Official Title of Study:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Induction and Maintenance Study to Evaluate the Efficacy and Safety of CC-93538 in Adult and Adolescent Japanese Subjects with Eosinophilic Gastroenteritis

NCT Number: NCT05214768

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

PROTOCOL NUMBER:	**CC-93538-EG-001**
COMPOUND NUMBER:	**CC-93538 (BMS-986355)**
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DATE AMENDMENT 1.0 FINAL	**29 Jun 2021**
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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

See Electronic Signature and Date on File in Electronic Document Management System.	
Signature of Celgene Therapeutic Area Head	**dd mmm yyyy**
[redacted]	
Printed Name of Celgene Therapeutic Area Head and Title	

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

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[redacted]	21 Sept 2023
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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 5.0:

Protocol Amendment 5 is being implemented to support the introduction of a new [redacted] presentation for administration of CC-93538 (BMS-986355) as a weekly subcutaneous (SC) dose by a single 2 mL injection at a concentration of 180 mg/mL. The details on the transition of current and new subjects to the new [redacted] presentation, timing of visits, [redacted] 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 [redacted] and pre-filled syringe (PFS) presentations. Additionally, there are minor clarification and administrative updates that have been included in this Amendment.

The following summary of changes outlines the revisions to the various sections of Protocol Amendment 5.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Throughout	In the OLE Phase, the description about [redacted] has been added 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 [redacted] presentation in the OLE Phase.
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.
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 single subcutaneous (SC) injections of CC-93538 administered using an [redacted] versus PFS.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
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 evaluatingCC-93538 for moderate-to-severe atopic dermatitis.
Section 1.2.2.6, Phase 1 Study, IM042-003 Section 1.3.2, 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 single dose 360 mg/2 mL [redacted] presentation.	To include the preliminary results of Phase 1 Study IM042-003 Part 1, which provides PK comparability, safety, tolerability, and immunogenicity of single SC injections of CC-93538 administered using an [redacted] versus PFS. The results of Study IM042-003 support the introduction of the single dose 360 mg/2 mL [redacted] presentation in Protocol Amendment 5.
Table 1, Study Objectives Table 2, Study Endpoints	A new [redacted] objective and endpoint has been added [redacted]	To account for the change in the presentation of administration of CC-93538 [redacted].
Section 3.1.1, Screening Period Section 4.2, Inclusion Criterion 4 Table 4, Table of Events for the Induction Phase; footnote "q" Section 6.4.2.1, Izumo Scale Questionnaire	Clarified that the Izumo Scale data collected before the investigational product (IP) administration on Day 1 can be used for confirming eligibility of study participation.	For clarification purposes.
Section 3.1.4, Open-label Long-term Extension Phase Table 6, Table of Events for the Open-	Increased the maximum acceptable interval between the last dose of investigational product (IP) in the Induction Phase or the Maintenance Phase to	Accounting for unavoidable situations that may cause delays in the first dose in OLE (eg. coronavirus disease 2019 restrictions, unavailability of

