CoV-2 serology[k]	X						X				X			X		
Phone call reminder[l]				X		X				X						
Modified Daily Symptom Diary (mDSD)[m]	X	X	X	X	X		X				X					

Table 3: Table of Events for the Open-label Extension Study

Study Procedures	Base-line[a]	Open-label Extension Treatment Period Year 1						Open-label Extension Treatment Period Year 2 and Beyond[b]				AI Visit[y]	EoE Flare Visit[c]	ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label (Q = Quarterly)	OLE Visit 1	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6	OLE Visit 7	OLE Q1 Visits	OLE Q2 Visits	OLE Q3 Visits	OLE Q4 Visits					
Visit Week (Window)	OLE Day 1	OLE Week 4 (Day 29 ±3d)	OLE Week 8 (Day 57 ±7d)	OLE Week 16 (Day 113 ±7d)	OLE Week 24 (Day 169 ±7d)	OLE Week 36 (Day 253 ±7d)	OLE Week 48 (Day 337 ±7d)	End of Quarter 1 (Year x + wk 13 [±14d])	Mid-point of Year (Year x + wk 26 [±14d])	End of Quarter 3 (Year x + wk 39 [± 14d])	End of Year (Year x +wk 52 [±14d])			Within 2 weeks After Final Dose	8 Weeks After Final Dose (±7d)	16 Weeks After Final Dose (±7d)
Patient Global Impression of Severity (PGI-S)	X	X			X		X		X		X		X	X		
Clinician Global Impression of Severity (CGI-S)	X	X			X		X		X		X		X	X		
Global Impression of Change in EoE Symptoms (GIC-EoE)[v]	X	X			X		X						X[n]	X[n]		
Eosinophilic Esophagitis Activity Index (EEsAI)	X	X			X		X		X		X		X	X		
Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS; adolescents only)	X	X			X		X		X		X		X	X		

Table 3: Table of Events for the Open-label Extension Study

Study Procedures	Base-line[a]	Open-label Extension Treatment Period Year 1						Open-label Extension Treatment Period Year 2 and Beyond[b]				AI Visit[y]	EoE Flare Visit[c]	ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label (Q = Quarterly)	OLE Visit 1	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6	OLE Visit 7	OLE Q1 Visits	OLE Q2 Visits	OLE Q3 Visits	OLE Q4 Visits					
Visit Week (Window)	OLE Day 1	OLE Week 4 (Day 29 ±3d)	OLE Week 8 (Day 57 ±7d)	OLE Week 16 (Day 113 ±7d)	OLE Week 24 (Day 169 ±7d)	OLE Week 36 (Day 253 ±7d)	OLE Week 48 (Day 337 ±7d)	End of Quarter 1 (Year x + wk 13 [±14d])	Mid-point of Year (Year x + wk 26 [±14d])	End of Quarter 3 (Year x + wk 39 [± 14d])	End of Year (Year x +wk 52 [±14d])			Within 2 weeks After Final Dose	8 Weeks After Final Dose (±7d)	16 Weeks After Final Dose (±7d)
Health-related quality of life (SF-12v2 in adults; SF-10 in adolescents)	X				X		X							X[o]		
Work Productivity and Activity Index (WPAI:SHP; adults only)	X				X		X							X[p]		
Health resource utilization	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
AI Administration Questionnaire[w]	X		X		X		X	X	X	X	X	X				
EGD with tissue biopsies[q]	X				X		X				X[r]		X[s]	X[t]		
EoE Endoscopic Reference Score (EREFS)	X				X		X				X[r]		X[s]	X[t]		
Informed consent/assent for EndoFLIP sub-study, if applicable	X															

Table 3: Table of Events for the Open-label Extension Study

Study Procedures	Base-line[a]	Open-label Extension Treatment Period Year 1						Open-label Extension Treatment Period Year 2 and Beyond[b]				AI Visit[y]	EoE Flare Visit[c]	ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label (Q = Quarterly)	OLE Visit 1	OLE Visit 2	OLE Visit 3	OLE Visit 4	OLE Visit 5	OLE Visit 6	OLE Visit 7	OLE Q1 Visits	OLE Q2 Visits	OLE Q3 Visits	OLE Q4 Visits					
Visit Week (Window)	OLE Day 1	OLE Week 4 (Day 29 ±3d)	OLE Week 8 (Day 57 ±7d)	OLE Week 16 (Day 113 ±7d)	OLE Week 24 (Day 169 ±7d)	OLE Week 36 (Day 253 ±7d)	OLE Week 48 (Day 337 ±7d)	End of Quarter 1 (Year x + wk 13 [±14d])	Mid-point of Year (Year x + wk 26 [±14d])	End of Quarter 3 (Year x + wk 39 [± 14d])	End of Year (Year x +wk 52 [±14d])			Within 2 weeks After Final Dose	8 Weeks After Final Dose (±7d)	16 Weeks After Final Dose (±7d)
EndoFLIP (optional sub-study)[x]	X				X		X				X[r]					
CC-93538 administration[u]	X	X	X	X	X	X	X	X	X	X	X	X				

Abbreviations: AE = adverse event; AI = autoinjector; CGI-S = Clinician Global Impression of Severity; d = day; EEsAI = Eosinophilic Esophagitis Activity Index; EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis; EREFS = EoE Endoscopic Reference Score; EoT = End of Treatment; ET: Early Termination; FCBP = females of childbearing potential; GIC-EoE = Global Impression of Change in EoE Symptoms; IgG = immunoglobulin G; IP = investigational product; mDSD = modified Daily Symptom Diary; OLE = Open-label Extension; PEESS = Pediatric Eosinophilic Esophagitis Symptom Severity Module; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; Q = quarterly; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SC = subcutaneous; SF-10 = 10-Item Short Form Health Survey for Children; SF-12v2 = 12-Item Short Form Health Survey; WPAI:SHP = Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

[a] All OLE Day 1 study procedures/assessments will serve as baseline assessments and will be completed prior to dosing unless otherwise noted. For subjects transitioning from Study CC-93538-EE-001, the OLE Day 1/Baseline assessments will include the Induction Phase Week 24 Visit assessments, or Maintenance Week 48 Visit assessments from Study CC-93538-EE-001, as applicable, as the transition from Study CC-93538-EE-001 to the OLE study is anticipated to occur on the same day for most subjects. Additional OLE baseline assessments not performed at the final Induction Phase (Week 24) or Maintenance Phase (Week 48) Visit should be conducted (or repeated) at the OLE Day 1 Visit. The EGD procedure should not be repeated at the OLE Day 1 Visit, with the exception as noted in Section 6.2. OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the Induction Phase Week 24 Visit, or Maintenance Phase Week 48 Visit, or OLE Day 1. For subjects transitioning from Study CC-93538-DDI-001, OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the End of Treatment Visit from Study CC-93538-DDI-001 or OLE Day 1 (in Study CC-93538-EE-002); the following baseline assessments will be performed at OLE Day 1, for these were not evaluated in the parent study: PGI-S, CGI-S, SF-

12v2, WPAI, and circulating biomarkers assessment. Subjects will not be allowed to enroll in the OLE study and receive CC-93538 on OLE Day 1 if there will be a delay of > 21 days from dosing in Study CC-93538-EE-001 or Study CC-93538-DDI-001 unless discussed with the Medical Monitor (refer to Section 6.2).

[b] After completion of Week 48 (Visit 7) plus an additional 4 weeks in the OLE Treatment Period (that is, after Week 52 of the OLE study), subjects will continue on into the second year of the OLE (Year 2 and beyond). During Year 2 and beyond, subjects will attend study visits every 13 weeks (±14 days) for a total of 4 quarterly study visits each year within a 52-week per year format. For each year of participation after Week 52, the Quarterly 1 Visit, Quarterly 2 Visit, Quarterly 3 Visit, and Quarterly 4 Visit will be completed. The Quarterly 2 and 4 Visits include additional assessments not conducted in the Quarterly 1 and 3 Visits.

[c] An EoE Flare Assessment Visit should be scheduled as close as possible to the time when an EoE flare is suspected.

[d] Subjects who discontinue study treatment at any time during the OLE will be asked to complete either an ET Visit, if discontinuation occurs before the Quarterly 4 Visit at the end of Year 2 (Week 104), or an EoT Visit, if discontinuation occurs at or after the Quarterly 4 Visit at the end of Year 2 (Week 104). The visit will occur within 2 weeks after the final dose of CC-93538.

[e] The timing of AE/SAE assessment documentation for the OLE study will begin at the time of or after the first dose in the OLE study (on OLE Day1); AE/SAEs occurring before this timeframe will be documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001. Ongoing AE/SAEs first documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will continue to be followed in the OLE study.

[f] Pre-dose assessments except for the ET/EoT Visit and 2 Safety Follow-up Visits.

[g] For females of childbearing potential (FCBP), a urine (or serum) pregnancy test must be performed at OLE Day 1/Baseline and the results reviewed on OLE Day 1 prior to the first OLE CC-93538 dose. A pregnancy test does not need to be repeated if it has been conducted at the final visit in Study CC-93538-EE-001 or Study CC-93538-DDI-001, and OLE Day 1 occurs on the same day (See Section 6.2). Urine pregnancy tests will be done at subsequent visits. 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 all study visits, the Investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.

[h] Complete physical examination will be performed at OLE Day 1, Week 24, Week 48, at the Quarterly 4 Visit, at the ET/EoT Visit, and at the 2 Safety Follow-up Visits; abbreviated physical examination will be performed at Weeks 4, 8, 16, 36, and at the Quarterly 1, 2, and 3 Visits.

[i] If anti-drug antibodies (ADAs) are detected, they will be further characterized as to whether the ADAs are neutralizing or not in nature.

[j] Blood samples will be obtained to evaluate levels of various circulating biomarkers, including but not limited to periostin, eotaxin-3, and IL-13.

[k] Serum will be collected at OLE Day 1, Week 48, at the Quarterly 4 Visit, and at the ET/EoT Visit as well as approximately 4 weeks after a documented or suspected SARS-CoV-2 infection, for possible measurements of anti-SARS-CoV-2 total or IgG per national and local requirements (see Section 6.7.1).

[l] 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 Week 24 (just prior to Week 22) and for Week 48 (just prior to Week 46). Additionally, for the end of Year 2 assessments, a phone call will take place within a couple of days prior to Week 100 as a reminder for the beginning of the 4-week mDSD collection period, as well as within a couple of days prior to the Week 102 as a reminder for the start of the 14-day mDSD collection period prior to Week 104 (the Quarterly 4 Visit at the end of Year 2).

[m] The mDSD will be completed daily after the last meal of the day prior to OLE Day 1/Baseline as required in Study CC-93538-EE-001 or as required in Study CC-93538-DDI-001, daily from OLE Day 1 through Week 24, for 4 consecutive weeks (28 days) prior to the Week 48 Visit, and for 4 consecutive weeks (28 days) prior to the Quarterly 4 Visit at the end of Year 2 (Week 104).