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
label Long-term Extension (OLE) Section 6.3.2, Open-label Long-term Extension (OLE) Phase	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 the Induction Phase or the Maintenance Phase, unless discussed with the Medical Monitor.	IP supplies, scheduling issues) and for increased flexibility for sites to enroll subjects on this study and receive CC-93538.
Section 3.1.6, Worsening of EGE Symptoms or Lack of Improvement Section 6.4.2.7, Worsening of EGE Symptoms, EGE Flare, the EGE 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 EGE symptoms in the OLE Phase. 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.
Table 6, Table of Events for the Open-label Long-term Extension (OLE)	• Included an additional [redacted] Administration Visit for switching to the new IP presentation. • Footnote "y" added to provide the window for the First [redacted] Administration Visit. [redacted]	• This First [redacted] Administration Visit is being added to expedite the switch to the new [redacted] presentation for subjects whose next scheduled visit is not within 4 weeks of the Protocol Amendment 5 implementation and IP availability at the site. [redacted]
Table 6, Table of Events for the Open-label Extension (OLE)	• Additional time points added for serum CC-93538 PK assessment at Week 36 of Year 1 and at Q1 and Q3 Visits at Year 2 and beyond.	To acquire more data on the drug product presentations.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Additional time points added for serum antibodies to CC-93538 assessment at Week 36 of Year 1 and at the Q1 and Q3 Visits at Year 2 and beyond.	
Section 6.1.2, Screening Failures and Rescreening of Potential Subjects	Updated to clarify that the most current results prior to dosing on Day 1 will be used to assess study inclusion if more than one set of laboratory tests are drawn.	For clarification purposes.
Section 6.2, Induction Phase and Maintenance Phase	Provided guidance regarding the Week 16 dose when out of window due to EGD scheduling.	For clarification purposes.
Section 6.2.1, EGE Flare Assessment Visit	• Provided guidance regarding Week 16/Week 48 Visit EGD requirements for subjects that had an EGD as part of their EGE Flare assessment. • Note added to clarify that samples do not need to be a pre-dose draw unless the subject is expected to dose later that day.	For clarification purposes.
Section 6.3.2, Open-label Long-term Extension (OLE) Phase	• Discussion with Medical Monitor was added if there is a delay of > 21 days from CC-93538 dosing in the Induction Phase or the Maintenance Phase to enrollment in the OLE Phase. • Revised and provided additional guidance on the baseline esophagogastroduodenoscopy (EGD) at Day 1. [redacted]	• Change in the number of days to align with the longest window allowed between dosing in the Induction Phase or the Maintenance Phase. • To provide further clarification on the timing of the baseline EGD procedure in the OLE Phase. • Overall simplification of text and consolidation of information to the Table of Events.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	[redacted]	
[redacted]		
Section 6.4.1, Esophagogastroduodenoscopy (EGD)	Added clarification for handling incidental findings of potential clinical relevance not associated with objectives of the study.	For clarification purposes.
Section 6.4.2.2, EGID Severity Score	Clarified that the scoring tables (Appendix C and D) used in this study refer to the ones posted on "Eosinophilic Gastro-Intestinal Disorder" disclosed by Japan Intractable Diseases Information Center.	For clarification purposes.
Section 6.4.2.11, Entry to Maintenance Phase	Included language to state that if the subject is eligible for the Maintenance Phase, but the investigator does not believe it is in the best interest of the subject to continue, a discussion with the Medical Monitor will be required prior to transitioning into the Open-Label Extension Phase.	Language for entry into the Maintenance Phase was updated to clarify that this decision should be made in conjunction with the Medical Monitor.
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.
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 7.1, Description of Investigational Product(s)	CC-93538 [redacted] information has been provided.	Treatment information for the [redacted] has been added.
Section 7.2, Treatment Administration and Schedule	• Included additional instructions about first introduction of [redacted] presentation [redacted]. Further, requirements for a First [redacted] Administration Visit are noted. • Additionally, text is included to clarify that if IP is not available on site at the time of Protocol Amendment 5 site approval, then subjects should continue receiving the single 2.0 mL weekly SC injection using the 360 mg/2 mL PFS presentation, until the availability of the new IP ([redacted] presentation.	• To provide clarification as to which assessments will be conducted in the First [redacted] Administration Visit. • To provide clarification on which IP presentation should be provided to subjects.
Section 8.2, Prohibited Concomitant Medications and Procedures	• Included JAK inhibitors andphosphodiesterase-4 inhibitors as examples of immunomodulating drugs and as prohibited concomitant medications on study. • Added language to clarify that corticosteroids can be used for an EGE flare, or used for an adverse event (AE) with consultation with the Medical Monitor, and will not result in	For clarification purposes.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 5.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	permanent discontinuation of IP.	
Section 9.1, Overview	Added details for database lock and clinical study report.	For clarification purposes.
Section 9.2, Study Population Definitions Section 9.6.1.2, Changes in Mean Number of Peak eos Count from Baseline to Week 16 (Induction Phase) Section 9.6.3.1, Analyses Methods	Removed the Per-protocol (PP) population.	The PP population was removed as the specified estimands better address the objectives, and the PP population would not add additional insights.
Section 9.7, Safety Analysis	Updated information based on the [redacted] administration has been added.	Updated per changes in Protocol Amendment 5.
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. Clarified that AESIs must be entered into EDC.	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 the IP.	For clarification purposes.
All	Minor formatting and typographical corrections.	Minor edits that do not change the content of the protocol were made to improve readability and consistency.

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Induction and Maintenance Study to Evaluate the Efficacy and Safety of CC-93538 in Adult and Adolescent Japanese Subjects with Eosinophilic Gastroenteritis

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 (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 gastrointestinal disorders (EGIDs) are a series of diseases that selectively affect the segments of gastrointestinal (GI) tract with eosinophilic inflammation in the absence of secondary causes for eosinophilia. These disorders can be divided into 2 principal groups: eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) for infants to adults (Rothenberg, 2004; Japan Intractable Diseases Information Center, 2021). They are considered to be caused by chronic allergic reactions to various allergens, including food and environmental antigens (Kinoshita, 2019). Eosinophilic gastroenteritis is associated with inflammation of the stomach and large intestine, with abdominal pain, nausea, diarrhea, and malnutrition being the main symptoms. Recurrence occurs repeatedly in about 60% of patients, and the disease becomes chronic and steroid-dependent, causing various adverse reactions associated with drug therapy. In Japan, there have been many case reports of EGE, but there are few cases of EoE. In contrast, EoE is more common and EGE is less common in Europe and the United States. The prevalence of EGE in Japan is unknown, but EGIDs is estimated to be present in approximately 5000 patients. The number of EGE patients is also unknown but has been estimated as 500 in 2010 (Japan Intractable Diseases Information Center, 2021). Although not approved in Japan, the most widely used treatment for EGE is systemic glucocorticoid administration. Prednisolone 20 to 40 mg/day is often orally administered, but there is no clear guidance on the dose, rate of dose reduction, timing of discontinuation, treatment for refractory cases, and treatments for recurrence or relapse. Systemic glucocorticoid therapy is often associated with long-term steroid side effects such as diabetes, osteoporosis, and depression because it is difficult to achieve effective remission of inflammation (Japan Intractable Diseases Information Center, 2021).

Although eosinophils are normally present in the lamina propria except in the esophagus, the number of eosinophils along the GI tract is variable, and the highest concentrations are found in the cecum and appendix (Oh, 2008; Ko, 2014). Eosinophils are involved in the mucosal immune system of the GI tract and have a role in host defense for healthy individuals (Lucendo, 2008). The number of eosinophils is increased in the pathogenesis of numerous inflammatory processes, including parasitic infections and allergic diseases. Activated eosinophils produce and release highly bioactive inflammatory mediators like eosinophil cationic protein (ECP) and major basic protein. These cationic proteins possessing ribonuclease and antiviral activity are cytotoxic to the

GI epithelium. This process can trigger degranulation of mast cells and release of cytokines (eg, IL-1, IL-3, IL-4, IL-5, IL-13, transforming growth factors), chemokines (eg, eotaxin, Regulation upon Activation Normal T-cell Expressed and Secreted [RANTES]), lipid mediators (eg, leukotrienes, platelet activating factor), and neuromediators (eg, substance P, vasoactive intestinal polypeptide) (Khan, 2005; Rankin, 2000; Hogan, 2004).

CC-93538 has a high affinity for wild-type IL-13 and a common variant of IL-13, Q110, which is associated with and enhances human allergic inflammation (Vladich, 2005). CC-93538 binds an IL-13 epitope, comprised of residues in helix A and helix D (Ying, 2010). This binding in turn prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2 (Ying, 2010), where IL-13 may be implicated in EGE pathogenesis (Pesek, 2020; Wechsler, 2018; Hershey, 2003; Fichtner-Feigl, 2006; Fichtner-Feigl, 2008).