[n] The GIC-EoE will only be collected at the ET Visit if at or before Week 48 and at the EoE Flare Visit occurring at or before Week 48, if applicable.

[o] The SF-12v2 in adults and SF-10 in adolescents will only be collected at the ET Visit if at or before Week 48.

[p] The WPAI:SHP in adults will only be collected at the ET Visit if at or before Week 48.

[q] The EGD biopsies will be measured for relevant tissue biomarkers when possible. Esophageal tissue biomarkers will not be assessed in subjects transitioning from Study CC-93538-DDI-001.

[r] Following the Week 48 time point, EGD is scheduled at one additional time point, at the Quarterly 4 Visit occurring at Week 104 (end of Year 2) but is not required if an EGD was performed within 24 weeks of the Week 104 Visit.

[s] The EGD is not required at EoE Flare Assessment Visits; if conducted, data should be collected when available, and if feasible, a sample may be collected and sent to the central reader.

[t] The EGD will be completed at the ET Visit if the visit occurs before or at Week 48 but is not required if within 8 weeks since the last EGD. The EGD is not required at ET Visits after Week 48.

[u] All subjects will receive weekly open-label CC-93538 360 mg during the OLE. Subjects will be given their first dose of CC-93538 at the OLE Day 1 Visit (which is anticipated to be the same day as the Induction Phase Week 24 Visit or Maintenance Phase Week 48 Visit in Study CC-93538-EE-001 for most subjects and may occur on the same day as the End of Treatment Visit in Study CC-93538-DDI-001 if it has been at least 7 days from the last CC-93538 dose). Subjects will then receive weekly doses throughout the Open-label Treatment Period for a minimum of 2 years or as long as they are participating in the study. The first 3 weekly SC doses (OLE Day 1, Week 1, and Week 2) 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. To ensure accurate dose administration and compliance with the new [redacted] weekly SC injection using the [redacted] AI presentation, for subjects who did not begin the study with the new [redacted] presentation (on OLE Day 1), one additional in-clinic weekly dose with at least a 30-minute observation is required for the first administration. This first dose will occur either at the time of the subject's next scheduled protocol required study visit or the First AI Administration Visit.

[v] GIC-EoE will only be completed in subjects transitioning from Study CC-93538-EE-001.

[w] The AI Administration Questionnaire will be conducted only in subjects who self-administer (as defined as per Section 7.2.1) with the new [redacted] injection CC-93538 [redacted] AI presentation. For in-clinic administration, the subject or caregiver should provide responses to the questionnaire immediately after dosing. For at home administration, the study staff will contact the subject/caregiver by phone within 24 hours of dose administration. In-clinic assessments include the first in-clinic dose (OLE Day 1 or applicable week), Week 8, Week 24, and Week 48 of Year 1, and the Quarterly 1 Visit, Quarterly 2 Visit, Quarterly 3 Visit, and Quarterly 4 Visit in Year 2 as applicable. In addition to the X's denoted in the Table of Events for the in-clinic assessments, additional time points to capture at home dosing include the first weekly dose at home (Week 3 or the applicable week), Week 6, Week 20, and Week 44 in Year 1, and Week 60, Week 72, Week 84, and Week 96 in Year 2, as applicable. Further, for subjects who receive their first dose of the AI at the "First Administration Visit" the AI Administration Questionnaire will be conducted. If a time point is missed, the questionnaire can be administered at the next weekly dose for the respective condition (in-clinic visit or at home administration).

[x] Only subjects transitioning from Study CC-93538-EE-001 and who have participated in the sub-study during enrollment in Study CC-93538-EE-001 are eligible to participate.

[y] A First AI Administration Visit will be required for subjects whose next scheduled protocol visit is not within 4 weeks of Protocol Amendment 2 site approval and IP availability. The visit may be scheduled at any time within this 4-week period.

6 PROCEDURES

Assessments and procedures for OLE Day 1 (Baseline), the OLE Treatment Period and the 2 Safety Follow-up Visits are outlined in Table 3. Study assessments and procedures are described in Section 6.2 and Section 6.3. The day of administration of the first dose of CC-93538 is defined as OLE Day 1.

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 assessment and procedures are performed at every visit):

- EoE clinical symptom assessment instruments and subject-reported outcomes
- Spontaneous or solicited AE reporting
- Vital signs
- Physical examination
- Clinical laboratory tests, including blood sampling for the assessment of serum CC-93538 PK concentrations, anti-drug antibodies (ADAs), and biomarkers
- 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.

For the purposes of this study, adolescents are defined as subjects aged 12 to 17 years at the time of signing the assent form in Study CC-93538-EE-001 (except where national or regional guidelines for the definition of adolescence differ from the definition stated above) and adults are defined as subjects aged 18 to 75 years at the time of signing the ICF in Study CC-93538-EE-001. Subjects who enter the study as adolescents should continue to complete the assessments specific for adolescents throughout the study and do not need to complete assessments that are only required in adult subjects. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

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

6.1 Screening Period

There is no Screening Period for the OLE study. Subject eligibility is described in Section 4.2 and Section 4.3. Baseline assessments are described in Section 6.2.

6.2 Open-label Extension Treatment Period

The OLE Day 1/Baseline assessments shown in Table 3 will be completed prior to the first dose of CC-93538 in the OLE study. For subjects transitioning from Study CC-93538-EE-001, OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the following visits from Study CC-93538-EE-001: Induction Phase Week 24 Visit or the Maintenance Phase Week 48 Visit, or OLE Day 1 (in Study CC-93538-EE-002). Transition to the OLE study should occur for most subjects on the same day as the Induction Phase Week 24 or the Maintenance Phase Week 48 Visit. For subjects transitioning from Study CC-93538-DDI-001, OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the End of Treatment Visit from Study CC-93538-DDI-001 or OLE Day 1 (in Study CC-93538-EE-002). The OLE Day 1 Visit may occur on the same day as the End of Treatment Visit if it has been at least 7 days from the last CC-93538 dose in the parent study.

However, for select assessments, baseline will be evaluated at earlier time points in Study CC-93538-DDI-001 (prior to End of Treatment) and no assessment will be conducted on OLE Day 1. These include EGD with tissue biopsies, EoE Endoscopic Reference Score (EREFS), and Eosinophilic Esophagitis Activity Index (EEsAI); assessments will continue in the OLE at post-baseline time points.

Importantly, for subjects transitioning from Study CC-93538-DDI-001, the following baseline assessments will be performed at OLE Day 1, for these were not evaluated in the parent study:

- Patient Global Impression of Severity (PGI-S)
- Clinician Global Impression of Severity (CGI-S)
- 12-Item Short Form Health Survey (SF-12v2)
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)
- Circulating biomarkers assessment

Lastly, not all assessments will be required at baseline or during the study for subjects transitioning from Study CC-93538-DDI-001: Global Impression of Change in EoE Symptoms (GIC-EoE), esophageal tissue biomarkers, and EndoFLIP will not be conducted in these subjects, as no baseline assessment will be available.

Subjects entering the OLE study will not complete the Safety Follow-up Visits in Study CC-93538-EE-001 or Study CC-93538-DDI-001. The Investigator will review all available information to confirm that the subject continues to meet all study enrollment criteria and will complete the additional OLE Day 1 activities for confirmation of eligibility. Written, signed, and dated informed consent/assent from the subject prior to the performance of any study related procedures not already completed for the Week 24 or Week 48 Visit in Study CC-93538-EE-001 or at the End of Treatment Visit (or prior to End of Treatment) in Study CC-93538-DDI-001 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/activities will be performed as specified in Table 3:

- Additional OLE Day 1 activities include informed consent/assent, confirmation that subjects qualified for and participated in Study CC-93538-EE-001 or Study CC-93538-DDI-001, review of CC-93538-EE-002 inclusion/exclusion criteria and confirmation of eligibility, AE assessment, health resource utilization monitoring, and review and documentation of any prior and concomitant therapies that began within 28 days of OLE Day 1.
- The baseline assessments will include those conducted for the Induction Phase Week 24 Visit or Maintenance Phase Week 48 Visit in Study CC-93538-EE-001, as applicable, or those conducted at the End of Treatment Visit (or prior to End of Treatment) in Study CC-93538-DDI-001, as applicable. Additional OLE baseline assessments not performed at the final Induction Phase (Week 24) or Maintenance Phase (Week 48) Visit in Study CC-93538-EE-001 or that are required on OLE Day 1 for subjects who participated in Study CC-93538-DDI-001, should be conducted at the OLE Day 1 Visit (or repeated in the case that the assessment requires re-evaluation on the same day just prior to dosing [eg, pregnancy test]) in accordance with the Table of Events (Table 3). Subjects will not be allowed to enroll in the OLE study and receive CC-93538 on OLE Day 1 if there will be a delay of > 21 days from CC-93538 dosing in Study CC-93538-EE-001 or in Study CC-93538-DDI-001, unless discussed with the Medical Monitor.
- Guidance regarding baseline EGD and transition from the parent study follows:
  - For subjects transitioning from Study CC-93538-EE-001, the EGD procedure does not need to be repeated at the OLE Day 1 Visit, as long as this assessment was conducted at the final Induction Phase (Week 24) or Maintenance Phase (Week 48) Visit.
  - For subjects transitioning from Study CC-93538-DDI-001, the EGD procedure does not need to be repeated at the OLE Day 1 Visit, as long as this assessment was conducted prior to the End of Treatment Visit.

    If not available in the parent study as noted above, an EGD conducted at the OLE Day 1 Visit will serve as the baseline for Study CC-93538-EE-002.
  - 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 in Study CC-93538-EE-001, an EGD will also be performed at Weeks 24 or 48, unless the EoE flare assessment occurred too close from the Week 24 or Week 48 Visits based on the Investigator's judgement, such that it is considered unsafe to perform another EGD in such a short interval. Discuss with the Medical Monitor well in advance of the OLE Day 1 Visit.

- For subjects transitioning from Study CC-93538-EE-001, if OLE Day 1 is not on the same day as the final Induction Phase (Week 24) or Maintenance Phase (Week 48) Visit in Study CC-93538-EE-001, a urine (or serum) β-subunit of human chorionic gonadotropin (β-hCG) pregnancy test (females of child-bearing potential only) must be performed on OLE Day 1 and the results reviewed on OLE Day 1 prior to the first OLE CC-93538 dose. For subjects transitioning from Study CC-93538-DDI-001, if a pregnancy test was not completed on the same day as OLE Day 1, then a pregnancy test (urine or serum) must be performed on OLE

Day 1 and the results reviewed prior to the first dose. A negative pregnancy test result must be obtained for these subjects prior to dosing. If the urine pregnancy test result is positive but this is believed to be a false positive, the site may perform a serum pregnancy test at the local laboratory to confirm pregnancy status.

After eligibility has been confirmed and baseline assessments have been completed, eligible subjects will receive CC-93538 360 mg in an open-label manner. 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 shown in Table 3.