Results of the Phase 2 Study, Study RPC02-201, conducted in 99 adult subjects with symptomatic EoE showed that administration of 180 mg and 360 mg subcutaneous injection (SC) once weekly of CC-93538 reduced mean esophageal eosinophil count (the primary endpoint) and improved other inflammatory and symptomatic parameters; improvements in dysphagia symptoms were observed with the 360 mg dose. The study also demonstrated the safety and tolerability of CC-93538 and showed continued clinical, endoscopic, and histologic improvements in subjects treated with 360 mg SC for up to 68 weeks of treatment and suggested that treatment was potentially effective in both steroid refractory and non-steroid refractory populations. These data support the continued development of CC-93538 as a novel treatment for EoE. As well as EoE, IL-13 is the dominant Th2 cytokine in the pathogenesis of EGE and CC-93538 is expected to act by neutralizing IL-13 and inhibiting infiltration and accumulation of eosinophils to inflammatory sites. Thus, the single pivotal Phase 3 Study in adult and adolescent subjects with EoE (Study CC-93538-EE-001) is designed to confirm and extend the findings obtained from the positive Phase 2 study (Study RPC02-201) with CC-93538.

In addition to the multicenter, multinational, 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 Open-label Extension Study (Study CC-93538-EE-002), the Phase 3 program includes a multicenter, open-label study to evaluate the efficacy and safety of CC-93538 in adult and adolescent Japanese subjects with EGE (Study CC-93538-EG-001). The study includes subjects who have an inadequate response with, lost response to, or were intolerant to standard therapies. In Japan, there is no approved drug indicated for EGIDs (EoE/EGE) as of February 2021, and the main treatment is symptomatic treatment such as systemic glucocorticoid administration and diet therapy using an elimination diet. As unmet medical needs exist for EGE, new therapies with an effective and favorable safety profile are required. The study will include an Induction Phase, Maintenance Phase and an Open-label Long-term Extension (OLE) Phase.

Objectives

The primary objective of the study is to assess the efficacy of CC-93538 versus placebo in obtaining histologic improvement based on tissue eosinophil (eos) count in EGE at Week 16.

The secondary objectives are:

- To assess the efficacy of CC-93538 versus placebo in reducing EGE-related symptoms at Week 16
- To assess the efficacy and the persistence of effect of CC-93538 versus placebo at 48 weeks in:
  - Obtaining histologic improvement based on tissue eos count in EGE
  - Reducing EGE-related symptoms
- To assess the persistence of effect of CC-93538 through administration of a less frequent dosing regimen at 48 weeks in:
  - Obtaining histologic improvement based on tissue eos count in EGE
  - Reducing EGE-related symptoms
- To evaluate the safety and tolerability of CC-93538 including characterization of the immunogenicity profile
- To evaluate the efficacy and the persistence of effect of CC-93538 versus placebo for 48 weeks in reducing concomitant corticosteroid use
- To evaluate the time to and frequency of EGE flare events and use of rescue therapy during the study
- To assess trough concentrations of CC-93538 in subjects with EGE

Study Endpoints (Primary and Key Secondary)

Primary Endpoint

- Changes in mean number of peak eos per high-power field (hpf) in GI biopsies from baseline to Week 16

Key Secondary Endpoints

- Changes from baseline in each of 5 domain scores of the Izumo Scale
- The proportion of responders defined as subjects who achieve both clinical and histologic response
- Safety and tolerability evaluated by the incidence, severity and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities and the presence of anti-drug antibodies, including neutralizing antibodies when warranted

Study Design

Study CC-93538-EG-001 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled induction and maintenance study to assess the efficacy and safety of CC-93538 in adult and adolescent subjects with EGE. The study will incorporate a 16-week Induction Phase followed by a 32-week Maintenance Phase and an OLE Phase for a minimum of 2 years, but may extend for a longer duration.