Following OLE Day 1, in the first year of the OLE study (OLE Treatment Period Year 1), subjects will attend study visits through Week 48. After completion of Week 48 plus an additional 4 weeks in the OLE Treatment Period (that is, after Week 52 in the OLE study), subjects will continue on into the second year of the OLE (Year 2 and beyond). During Year 2 and beyond, subjects will attend study visits every 13 weeks (±14 days) for a total of 4 quarterly study visits each year within a 52-week per year format. For each year of participation after Week 52, the Quarterly 1 Visit, Quarterly 2 Visit, Quarterly 3 Visit, and Quarterly 4 Visit will be completed. The Quarterly 2 and 4 Visits will include additional assessments not conducted in Quarterly 1 and 3 Visits. The time points for these visits are as follows:

- Quarterly 1 Visits will occur at the end of the first quarter of each year after Week 52 (Year x + Week 13 [± 14 days])
- Quarterly 2 Visits will occur at the mid-point of each year after Week 52 (Year x + Week 26 [± 14 days])
- Quarterly 3 Visits will occur at the end of the third quarter of each year after Week 52 (Year x + Week 39 [± 14 days])
- Quarterly 4 Visits will occur at the end of each year after Week 52 (Year x + Week 52 [± 14 days])

For example, for the Quarterly 1 Visit occurring at Week 13, where Year x is Year 2, the visit will occur at 52 Weeks plus 13 Weeks = Week 65, and for the Quarterly 4 Visit, where Year x is Year 2, the visit will occur at 52 Weeks plus 52 Weeks = Week 104.

The following will be performed during the Open-label Extension Treatment Period as specified in the Table 3:

- Prior therapy and concomitant therapy. The use of concomitant medication and procedures will be monitored throughout the study. Refer to Section 8 for prohibited concomitant therapies.
- Adverse event assessment begins when the subject signs the informed consent/assent form (in either parent study, Study CC-93538-EE-001 or Study CC-93538-DDI-001). 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. Ongoing AEs

first documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will continue to be followed in the OLE study. The timing of AE assessment documentation for the OLE study will begin at the time of or after the first dose in the OLE study (on OLE Day 1); AEs occurring before this timeframe will be documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001, respectively. Refer to Section 10 for definitions of AEs/SAEs, monitoring, and reporting. In addition, AI/PFS device failures or malfunctions should be captured, and device related AEs should also be collected.

- Hematology, chemistry, 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: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, random glucose, albumin, alkaline phosphatase, creatinine, creatine phosphokinase (CPK), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), gamma glutamyltransferase (GGT), amylase, total bilirubin, direct bilirubin and C-reactive protein (CRP)
  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - The hematology, chemistry, and urinalysis will be performed pre-dose (except for the ET/EoT Visit and 2 Safety Follow-up Visits) at the time points outlined in the Table of Events (Table 3).
- Pregnancy test (only for FCBP): A urine (or serum) pregnancy test for β-hCG will be performed at OLE Day 1/Baseline and urine pregnancy tests will be done at subsequent visits according to the Table of Events (Table 3). 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. A pregnancy test does not need to be repeated if it has been conducted at the final visit in Study CC-93538-EE-001 or Study CC-93538-DDI-001, and OLE Day 1 with dosing of CC-93538 occurs on the same day that the test was conducted and results reviewed.
- 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 3). All significant findings that were present at screening in Study CC-93538-EE-001 or Study CC-93538-DDI-001 must be reported on the relevant medical history/current medical conditions eCRF. Significant findings made at the time of or after the first dose in the OLE study (on OLE Day 1) that meet the definition of an AE must be recorded in the OLE Study. Note that ongoing AEs first documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will be followed during the OLE study.

- Height and weight: Height will be measured in centimeters in all subjects for the OLE Day 1 assessment but will only be required in adolescent subjects at subsequent time points; weight will be measured in kilograms in all subjects during the study.
- 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.
- Serum antibodies to CC-93538 (Section 6.5)
- Serum CC-93538 PK assessment (Section 6.6)
- Circulating biomarkers assessment (Section 6.7.1)
- SARS-CoV-2 serology assessment (Section 6.7.1)
- Modified Daily Symptom Diary (mDSD) (Section 6.4.2.1)
- Phone call reminder for mDSD completion (just prior to Week 22, Week 46, Week 100, and Week 102)
- PGI-S (Section 6.4.2.2)
- CGI-S (Section 6.4.2.3)
- GIC-EoE in subjects transitioning from Study CC-93538-EE-001 only (Section 6.4.2.4)
- EEsAI (Section 6.4.2.5)
- Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS) in adolescents only (Section 6.4.2.6)
- Health-related quality of life (SF-12v2 in adults; 10-Item Short Form Health Survey for Children [SF-10] in adolescents) (Section 6.9)
- WPAI:SHP in adults only (Section 6.9)
- [redacted]
- Health resource utilization will be monitored throughout the study and recorded at each study visit including but not limited to emergency department visits or hospitalizations for food impaction, procedures such as esophageal dilation, urgent care visits, health care provider office visits, or use of rescue therapy.
- EGD with tissue biopsies: Note that SARS-CoV-2 molecular testing through local laboratory assessment may be performed per standard of care and as required per institutional and local guidance prior to the EGD (Section 6.4.1)
- EREFS (Section 6.4.1)
- Informed consent/assent for the optional EndoFLIP sub-study, if applicable
- Optional EndoFLIP sub-study in subjects transitioning from Study CC-93538-EE-001 only (Section 6.11)
- IP administration (refer to Section 7.2)

6.2.1 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 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.

In addition, for COVID-19 detection and prevention measures, SARS-CoV-2 molecular testing through local laboratory assessment may be performed per standard of care and as required per institutional and local guidance.

6.2.2 First Autoinjector Administration Visit

An additional First AI Administration Visit will be required for all subjects currently in the study whose next scheduled protocol visit is not within 4 weeks of Protocol Amendment 2 site approval and once IP is available on site.

The following evaluations will be performed as specified in Table 3:

- Concomitant therapy
- Assessment of AEs/SAEs
- AI Administration Questionnaire (Section 6.9.2)
- IP administration (Section 7.2)

6.2.3 EoE Flare Assessment Visit

Subjects with a worsening of EoE symptoms during the study will be required to complete the EoE Flare Assessment Visit as shown in the Table of Events (Table 3). 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 a subject discontinues the study due to an EoE flare, the ET/EoT Visit will also be completed, but procedures performed at the EoE Flare Assessment Visit do not need to be repeated for the ET/EoT Visit.

The following evaluations will be performed as specified in Table 3:

- Concomitant therapy
- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis
- Weight
- Vital signs
- PGI-S
- CGI-S
- GIC-EoE
- EEsAI
- PEESS in adolescents only
- Health resource utilization
- EGD with tissue biopsies*
- EREFS*

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

6.2.4 Early Termination or End of Treatment Visit

For subjects who discontinue the study for any reason, the assessments detailed in the ET/EoT Visit should be completed within 2 weeks after the final CC-93538 dose (Table 3). The ET Visit will be completed if discontinuation occurs before the Quarterly 4 Visit at the end of Year 2 (Week 104); the EoT Visit will be completed if discontinuation occurs at or after the Quarterly 4 Visit at the end of Year 2 (Week 104). If the EoT Visit occurs at the scheduled Quarterly 4 Visit at the end of Year 2 (Week 104), the subject will complete all assessments required for each of the 2 visits collectively (ie, assessments do not need to be repeated). In addition, these subjects should return for the Interim 8-week and Final 16-week Safety Follow-up Visits (Section 6.3.1).

The following evaluations will be performed as specified in the Table 3:

- Concomitant therapy
- Assessment of AEs
- Hematology, chemistry, and urinalysis
- Pregnancy test (only for FCBP)
- Physical examination
- Height (in adolescents only) and weight
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment

* Note that EGD is not required at EoE Flare Assessment Visits; if EGD is conducted, data should be collected when available, and if feasible, a sample may be collected and sent to the central reader for histologic analysis.

- Circulating biomarkers assessment
- SARS-CoV-2 serology assessment
- PGI-S
- CGI-S
- GIC-EoE
- EEsAI
- PEESS in adolescents only
- SF-12v2 in adults and SF-10 in adolescents
- WPAI:SHP in adults only
- Health resource utilization
- EGD with tissue biopsies*
- EREFS*
- Adverse event evaluation (monitored through 16 weeks after the last dose of IP)

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 CC-93538 for AE reporting, as well as SAEs made known to the Investigator at any time thereafter that are suspected of being related to CC-93538, as described in Section 10.2.3. All subjects should return at both 8 weeks and 16 weeks (± 7 days) after their last dose of CC-93538 to complete the Interim 8-week and Final 16-week Safety Follow-Up Visits and assessments shown in Table 3.

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 at a centralized reading facility, and sites will send the biopsy specimens to the centralized reading facility. For the OLE Day 1/Baseline EGD only (ie, the EGD conducted in Study CC-93538-EE-001 at either the Week 24 Visit or Week 48 Visit), biopsy results will be read blinded to treatment allocation and results will be blinded to investigative sites. 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 judgment. More detailed instructions for specimen collection, processing, storage, and shipping will be provided in a separate Biopsy Quick Reference Card and a Study Laboratory Manual.

* The EGD will be completed at the ET Visit if the visit occurs before or at Week 48 but is not required if within 8 weeks since the last EGD. The EGD is not required at ET Visits after Week 48.

Endoscopic procedures will be performed as follows:

- EGD will be performed at the time points specified in the Table of Events (Table 3). Note that SARS-CoV-2 molecular testing through local laboratory assessment may be performed per standard of care and as required per institutional and local guidance prior to the EGD.
- Biopsies should be obtained from 3 levels, the proximal, mid, and distal esophagus 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 (approximately mid-way between the proximal and distal biopsies)
- All subsequent biopsies should be obtained from the same levels as the screening biopsies in Study CC-93538-EE-001 or Study CC-93538-DDI-001 (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.
- 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 including but not limited to the 5 classification categories will be assessed by each Investigator using the EREFS (Hirano, 2013) at the time points specified in the Table of Events (Table 3). 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 exploratory endpoint determination, the esophageal biopsies will be used for evaluation of potential diagnostic and pharmacodynamic markers 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)

[redacted]

[redacted]

6.4.2.2 Patient Global Impression of Severity (PGI-S)

The PGI-S is a single-item assessment of disease severity where subjects are asked, "Please rate the severity of your EoE symptoms over the past 2 weeks." A 5-point verbal response scale is used, including "None," "Mild," "Moderate," "Severe," and "Very severe."

The PGI-S will be assessed via an eDiary according to the time points detailed in the Table of Events (Table 3).

6.4.2.3 Clinician Global Impression of Severity (CGI-S)

The CGI-S is a single-item assessment of disease severity where clinicians are asked, "Please rate the severity of the patient's EoE symptoms over the past 2 weeks." A 5-point verbal response scale is used, including "None," "Mild," "Moderate," "Severe," and "Very severe."

The CGI-S will be completed by clinicians via paper or electronic methods. The CGI-S will be assessed as specified in Table 3. Whenever possible, the same assessor should perform the CGI-S for all time points for a given subject.

6.4.2.4 Global Impression of Change in EoE Symptoms (GIC-EoE)

In the OLE study, the GIC-EoE is a single-item assessment where subjects are asked, "Since you completed your participation in Study CC-93538-EE-001, how would you describe the change in your EoE symptoms?" Response options include "A lot better", "A little bit better", "Stayed the same", "A little worse", and "Much Worse". Only subjects transitioning from Study CC-93538-EE-001 will complete the GIC-EoE.

The GIC-EoE will be assessed via an eDiary at time points outlined in Table 3.

6.4.2.5 Eosinophilic Esophagitis Symptom and Activity Index (EEsAI)

The EEsAI was developed in the English language as a paper-based patient-reported outcome (PRO) with a 7-day recall period and takes less than 10 minutes to complete (Schoepfer, 2014b). For the CC-93538 Phase 3 studies, only the 10-item symptoms (dependent on eating and drinking) domain will be included.

The EEsAI includes the visual dysphagia question (VDQ) which addresses the severity of dysphagia when consuming food of 8 distinct consistencies. The 8 food consistencies and examples of foods to illustrate those consistencies are as follows: (1) solid meat (such as steak, chicken, turkey, and lamb), (2) soft foods (such as pudding, jelly, and apple sauce), (3) dry rice or sticky Asian rice, (4) ground meat (hamburger and meatloaf), (5) fresh white untoasted bread or similar foods (such as doughnuts, muffins, and cake), (6) grits, porridge (oatmeal), or rice pudding, (7) raw fibrous foods (such as apples, carrots, and celery), and (8) French fries (Schoepfer, 2014b). Each VDQ food consistency is answered with a Likert-like scale ranging from "no difficulties" to "severe difficulties." Further, the behavioral adaptations of avoidance, modification, and slow eating (AMS) are assessed for the same 8 food consistencies. The AMS section contains 4 yes/no questions for each of the 8 food consistencies. Additionally, the questionnaire includes items assessing the frequency and duration of trouble swallowing and pain associated with swallowing.

The EEsAI total score ranges from 0 to 100, with a high score indicating more dysphagia symptoms and behavioral adaptations. A score from 0 to 20 has been previously defined as clinical remission (Safroneeva, 2015a; Safroneeva, 2015b).

The EEsAI will be assessed at time points outlined in Table 3.

6.4.2.6 Pediatric Eosinophilic Esophagitis Symptom Severity Module (PEESS)

The Pediatric Eosinophilic Esophagitis Symptom Severity Module, version 2.0 (PEESS v2.0) is a validated instrument that assesses symptoms of EoE in children and adolescents aged 2 to 18 years (Franciosi, 2011). A parent proxy report for children and teenage children ages 2 to 18 and a children and teen report for ages 8 to 18 are available; the children and teen report will be used for this study and will be assessed in adolescent subjects only. The module assesses the frequency and severity (depicted with ideograms) of symptoms in the past month with each item on a scale of 0 to 4 (4 being the highest level of frequency/severity). Scores for each item are transformed to a 0 to 100 point scale and the total metric score will be computed as the mean of the item scores.

The PEESS will be assessed at time points according to Table 3.

6.4.2.7 Worsening of EoE Symptoms, EoE Flare, the EoE Flare Assessment Visit, and Lack of Improvement

Subjects with a worsening of EoE symptoms during the study will be required to complete the EoE Flare Assessment Visit as shown in the Table of Events (Table 3). 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, which should be scheduled as close as possible to the time that an EoE flare is suspected.

An EoE Flare Assessment Visit including safety and efficacy evaluations can occur at any time during the study. While EGD is not required, if an endoscopy is conducted as an intervention for a subject with a worsening of symptoms or flare, details of the endoscopic procedure should be collected when available, and if feasible, a sample may be collected and sent to the central reader. 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.

During the course of the study, subjects who demonstrate a persistent lack of improvement or worsening of EoE symptoms should be evaluated to determine if continuing the study treatment is appropriate. While subjects will have the opportunity to continue participation in the OLE with use of rescue therapy as needed, based on clinical judgment, the Investigator should discontinue any subject in which study participation no longer is in the best interest of the subject.

Subjects who are discontinued from the OLE study will be asked to complete an ET/EoT Visit (Section 6.2.4) and the 2 Safety Follow-up Visits (Section 6.3.1). The ET/EoT Visit procedures performed at the EoE Flare Assessment Visit do not need to be repeated for subjects who discontinue the study due to an EoE flare.

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/EoT Visit and 2 Safety Follow-up Visits) at the time points outlined in the Table of Events (Table 3).

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, pharmacodynamic, 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 Termination and 2 Safety Follow-up Visits) at the time points described in the Table of Events (Table 3). In the event that dosing occurs during a non-clinic visit day, it is still acceptable to obtain the serum samples. CC-93538 concentration data will be used for population PK analysis and determination of exposure-response and pharmacodynamic relationships as described in Section 9.9.1.

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

6.7 Biomarkers, Pharmacodynamics, Pharmacogenomics

6.7.1 Circulating Biomarker Assessments

Blood samples will be obtained pre-dose (except for the ET/EoT Visit and 2 Safety Follow-up Visits) to evaluate levels of various circulating biomarkers including, but not limited to, periostin, eotaxin-3, IL-13, and possible assessments of SARS-CoV-2 serologic status according to the Table of Events (Table 3). Data obtained from the pharmacogenomic sample (eg, IL-13 single nucleotide polymorphism [SNP] characterization) collected in Study CC-93538-EE-001 will be included in the biomarker endpoint analysis for this study. Serum will be collected for measurements of SARS-CoV-2 serology (anti-SARS-CoV-2 total or IgG) per national and local regulations. Of note, in addition to the scheduled time points listed in Table 3, serum will also be collected for SARS-CoV-2 serology approximately 4 weeks after a documented or suspected SARS-CoV-2 infection.

These samples will be shipped to a central laboratory for analysis. Details of the procedures to be followed for sample collection, processing, storage, and shipment will be documented in a separate Study Laboratory Manual.

6.7.2 Tissue Biomarker Assessments

Tissue biomarkers will be evaluated using tissue obtained from the study-specified esophageal biopsies when possible at time points detailed in Table 3. Sample collection and processing will be described in a separate Study Laboratory Manual. Biomarkers that will be evaluated are thought to play a role in EoE disease pathogenesis and may have diagnostic or prognostic importance; methodologies such as immunohistochemistry and transcriptome analysis may be employed. These biomarkers include but are not limited to markers of epithelial mesenchymal transition (EMT), eotaxin-3, and periostin. These biomarker assessments will be performed at a central

laboratory and other specialized laboratories. Esophageal tissue biomarkers will not be assessed in subjects transitioning from Study CC-93538-DDI-001.

6.8 Additional and Optional Research

Additional and optional research (requiring subject consent/assent) as described below may be performed using left-over samples originally collected for another test required in this study or using samples collected specifically for biomarker testing. The research may involve genetic tests using DNA or RNA and may lead to the development of new diagnostic tests.

6.8.1 Additional Research

Additional research related to the study drug and/or disease may be performed. The results of this additional research could help to improve the diagnosis and/or the treatment of this disease in the future.

6.8.2 Optional Research

Optional research not related to the study drug or the subject's disease may be performed. The subject's decision to participate in this optional research will not impact their ability to participate in the main study.

6.9 Subject-Reported Outcomes

6.9.1 Health-related Quality of Life

The 12-Item Short Form Health Survey (SF-12v2; Ware, 1996) and the 10-Item Short Form Health Survey for Children (SF-10; Saris-Baglama, 2007) will be used to measure health-related quality of life (HRQoL). Adult subjects will be administered the SF-12v2 while adolescent subjects will be given the SF-10 Survey. The SF-12v2 contains 12 questions and measures 8 domains including physical and mental aspects of health. The SF-10 contains 10 questions and is completed by the parent.

The Work Productivity and Activity Impairment Questionnaire (WPAI) measures work productivity and the ability to perform activities (Reilly, 1993). The WPAI: Specific Health Problem V2.0 (WPAI:SHP) adapted for this study includes 6 questions that assess the impact of the subject's EoE symptoms on work productivity and other activities. As such, the assessment utilized in this study is also designated as Work Productivity and Activity Impairment Questionnaire: Eosinophilic Esophagitis (WPAI:EE). The questionnaire will be administered to adult subjects only.

Subjects will complete these instruments according to Table of Events as detailed in Table 3.

6.9.2 Autoinjector (AI) Administration Questionnaire/PFS Administration Questionnaire

The CC-93538 AI was developed to enable a safe, effective, consistent, and convenient SC administration of IP by subjects in an at home environment, in addition to administration in the clinic. For study conduct under Protocol Amendment 1 (dated 10 May 2022), the PFS Administration Questionnaire was employed to evaluate the success of self-administration of CC-93538 by the [redacted] PFS presentation; with the implementation of Protocol

Amendment 2, only the AI Questionnaire will be employed going forward. The purpose of the AI/PFS Administration Questionnaire is to evaluate the success of self-administration of CC-93538 by the AI/PFS during actual use under both supervised (in-clinic) and unsupervised (at home) conditions during the study. [redacted]

6.10 Health Resource Utilization

Health resource utilization will be evaluated during the OLE study as indicated in the Table of Events (Table 3) through documentation of complications of EoE including but not limited to emergency department visits or hospitalizations for food impaction, procedures such as esophageal dilation, urgent care visits, and health care provider office visits, or use of rescue therapy. After study discontinuation or completion, subjects may be contacted for follow-up health resource utilization information.

6.11 Endolumenal Functional Lumen Imaging Probe (EndoFLIP™) Sub-study

An optional sub-study will be performed at a subset of clinical sites utilizing an EndoFLIP to evaluate the effects of CC-93538 on esophageal distensibility. The EndoFLIP assessment evaluates esophageal function and is a tool that will complement histologic, endoscopic, and symptomatic findings. An EndoFLIP will be placed into the esophagus transorally during EGD and positioned with recording sites covering a 16 cm span of the proximal to distal esophagus. Cross sectional areas within the esophagus and intrabag pressure will be measured.

The EndoFLIP procedure is an optional assessment. Only subjects transitioning from Study CC-93538-EE-001 and who have participated in the sub-study during enrollment in Study CC-93538-EE-001 are eligible to participate in this assessment for Study CC-93538-EE-002. For sites who participate and subjects who consent to participation in the EndoFLIP sub-study, this procedure should be performed at the time of the scheduled EGD at visits indicated per the Table of Events in Table 3. Please refer to the EndoFLIP™ Procedure Manual for complete information on EndoFLIP procedure instructions and required equipment and supplies.