Following a 4-week Screening Period, subjects meeting all inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the 16-week Induction Phase. Subjects (N = approximately 45) will be randomized (2:1) to receive CC-93538 360 mg subcutaneously (SC) once weekly or matching placebo, in a double-blind fashion for the 16 weeks of the Induction Phase. At the beginning of the Maintenance Phase, subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized (1:1) to CC-93538 360 mg SC once weekly or CC-93538 360 mg SC once every other week, and subjects who are randomized to receive matching placebo in the Induction Phase will continue placebo in the Maintenance Phase. A double-blind fashion will be kept in the Maintenance Phase. Subjects will be required to have weekly symptom scores of ≥ 4/15 for any of Gastric Pain Symptom domain, Stomach Heaviness Symptom domain, and /or Diarrhea Symptom domain as assessed by the patient-reported outcome (PRO) questionnaire (referred to as Izumo Scale) with electronic device over the 2 consecutive weeks before the investigational product (IP) administration on Day 1 and has histologic evidence of EGE with ≥ 30 eos/hpf in at least 5 hpf in the stomach and/or ≥30 eos/hpf in at least 3 hpf in the duodenum; both assessments will be conducted while on stable concomitant corticosteroid therapy (up to 10 mg/day as prednisone). Peak gastric/duodenum eos count will be confirmed by a centrally read histological assessment of an esophagogastroduodenoscopy (EGD) specimen. Subjects weighing ≥ 30 kg will be enrolled in this study. Currently, there is no administration experience of CC-93538 360 mg once weekly in subjects weighing < 40 kg. Careful and close safety monitoring should be implemented for this population. For subjects weighing ≥ 30 kg and <40 kg, the first 3 weekly SC doses will be administered in the clinic with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation and be monitored every 2 weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until Week 16 (ie, Week 6 [Day 43 ± 3 days], Week 10 [Day 71 ± 3 days], and Week 14 [Day 99 ± 3 days]).

Treatment assignment at baseline will be stratified by (with/without) concomitant corticosteroid treatment at baseline (up to 10 mg/day as the equivalent of prednisone) to ensure an equal balance in the treatment arms.

The dosage regimen of permitted anti-inflammatory therapy (including concomitant corticosteroid treatment at baseline; up to 10 mg/day as the equivalent of prednisone) must be kept stable until Week 16.

After completion of Week 16 of the Induction Phase, subjects will be eligible to enter the Maintenance Phase if none of the conditions that would disqualify subjects from continuing have been met, including the need for endoscopic intervention or concomitant use of rescue therapy for a severe EGE flare.

If the reduction of EGE-related symptoms is observed at/after Week 16 (in the Maintenance Phase), the investigator should begin tapering the dosage regimen of concomitant corticosteroids treatment after Week 16. The dose reduction should be 2.5 mg/week (as the equivalent of prednisone). If the symptoms worsen after tapering of the dosage regimen of concomitant corticosteroid treatment, the dose can be increased to the baseline dose in the Induction Phase.

Clinical laboratory tests, vital signs, physical examinations [redacted], pregnancy tests, EGD, clinical symptom assessment, subject-reported outcomes, serum CC-93538 pharmacokinetic concentrations, serum antibodies to CC-93538 (to assess immunogenicity), concomitant medications, and AE/SAE assessments will be performed. [redacted]

Subjects experiencing a severe EGE flare in the Induction Phase may continue to participate with concomitant rescue therapy as needed and will not be eligible to enter the Maintenance Phase but will be eligible to enter the OLE Phase following completion of Week 16 of the Induction Phase. If the results of the gastric/duodenal eos count is required to determine the need for rescue therapy during the Induction Phase, the subject is to be discontinued from the study and will not be allowed to enter either Maintenance Phase or OLE. Subjects who complete Week 48 of the Maintenance Phase are eligible to enter the OLE Phase. During the Maintenance Phase, subjects experiencing a severe EGE flare that requires rescue therapy and/or experience worsening of EGE symptoms (for 2 consecutive visits, 4 weeks apart) may also enter the OLE Phase during the Maintenance Phase.

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

During the OLE Phase, all subjects will be administered CC-93538 at a dose of 360 mg SC once weekly. Subjects may discontinue from the study at any time. Furthermore, subjects who demonstrate a persistent lack of improvement or worsening of EGE symptoms during the course of the study should be evaluated to determine if continuing the study treatment is appropriate . Subjects who discontinue the study at or after 2 years of participation (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 OLE Week 104 will complete an Early Termination Visit.

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

Study Population

The study population will consist of males and females aged 12 to 75 years (inclusive) with EGE. Approximately 45 adults (aged 18 to 75 years) and adolescents (aged 12 to 17 years) with a weight of ≥ 30 kg will be enrolled in the study.

Length of Study

The maximum duration of subject participation in the Screening Period, Induction and Maintenance Phases is approximately 72 weeks, including the Interim and the Final Safety Follow-

up Visits. Subjects will participate for up to 4 weeks in the Screening Period (the screening EGD may be completed up to 8 weeks prior to Day 1), 16 weeks in the Induction Phase, and 32 weeks in the Maintenance Phase of the study. Subjects completing the Maintenance Phase who do not continue IP administration in the OLE Phase will complete the Interim and the Final Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration.

Subjects entering the OLE Phase at Induction Phase Week 16, during the Maintenance Phase or at Maintenance Phase Week 48 will receive weekly doses of CC-93538 during the OLE Phase for a minimum of 2 years or as long as they continue to participate while the study is active, will complete an Early Termination Visit or an End of Treatment Visit within 2 weeks after the final dose, and complete the two Safety Follow-up Visits at 8 and 16 weeks after the final dose. Subjects may participate in the OLE Phase as early as 16 weeks after beginning enrollment in the Induction Phase or as late as following Week 48 of the Maintenance Phase. Individual subject participation in the OLE Phase may be a minimum of 2 years but may extend for a longer duration, provided the subject does not withdraw from the OLE Phase prior to Year 2 of the OLE. The terms "this study" in this protocol will automatically be replaced with "post-marketing clinical study" on and after the date of marketing approval in Japan.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up (the Final Safety Follow-up Visit), or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will be randomized 2:1 to the following treatment arms for the 16-week Induction Phase:

- CC-93538 360 mg SC once weekly for 16 weeks
- Matching placebo SC once weekly for 16 weeks

Subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized 1:1 to the following treatment arms for the 32-week Maintenance Phase:

- CC-93538 360 mg SC once weekly for 32 weeks
- CC-93538 360 mg SC once every other week for 32 weeks. During the Maintenance Phase, matching placebo will be administered once every other week on alternate weeks to maintain the blind.

Subjects who are randomized to receive matching placebo in the Induction Phase will continue the following treatment arm.

- Matching placebo SC once weekly for 32 weeks

The CC-93538 360 mg SC dose will be administered by 2 injections of 1.2 mL each provided in 150 mg/mL pre-filled syringes (PFS) during the Induction Phase and the Maintenance Phase.

Subjects entering the OLE Phase will receive the following treatment:

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

For the OLE Phase, all subjects will receive CC-93538 360 mg SC once weekly during the OLE Phase. The 360 mg dose of CC-93538 will be administered by a single injection of the 360 mg/2 mL [redacted] at a concentration of 180 mg/mL CC-93538. All subjects currently in the OLE Phase will start receiving a single injection of the 360 mg/2 mL [redacted] once Protocol Amendment 5 is implemented, informed consent is obtained, and IP is available on-site. For currently enrolled subjects, a switch to the new [redacted] presentation will occur at the next regularly scheduled study visit or at a First [redacted] Administration Visit in case the next scheduled protocol visit is not within 4 weeks of Protocol Amendment 5 site approval, once the IP is available on site. This First [redacted] Administration Visit is added to expedite the switch to the new [redacted] presentation.

The dosing regimen for the OLE may be revised, via an amendment to the protocol, after results from the core Induction Phase and Maintenance Phase are available and the most effective and safest dosing regimen is confirmed.

Overview of Key Efficacy Assessments

- Enumeration of gastric and/or duodenal eos count (peak gastric and/or duodenal eos count) by analysis of hematoxylin and eosin (H&E) stained gastric and/or duodenal biopsies
- Gastrointestinal symptom score using the PRO questionnaire (Izumo Scale)

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 consequences of anti-drug antibodies (ADAs)

Statistical Methods

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

Analysis details not explained in the statistical section of the protocol will be provided in the Statistical Analysis Plan (SAP).