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 product (CC-93538) is to be stored at [redacted] to [redacted]C. The IP should not be [redacted]. The labeling will be in accordance with GCP and any other local regulatory requirements. During the study, IP will be dispensed in an AI presentation provided by the Sponsor. The 360 mg dose of CC-93538 will be administered by a [redacted] at a concentration of [redacted] mg/mL.

Specific handling and dispensing instructions are provided below.

IP in AI

An AI presentation containing CC-93538 drug product at a concentration of [redacted] mg/mL in a [redacted] fill (for a total of [redacted]) will be utilized in this study. The CC-93538 360 mg in an AI is a single use, disposable, ready-to-use SC combination product consisting of CC-93538 injection in the bulk-filled syringe integrated into a functional AI device. No additional drug preparation is required prior to administration. CC-93538 solution for injection will be provided as a sterile liquid in an AI at a concentration of [redacted] mg/mL packaged in cartons (one AI per carton). 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 AI.

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 OLE study is as follows:

- CC-93538 360 mg SC once weekly during the OLE treatment Period

All subjects in the OLE study will receive CC-93538 360 mg SC once weekly during the OLE Treatment Period. The dosing regimen for the OLE may be revised, via an amendment to the protocol, after results from the core Induction and Maintenance Study, CC-93538-EE-001, are available and the optimal dosing regimen is confirmed.

On OLE Day 1, eligible subjects will be administered CC-93538 (360 mg) as a [redacted] CC-93538 SC injection. Subjects will receive [redacted] CC-93538 SC injection once weekly throughout their participation in the OLE study ([redacted] at [redacted] mg/mL CC-93538 = 360 mg CC-93538/week).

The original protocol required CC-93538 weekly SC dosing to be administered by [redacted] of [redacted] mL each at a concentration of [redacted] mg/mL (for a total dose of 360 mg SC once weekly). Protocol Amendment 1 (dated 10 May 2022) required CC-93538 weekly SC to be administered using a PFS by a [redacted] at a concentration of [redacted] mg/mL (for a total dose of 360 mg SC once weekly).

All subjects currently in the study and any new subjects entering the study will start receiving a [redacted] of the [redacted] AI once the second amendment to the protocol (Protocol Amendment 2) is implemented, informed consent is obtained, and IP is available at the site. For currently enrolled subjects who did not begin the study with the new AI presentation, a switch to the new AI presentation will occur at the next regularly scheduled study visit. However, a First AI Administration Visit will be required for subjects whose next scheduled protocol visit is not within 4 weeks of Protocol Amendment 2 site approval and IP is available on site to expedite presentation switch from PFS to AI. The visit may be scheduled at any time within this 4-week period.

During the study, weekly SC doses should be administered on the same day each week at approximately the same time of day. As the OLE will include subjects previously treated with placebo, to ensure safety, and to preserve the maintenance of the blind from Study CC-93538-EE-001, the first 3 weekly SC doses will be required to be administered in the clinic for all subjects entering OLE. 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. To ensure accurate dose administration and compliance with the new [redacted] weekly SC injection using the [redacted] AI presentation, for subjects who did not begin the study with this new presentation (on OLE Day 1), one additional in-clinic weekly dose with at least a 30-minute observation is required for the first administration. This first dose will occur either at the time of the subject's next scheduled protocol required study visit or the First AI Administration Visit as described in Table 3. Further, subjects will complete the AI Administration Questionnaire at the time of this first in-clinic dose.

In the event the IP (AI) is not available on-site at the time of Protocol Amendment 2 site approval, subjects should continue receiving the [redacted] weekly SC injection using the [redacted] PFS presentation until the IP (AI) is available. Subjects who self-administer (as defined in Section 7.2.1) with the PFS presentation should continue to complete the PFS Administration Questionnaire until the switch to the new AI presentation occurs.

The SC doses should be administered as described in the Instructions for Use document, avoiding any blood vessels, thickened or tender skin, scars, fibrous tissue, stretch marks, bruises, redness, nevi, or other skin imperfections. Refer to the Pharmacy Manual and Instructions for Use for additional specifications regarding administration, including guidance regarding anatomical locations for injection and rotation of the injection site.

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 of CC-93538 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 CC-93538 by the AI 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, self-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 dose administration and is independent of the subject's age. To ensure the subject's suitability for self-administration, the Investigator and site staff will evaluate each subject for adherence to protocol requirements and must feel comfortable that the subject is willing to comply with the [redacted] regimen no matter how well the subject may feel during the study. Subjects who self-administered IP in Study CC-93538-EE-001 or Study CC-93538-DDI-001 should continue this practice in the OLE. Subjects who initiate self-administration in the OLE will be required to perform, at a minimum the first 3 weekly injections on-site in the presence of site personnel. The number of on-site injections may be increased based on Investigator judgment or other local requirements. This will allow for on-site 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 on-site at the scheduled study visits. As subjects transition from the parent study to the OLE study, subjects will be allowed to switch their method of administration (eg, from in-clinic or home health nurse service to self-administration) based on Investigator judgment if it is in the best interest of the subject, the subject demonstrates proficiency, and a change is not anticipated to impact compliance. To help promote consistency within the data, it is preferred that subjects do not switch their injection method during the conduct of the OLE study, unless there is a reasonable rationale for doing so (eg, change in injection proficiency, treatment compliance issue, etc) per the clinical judgment of the Investigator. 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 during the OLE study.

7.2.2 Missed Dose(s)

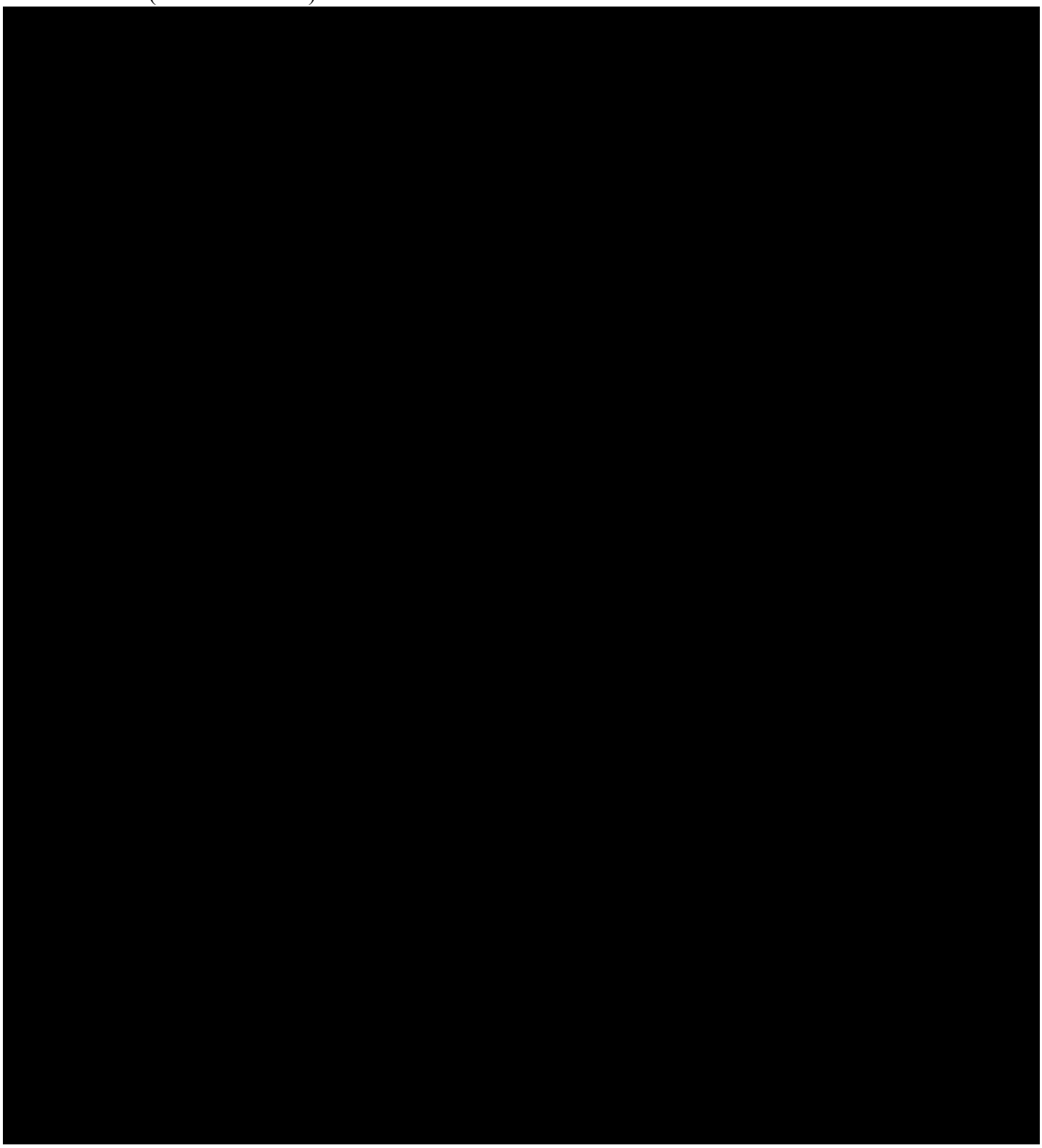
If a subject is unable to take a dose of CC-93538 on the usually scheduled day:

- 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

[redacted], 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 CC-93538, as determined by the Investigator, will be permanently discontinued from IP (see Section 11.1).



[redacted]

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 CC-93538. 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. Subjects that discontinue the study will be asked to complete the ET/EoT Visit and the Interim 8-week and Final 16-week Safety Follow-up Visits.

7.2.6 Rescue Therapy

During the study, subjects with a worsening of EoE symptoms requiring rescue therapy may continue study participation with concomitant therapy as described in Section 8.1.1.

7.3 Method of Treatment Assignment

Prospective subjects must provide proper informed consent/assent before any study procedures are performed (refer to Section 12.3 for further details regarding obtaining subject's informed consent/assent). After all OLE baseline assessments have been completed and the Investigator has confirmed continued eligibility of the subject per the inclusion (Section 4.2) and exclusion criteria (Section 4.3), all eligible subjects will be assigned to the same IP and will receive open-label CC-93538 360 mg SC starting on OLE Day 1 and once weekly throughout the OLE study.

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.

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 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 OLE Day 1/Baseline and 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; if the treatment started and stopped prior to the first dose on OLE Day 1, documentation is only required on the parent study eCRF. A history of previous treatments for EoE used prior to participation in the core Induction and Maintenance Study, CC-93538-EE-001, or the Phase 1 Study, CC-93538-DDI-001, will be documented as part of Study CC-93538-EE-001 or Study CC-93538-DDI-001, respectively.

All concomitant treatments, including blood and blood products, used from 28 days prior OLE Day1/Baseline until 16 weeks after the last dose of IP (ie, until the Final 16-week Safety Follow-up Visit), must be reported on the eCRF. Treatment that started prior to the time of the first dose on OLE Day 1 will be documented in the parent study only, unless the use of such treatment is ongoing at or after the time of the first dose on OLE Day 1. All treatments ongoing or started at the time of or after the first dose on OLE Day 1 will be documented in the CC-93538-EE-002 eCRF.

8.1 Permitted Concomitant Medications and Procedures

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 in the parent 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.

8.1.1 Rescue Therapy

Prior to entry into the OLE study or during OLE study participation, subjects with a worsening of EoE symptoms requiring rescue therapy (defined as a severe EoE flare; refer to Section 6.4.2.7) may continue to participate in the study with concomitant rescue therapy. Rescue therapy includes EoE standard of care pharmacotherapy (including but not limited to corticosteroids), dietary modification (eg, food elimination diet), and/or dilation procedure.

8.2 Prohibited Concomitant Medications and Procedures

Concomitant medications and procedures that are prohibited in the Induction and Maintenance Study, CC-93538-EE-001, and the Phase 1 Study, CC-93538-DDI-001, and for the duration of the OLE Study, CC-93538-EE-002, (until the Final 16-week Safety Follow-up Visit) include:

- 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 in Study CC-93538-EE-001 or Study CC-93538-DDI-001 and through the duration of the OLE study. Use of any of the aforementioned medications during study participation will result in the subject's permanent discontinuation from IP.

- Subjects may not receive oral or sublingual immunotherapy from the first Screening Visit in Study CC-93538-EE-001 and through the end of the OLE study. Subjects should not have received oral or sublingual immunotherapy within 6 months prior to the first Screening Visit in Study CC-93538-EE-001 or Study CC-93538-DDI-001.
- Subjects must not have received a live attenuated vaccine within 1 month of the first Screening Visit in Study CC-93538-EE-001 or Study CC-93538-DDI-001 through the end of the OLE study.
- Concurrent treatment with another IP, including an investigational treatment or investigational 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 the first Screening Visit in Study CC-93538-EE-001 or within 30 days or 5 drug half-lives (whichever is longer) prior to the first Screening Visit in Study CC-93538-DDI-001 and through the end of the OLE study. Subjects who received an investigational COVID-19 vaccine as part of a clinical trial during the course of Study CC-93538-EE-001 will not be eligible to participate unless it is determined by discussion between the Investigator and the Clinical Trial Physician that the biologic impact of the vaccine is stabilized.

8.3 Required Concomitant Medications and Procedures

See Section 6.4.1 for EGD requirements.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

The OLE study is a Phase 3, open-label, uncontrolled study to explore the long-term effects of treatment with CC-93538 360 mg SC once weekly in adult and adolescent subjects with EoE who had previously participated in the Induction and Maintenance Study, CC-93538-EE-001, or Study CC-93538-DDI-001. An independent Data Monitoring Committee (DMC) will be implemented to review the safety data regularly during the course of the study.

All efficacy and safety data will be listed by subject. Descriptive statistics will consist of the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables and counts and percentages for categorical variables.

For the OLE, all endpoints will be summarized using descriptive statistics and no hypothesis testing will be performed. Comparisons between the different parent studies or cohorts will not be conducted.

All analyses including summaries and listings will be performed using SAS® software version 9.4 or higher.

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:

Analysis Population

OLE Population

The analysis population that will be used in the statistical analysis is the OLE population which consists of all subjects receiving at least one dose of IP during OLE.

The OLE population consists of subjects who were originally randomized to the 3 arms in Study CC-93538-EE-001 as well as subjects who participated in the parent Study CC-93538-DDI-001.

For subjects transitioning from Study CC-93538-EE-001, the 3 arms in the parent study were: placebo in both the Induction Phase and the Maintenance Phase, CC-93538 360 mg SC once weekly in the Induction Phase and CC-93538 360 mg SC once every other week in the Maintenance Phase, and CC-93538 360 mg SC once weekly in both the Induction Phase and the Maintenance Phase. These subjects can enter the OLE either: after completing Week 24 of the Induction Phase or after completing Week 48 of the Maintenance Phase.

Subjects will be analyzed based on the treatments received during the core Induction and Maintenance Study, CC-93538-EE-001, defined as:

- For subjects who enter OLE after completing Week 24 of the Induction Phase, based on the treatment(s) the subjects received in CC-93538-EE-001 before they enter OLE, there are 2 different cohorts:
  - Cohort A: Subjects receiving placebo in the Induction Phase but did not enter the Maintenance Phase (denoted as “PBO/-”)

  - Cohort B: Subjects receiving CC-93538 360 mg SC once weekly in the Induction Phase but did not enter the Maintenance Phase (denoted as "360 mg QW/-")
- For subjects who enter after completing Week 48 of the Maintenance Phase, based on the treatment(s) the subjects received in CC-93538-EE-001 before they entered OLE, there are 3 different cohorts:
  - Cohort C: Subjects receiving placebo in both the Induction Phase and the Maintenance Phase (denoted as "PBO/PBO")
  - Cohort D: Subjects receiving CC-93538 360 mg SC once weekly in the Induction Phase and CC-93538 360 mg SC once every other week in the Maintenance Phase (denoted as "360 mg QW/360 mg Q2W")
  - Cohort E: Subjects receiving CC-93538 360 mg SC once weekly in both the Induction Phase and the Maintenance Phase (denoted as "360 mg QW/360 mg QW")

For subjects transitioning from Study CC-93538-DDI-001, their data will be summarized separately.

9.3 Sample Size and Power Considerations

As this is an OLE study for subjects who participated in the prior Study CC-93538-EE-001 or Study CC-93538-DDI-001, there is no statistical basis for the sample size. This is a descriptive study and comparisons between the parent studies or cohorts are not appropriate. It is anticipated that approximately 259 subjects who participated in Study CC-93538-EE-001 will be eligible for treatment in this study assuming an overall drop-out rate of 35% in Study CC-93538-EE-001 and approximately [redacted] subjects who participated in Study CC-93538-DDI-001 will be eligible for treatment in this study.

9.4 Background and Demographic Characteristics

Subject demographics from CC-93538-EE-001 will define the subject demographics for Cohorts A through E for CC-93538-EE-002. Subject demographics from CC-93538-DDI-001 will be summarized separately.

OLE baseline will be defined by the last observed measurement captured prior to the OLE Day 1 administration of CC-93538. Descriptive summaries will be presented. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Additional details are provided in the Statistical Analysis Plan (SAP).

9.5 Subject Disposition

Subject disposition, including the number of subjects enrolled, dosed, completing the study and discontinuing the study with reasons for discontinuation, will be summarized with numbers and percentages by cohorts. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

Subjects from CC-93538-DDI-001 will be summarized separately.

9.6 Efficacy Analysis

Efficacy analyses will be descriptive for each of the pre-defined cohorts (subjects from Study CC-93538-DDI-001 will be summarized separately) and will include the exploratory endpoints except for PK and biomarker endpoints. The analyses for the PK endpoints and the immunogenicity secondary endpoint will be described separately in the PK Analysis Plan. The biomarker endpoints and the related analyses will be described separately in the Biomarker Analysis Plan.

For continuous endpoints (ie, mean change over time), descriptive statistics including number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum will be provided by cohort at appropriate time points (for example, OLE Weeks 4, 8, 16, 24, 36, and 48 for the mean change in DD). In addition, the 95% confidence interval (CI) for the mean estimates will be presented for the following endpoints: [redacted] the mean change over time in the endoscopic features of EoE as measured by the EREFS from baseline, the mean change over time in the histologic features of EoE as measured by the EoEHSS from baseline, and the mean change over time in mDSD composite score from baseline.

For categorical endpoints (ie, proportions), descriptive statistics including counts and percentages will be provided by cohort at each time point. In addition, the 95% CI for the mean estimates will be presented for the following endpoints: the proportion of subjects with histologic response defined as a peak esophageal eosinophil count $\leq$ 6/hpf and the proportion of subjects with histologic response defined as a peak esophageal eosinophil count < 15/hpf.

For subjects who enter the OLE study with clinical, histologic, or clinical and histologic response after completing the Maintenance Phase in Study CC-93538-EE-001 (Cohorts C, D and E), the durability of response will be reported as the proportion of subjects who continue having their clinical, histologic, or clinical and histologic response at each time point, and will be reported by cohort.

For change from baseline endpoints, details regarding baseline definitions will be described in the SAP.

9.7 Safety Analysis

Adverse events will be monitored during the study and the data analyzed with respect to incidence as well as severity and potential relationship of the AEs to CC-93538.

All AEs with a start date before the first open-label dose date, and that are ongoing from a previous study to this Open-label Extension study, will be listed in the AE data listing and labeled as "Prior Adverse Event."

Adverse events with an onset on or after the first dose of CC-93538 in this study, or with an onset prior to the first dose of CC-93538 that increase in severity on or after the first dose of CC-93538, will be considered treatment emergent. Treatment-emergent Adverse events will be summarized by system organ class (SOC) and preferred term and presented in descending order of frequency within each SOC. Serious AEs, AEs leading to discontinuation of treatment, and AEs leading to discontinuation of the study will be summarized similarly.

Associated laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual subject values outside the standard reference range will be flagged and listed. Shift tables will be produced showing the frequency of shifts from baseline to the lowest and to the highest on-study value in and out of the normal range as well as by visit. Changes from baseline to each visit for each laboratory parameter will also be summarized.

The change from baseline to each visit for each of the vital sign variables will be summarized. Abnormal vital sign values will be flagged and listed.

By-subject listings will be provided for all relevant safety data. Graphical displays and figures may be provided where useful to assist in the interpretation of results.

No statistical hypothesis testing will be performed on any safety results.

Overall safety and tolerability will be summarized for each drug presentation (the 360 mg dose of CC-93538 administered by [redacted] injections of [redacted] mL each at a concentration of [redacted] mg/mL CC-93538 or by [redacted] injection of [redacted] mL at a concentration of [redacted] mg/mL CC-93538 administered with the PFS device constituent part or by [redacted] injection of [redacted] mL at a concentration of [redacted] mg/mL CC-93538 administered with the AI device constituent part) utilizing descriptive statistics.

9.8 Interim Analysis

There are no interim analyses planned for this study.

9.9 Other Topics

9.9.1 Pharmacokinetics, Pharmacodynamics and Exposure-Response

Serum trough concentrations (C_{trough}) of CC-93538 will be summarized with descriptive statistics by treatment group as received in the core Induction and Maintenance Study, CC-93538-EE-001, and by visit. C_{trough} of CC-93538 following administration with the different drug product presentations at steady state received in the OLE Study, CC-93538-EE-002, will be summarized with descriptive statistics. C_{trough} of CC-93538 for subjects transitioning from the Phase 1 Study, CC-93538-DDI-001 will be summarized separately. Additional analysis may be conducted as appropriate (eg, by ADA status).

Population PK analysis will be performed using nonlinear mixed-effects modeling utilizing PK data from CC-93538-EE-001 and CC-93538-EE-002 to characterize the population PK of CC-93538 and to identify key covariate effects (eg, immunogenicity, intrinsic and extrinsic factors). Data from other studies may be included in the population PK analysis if appropriate. Exposure-response and pharmacodynamic relationships will be conducted for efficacy, safety, and biomarker endpoints, as appropriate. 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.

9.9.2 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).

9.9.3 External Data Monitoring Committee

Safety monitoring will also be performed by an external, independent Data Monitoring Committee (DMC). A 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 the duration of DMC implementation during the OLE study, will also be described in the DMC Charter.

9.9.4 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 judgment 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, AI) failures or malfunctions should be captured during the study, and any device related AEs should also be documented. 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. In addition, AEs or SAEs related to SARS-CoV-2 infection will also trigger additional data collection through supplementary safety report forms, which will allow the Sponsor to further evaluate these events.

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 (in Study CC-93538-EE-001 or Study CC-93538-DDI-001) until 16 weeks after the last dose of IP in the OLE study as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. The timing of AE assessment documentation for the OLE study will begin at the time of or after the first dose in the OLE study (on OLE Day1); AEs occurring before this timeframe will be documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001. 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 by completing the paper SAE Report Form and sending it directly to Celgene Drug Safety (see Section 10.5). In addition, COVID-19 or positive SARS-CoV-2 test results should also be reported within 24 hours of the Investigator's knowledge of the event regardless of the seriousness criteria.

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 judgment 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. Ongoing AE/SAEs first documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will continue to be followed in the OLE study. 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 within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as an SAE. 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 as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

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 within 24 hours of the Investigator's knowledge of the event per the instruction provided on Celgene's Serious Adverse Event Report Form Completion Guidelines. This instruction pertains to initial SAE reports as well as any follow-up reports.

For Study CC-93538-EE-002, the reporting of SAE data (both initial and follow-up) to Celgene Drug Safety, will transition to a paper format rather than the electronic format being utilized in the parent studies (CC-93538-EE-001 and CC-93538-DDI-001). The Investigator is required to ensure that the data on the paper SAE Report Form is accurate and consistent. In Study CC-93538-EE-002, this requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject receives the first dose of IP [on OLE Day 1] until 16 weeks after the last dose of IP [through the Final 16-week Safety Follow-up Visit]) 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 the first dose of OLE IP administration, but after signing the OLE ICF/assent, will be recorded on the appropriate eCRF of the parent study (CC-93538-EE-001 or CC-93538-DDI-001). Therefore, for SAEs occurring prior to the first dose of IP in the OLE study (OLE Day 1), the SAE onset date will be recorded in the appropriate parent study (CC-93538-EE-001 or CC-93538-DDI-001) and reported to Celgene Drug Safety per the instructions provided in those protocols. Ongoing AEs/SAEs first documented in Study CC-93538-EE-001 or Study CC-93538-DDI-001 will then continue to be followed in the OLE study.

The SAE report 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 as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent directly to Celgene Drug Safety. Follow-up safety data should also be recorded in the eCRF, as applicable.

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.

10.5.1 Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 5 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6 Adverse Events of Special Interest

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

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, expedited reports sent to the Food and Drug Administration (FDA) by the Sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 Code of Federal Regulations (CFR) 312.32. For reporting to the FDA, events that are not suspected to be causally related to CC-93538 by the Sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population, will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

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, suspected unexpected serious adverse reactions (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 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 CC-93538:

- Adverse event
- Physician decision
- Lack of efficacy
- Protocol deviation that may impact subject safety
- 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 CC-93538 (permanent discontinuation of CC-93538 will result in study discontinuation):

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 CC-93538 will also be discontinued from the study (see Section 11.2).

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:

- Screen failure
- Adverse event
- Physician decision
- Lack of efficacy
- Protocol deviation that may impact subject safety
- Withdrawal by subject or parent/guardian
- Death
- Lost to follow-up
- Non-compliance with IP
- Other (to be specified on the eCRF)
- Events requiring permanent CC-93538 discontinuation as listed in Section 11.1 will result in study discontinuation

Subjects who demonstrate a persistent lack of improvement or worsening of EoE symptoms should be discontinued. While subjects will have the opportunity to continue participation in the OLE with use of rescue therapy as needed, based on clinical judgment, the Investigator should discontinue any subject in which study participation no longer is in the best interest of the subject.

During the 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.

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.

For the OLE study, subjects who discontinue the study will have an ET/EoT Visit within 2 weeks after final CC-93538 administration and an Interim 8-week and Final 16-week Safety Follow-up Visit at 8 weeks and at 16 weeks, respectively, after final CC-93538 administration for the assessment of safety and clinical status. Assessments should be performed in accordance to the Table of Events (Table 3).

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.

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. Adolescent subjects who reach the legal age of consent while participating in the study will be asked to sign an ICF (referred to as a Transitional ICF) themselves to acknowledge their willingness to continue in the study. For the purposes of this study, adolescents are defined as subjects aged 12 to 17 years at the time of signing the assent form in Study CC-93538-EE-001 (except where national or regional guidelines for the definition of adolescence differ from the definition stated above). As described in the Transitional ICF, subjects who enter the study as adolescents should continue to complete the assessments specific for adolescents throughout both CC-93538-EE-001 and CC-93538-EE-002 and do not need to complete assessments that are only required in adult subjects. In Austria, Germany, Spain, and Switzerland, adolescent subjects will not be enrolled.

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.

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 your 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, labelling, 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 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 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADL	Activities of daily life
AE	Adverse event
AESI	Adverse events of special interest
AI	Autoinjector
ALT	Alanine aminotransferase
AMS	Avoidance, modification, and slow eating
AST	Aspartate aminotransferase
AUC	Area under the curve
AxMP	Auxiliary medicinal product
β-hCG	β-subunit of human chorionic gonadotropin
BMS	Bristol-Myers Squibb
CFR	Code of Federal Regulations
CGI-S	Clinician Global Impression of Severity
CI	Confidence interval
C_{max}	Observed maximum serum concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
C_{trough}	Serum trough concentration
CYP	Cytochrome P450
DB	Double-blind
DD	Dysphagia day(s)
DMC	Data Monitoring Committee
DSD	Daily Symptom Diary
EC	Ethics Committee
EC_{50}	Half maximal effective concentration
eCRF	Electronic case report form

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
EDC	Electronic data capture system
eDiary	Electronic diary
EEA	European Economic Area
EEsAI	Eosinophilic Esophagitis Activity Index
EGD	Esophagogastroduodenoscopy
EMA	European Medicines Agency
EMT	Epithelial mesenchymal transition
EndoFLIP	Endolumenal Functional Lumen Imaging Probe
EoE	Eosinophilic esophagitis
EoEHSS	EoE histology scoring system
EoT	End of Treatment
EREFS	EoE Endoscopic Reference Score
ET	Early Termination
EU	European Union
[redacted]	[redacted]
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
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
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hpf	High-power field
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFNα	Interferon alpha

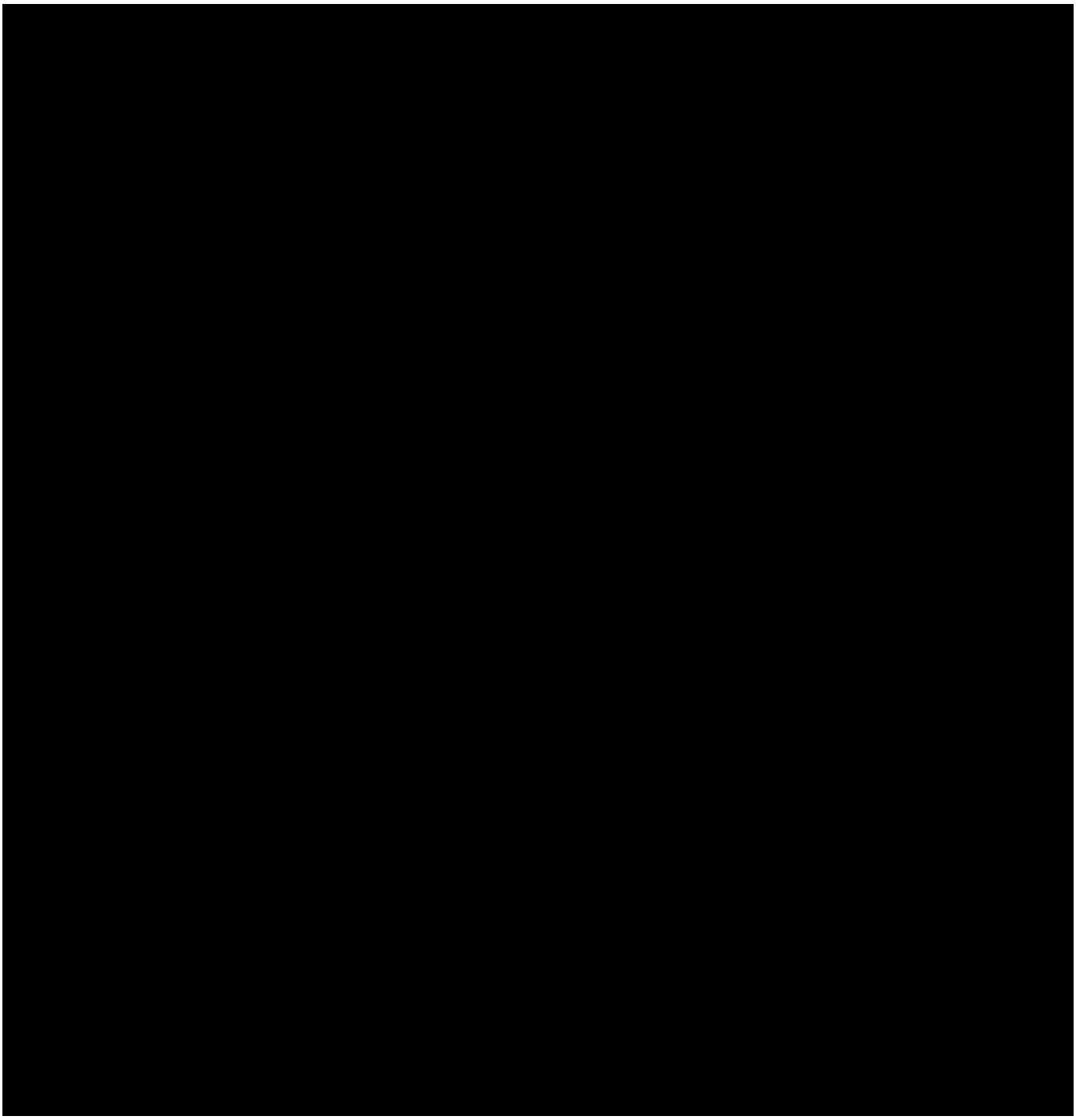
Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgG1κ	Immunoglobulin G1 kappa
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
IL-17	Interleukin-17
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
[redacted]	[redacted]
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous/ly
JAK	Janus kinase
LA	Los Angeles
mAb	Monoclonal antibody
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mDSD	Modified Daily Symptom Diary
MedDRA	Medical Dictionary for Regulatory Activities
N / n	Number of subjects
NIMP	Non-investigational medicinal product
OLE	Open-label Extension
OTC	Over the counter
PDE	Phosphodiesterase
PEESS	Pediatric Eosinophilic Esophagitis Symptom Severity Module

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
PFS	Pre-filled syringe(s)
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
QW	Once weekly
Q2W	Once every 2 weeks (ie, once every other week)
RBC	Red blood cell
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
SF-10	10-Item Short Form Health Survey for Children
SF-12v2	12-Item Short Form Health Survey
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMT	Safety Management Team
SNP	Single nucleotide polymorphism
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th2	Type 2 T helper (cell)
t_{max}	Time to the observed maximum concentration
TNFα	Tumor necrosis factor alpha
[redacted]	[redacted]
US	United States
VDQ	Visual dysphagia question
WBC	White blood cell
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

APPENDIX B MODIFIED DAILY SYMPTOM DIARY (MDSD)



OVERALL RATIONALE FOR PROTOCOL AMENDMENT 1:

This global protocol amendment 1 is created to support the introduction of a new presentation of CC-93538 [redacted] pre-filled syringe (PFS) at a concentration of [redacted]. The new presentation allows subjects to receive the 360 mg weekly dose of CC-93538 by a [redacted] subcutaneous (SC) injection. This protocol amendment also allows subjects who complete the Phase 1 Study CC-93538-DDI-001 the opportunity to transition to Study CC-93538-EE-002 and continue to receive access to open-label CC-93538. Additionally, details regarding the timing of and the assessments for those subjects transitioning from Study CC-93538-DDI-001 into the Open-label Extension (OLE) study are included.

The following summary of changes outline the revisions to the various sections of the original protocol.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page and Signature Pages	Sponsor address and personnel changes.	Administrative changes.
Title Page; Protocol Summary; Section 1.2.1: Mechanism of Action	Bristol-Myers Squibb (BMS) compound number added.	For clarification purposes.
Protocol Summary	Language has been added regarding study eligibility, clarifying that in Germany, Spain, and the United Kingdom, only subjects who have had an inadequate response to corticosteroids or are intolerant to corticosteroids will be enrolled in the Phase 3 Studies CC-93538-EE-001 and CC-93538-EE-002.	Local restrictions prohibit enrollment of subjects who are naive or have had an adequate response to corticosteroids in Germany, Spain, and the United Kingdom.
	Language has been updated to indicate that in Austria, Germany, Spain, and Switzerland, only adult subjects will be enrolled, and adolescent subjects will not be included in the Phase 3 Studies CC-93538-EE-001 and CC-93538-EE-002.	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.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 1.2.2: Clinical Studies	New protocol Section 1.2.2.4 (Phase 1 Study, CC-93538-CP-002) has been added.	To include the results of Study CC-93538-CP-002, which provide the pharmacokinetic (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.
Protocol Summary; Section 1.3.1: Study Rationale and Purpose; Section 1.3.2: Rationale for the Study Design; Section 3.2: Open-label Extension Study Design; Section 3.2.1: Open-label Treatment Period; Section 3.3: Study Duration for Subjects; Section 4.1: Number of Subjects; Section 4.2: Inclusion Criteria (1, 2, 3, 4a); Section 4.3: Exclusion Criteria; (6, and 14) Section 5: Table of Events; Section 8.2: Prohibited Concomitant Medications and Procedures; Section 9.1: Overview;	• New language was added for subjects who complete Study CC-93538-DDI-001 and are eligible to transition to Study CC-93538-EE-002. • Open-label Extension Study Schema (Figure 2) was updated to include subjects from Study CC-93538-DDI-001 who complete Period 2 and are eligible to transition to Study CC-93538-EE-002. • New Inclusion Criterion 1b was added, and Inclusion Criteria (2, 3, and 4a), Exclusion Criteria (6 and 14), and footnotes for Table 3 (Table of Events for the Open-label Extension Study) were updated to reflect Study CC-93538-DDI-001 details.	In addition to subjects participating in the Induction and Maintenance Study CC-93538-EE-001, subjects who participate in the Phase 1 Study CC-93538-DDI-001 and complete Period 2 will be offered the opportunity to transition into Study CC-93538-EE-002, allowing for continued access to CC-93538.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.3: Sample Size and Power Considerations; Section 10.2.6: Outcome		
Section 1.3.1.1: Benefit-Risk Assessment; Section 8.1: Permitted Concomitant Medications and Procedures	Information related to concomitant use of coronavirus disease 2019 (COVID-19) vaccines in subjects receiving CC-93538 was added.	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 1.3.3: Rationale for Dose, Schedule and Regimen Selection; Section 2: Study Objectives and Endpoints; Section 5: Table of Events; Section 6.2: Open-label Extension Treatment Period; Section 6.9: Subject-Reported Outcomes; Section 7.1: Description of Investigational Product(s); Section 7.2: Treatment Administration and Schedule	• Language was added to describe the introduction of the [redacted] of the [redacted] PFS, which is replacing the [redacted] that were administered in Study CC-93538-EE-001 and the original protocol for Study CC-93538-EE-002. • For subjects currently enrolled in the study, added language states the timing for the switch to the new presentation will occur at the subject's next scheduled visit, and the first dose will be administered during an in-clinic visit for all subjects to ensure accurate dose administration and compliance. • A new exploratory objective and study endpoint were added to evaluate the successful self-administration of CC-93538 using the new [redacted]	• Upon the implementation of this amendment, the CC-93538 360 mg SC dose will be administered by [redacted] of [redacted] provided in a [redacted] PFS in order to study the higher concentration and higher volume presentation for use with long-term CC-93538 treatment. • The PFS Administration Questionnaire is introduced to assess subjects' success in self-administration of CC-93538 by the new [redacted] PFS presentation in-clinic or at home.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
	PFS presentation by [redacted]. • [redacted] • New protocol Section 6.9.2: PFS Administration Questionnaire has been added.	
Section 3.2: Open-label Extension Study Design; Section 4.1: Number of Subjects; Section 4.2: Inclusion Criteria (Inclusion Criterion 7); Section 6: Procedures; Section 12.3: Subject Information and Informed Consent	Protocol sections were updated to indicate that in Austria, Germany, Switzerland, and Spain, only adult subjects will be enrolled, and adolescent subjects will not be included in the Phase 3 Studies CC-93538-EE-001 and CC-93538-EE-002.	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	The sentence in Inclusion Criterion 7) regarding legal maturity in Japan at the age of 20 was removed to reflect a change in the country's age of legal maturity.	Updates were made to reflect country specific requirements.
Section 4.3: Exclusion Criteria	With respect to gastritis, Criterion 8) was updated to clarify that only a medical diagnosis of gastritis which is deemed by the Investigator to be clinically significant is exclusionary.	As the term "gastritis" may have a broader meaning including multiple gastrointestinal symptoms, the criterion is revised to clearly define the condition for study eligibility.
Section 5: Table of Events; Section 6.4.2.4: Global Impression of Change in EoE Symptoms (GIC-EoE);	• Table 3 (Table of Events for the Open-label Extension Study) now provides additional footnotes for the Global Impression of Change in Eosinophilic Esophagitis	• For subjects transitioning from Study CC-93538-DDI-001, not all assessments will be required: GIC-EoE and EndoFLIP will not be

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 6.11: Endolumenal Functional Lumen Imaging Probe (EndoFLIP™) Sub-study	Symptoms (GIC-EoE) and the EndoFLIP (optional sub-study). • EndoFLIP procedure instructions were removed from the protocol.	conducted in these subjects, as no baseline assessment will be available. • Complete EndoFLIP procedure instructions will be included in a separate manual.
Section 5: Table of Events; Section 6.7.2: Tissue Biomarker Assessments	Section 6.7.2 and Table 3 were updated to clarify that esophageal tissue biomarkers will not be assessed in subjects transitioning from Study CC-93538-DDI-001.	Esophageal tissue biomarkers will not be assessed in subjects transitioning from Study CC-93538-DDI-001 as there is no baseline measure, precluding the assessment of any post-baseline changes.
Section 5: Table of Events; Section 6.2: Open-label Extension Treatment Period	Details have been added regarding subjects who transition from Study CC-93538-DDI-001 into the OLE study.	To provide requirements for OLE Day 1/Baseline assessments for patients transitioning from Study CC-93538-DDI-001 to OLE Study CC-93538-EE-002 as well as assessments that will not be required during the study for those subjects transitioning from CC-93538-DDI-001.
	Language has been added regarding pregnancy testing for subjects who transition from Study CC-93538-DDI-001 into the OLE study.	For subjects transitioning from Study CC-93538-DDI-001, if a pregnancy test has not been completed on the same day of OLE Day 1, then a pregnancy test in urine or serum must be repeated prior to dosing.
Section 6.9.1: Health-related Quality of Life	Language has been included to state that Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) is also referred to as WPAI: Eosinophilic Esophagitis (EE).	To clarify the name change of the instrument in the electronic data capture system (EDC) to denote EoE as the specific health problem.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2.1: Self-Administration	Clarification has been provided regarding a switch from in-clinic or home health nurse service to self-administration.	Subjects that transitioned from the parent studies to the OLE study will be allowed to switch their method of administration (eg, from in-clinic or home health nurse service to self-administration) based on Investigator judgment.
Protocol Summary; Section 9.2: Study Population Definitions; Section 9.4: Background and Demographic Characteristics; Section 9.5: Subject Disposition; Section 9.6: Efficacy Analysis	Language was added to clarify that data collected for subjects who transitioned from Study CC-93538-DDI-001 will be summarized separately from subjects who transitioned from CC-93538-EE-001.	Data for subjects who transitioned from the two parent studies will be summarized separately because of the difference in prior CC-93538 treatment durations.
Section 9.7: Safety Analysis	Clarification has been provided, stating that the overall safety and tolerability data will be summarized by presentation utilizing descriptive statistics.	Text was added to describe the assessment of the safety profile of CC-93538 based on PFS presentation the subjects received during the trial.
Section 10: Adverse Events; Section 10.5: Reporting of Serious Adverse Events	Modifications were made for reporting of serious adverse events (SAEs), adverse events of special interest (AESI), and adverse events (AEs) related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection using a paper reporting form.	All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by completing the paper SAE Report Form and sending it directly to Celgene Drug Safety. This reporting process aligns with company policy, namely that open-label extension studies will not utilize the electronic safety reporting process.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 1		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.5.1: Safety Queries	Details for reporting SAEs and urgent safety queries have been added.	Guidance is provided that urgent queries (eg, missing causality assessment) may be reported by phone.
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 (US FDA) 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-002 protocol.
All	Minor formatting and editorial changes have been made.	Minor edits that do not change the content of the protocol were made to improve readability and consistency.