Sample Size

The sample size is based on two-sample t-test for the primary endpoint, changes in mean number of peak eos per hpf in GI biopsies from baseline to Week 16. The null hypothesis and the alternative hypothesis for the primary endpoint are as follows;

- Changes in mean number of peak eos from baseline at Week 16

  Null hypothesis H_0: $\mu_{CC\text{-}93538} = \mu_{Placebo}$

Alternative hypothesis H_a: $\mu_{CC\text{-}93538} \neq \mu_{Placebo}$,

where $\mu_{CC\text{-}93538}$ represents the true mean change value relative to CC-93538 and $\mu_{Placebo}$ represents true mean change value relative to placebo.

Using this hypothesis, if the expected mean change in eos count in the active treatment group was -70, the expected mean change in eos count in the placebo group was 0, and the standard deviation (SD) was 70, the sample size necessary to achieve at least 80% power in a t-test at a significance level of 0.05 was calculated. Using a 2:1 ratio of active to placebo, 39 subjects are required. Assuming a Week 16 drop-out rate of approximately 10%, the goal is to enroll a total of 45 subjects.

Primary Analysis

The primary analysis will be conducted on the ITT population based on an analysis of covariance (ANCOVA) model with treatment group, concomitant steroid use (yes or no), and baseline eosinophil count included in the model. The comparison between CC-93538 360 mg SC once weekly and placebo for change in eos count from baseline at Week 16 will be made using the difference in least squares mean (LSM) at a 5% 2-sided significance level. Point estimates for the mean difference between the two treatment groups using the LSM changes and corresponding 95% Wald confidence intervals (CI) will be reported. In addition, LSM (standard error [SE]), arithmetic means (SD), and arithmetic mean changes (SD) will be summarized by treatment group.

Multiplicity Adjustment

Only one formal statistical test will be performed for the primary endpoint. For any other comparisons, nominal p-value (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than a formal statistical test. Therefore, the multiplicity adjustment is not applicable in this study.

Safety Population

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

Overall safety and tolerability will also be summarized for each drug presentation : the 360 mg dose of CC-93538 administered by two injections of 1.2 mL each at a concentration of 150 mg/mL CC-93538, or by one injection of 2.0 mL at a concentration of 180 mg/mL CC-93538 administered with the PFS device, or by one injection of 2 mL at a concentration of 180 mg/mLCC-93538 administered with the [redacted] device utilizing descriptive statistics.

External Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) will be convened and will be comprised of physician experts with experience in treating subjects with EGE and a statistician, all of whom are not otherwise involved in the study conduct and for whom there is no identified

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

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1 INTRODUCTION

1.1 Disease Background

Eosinophilic gastrointestinal disorders (EGIDs) are a series of diseases that selectively affect the segments of the gastrointestinal (GI) tract with eosinophilic inflammation in the absence of secondary causes for eosinophilia. These disorders can be divided into 2 principal groups: eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) for infants to adults including the elderly (Rothenberg, 2004; Japan Intractable Diseases Information Center, 2021). Eosinophilic esophagitis is characterized by inflammation in the esophagus, and causes symptoms such as difficulty in swallowing and a feeling of choking, which interfere with activities of daily living due to dysphagia. In long-term cases, it may cause esophageal fibrosis and stenosis. Eosinophilic gastroenteritis is associated with inflammation of the GI tract from the esophagus / stomach to the large intestine, with abdominal pain, nausea, diarrhea, and malnutrition being the major symptoms. Recurrence occurs repeatedly in about 60% of patients, and the disease becomes chronic and steroid-dependent, causing various adverse reactions associated with drug therapy. In Japan, there have been many case reports of EGE, but there are few cases of EoE. In contrast, EoE is more common and EGE is less common in Europe and the United States (US). The prevalence of EGE in Japan is unknown, but EGIDs are estimated to be present in approximately 5000 patients. The number of EGE patients is also unknown but has been estimated as 500 in 2010 (Japan Intractable Diseases Information Center, 2021). The exact prevalence of EGIDs in the US is unknown, but the estimated prevalence of EoE is reported as 56.7/100,000 (Dellon, 2014) and that of EGE is 14.7/100,000 (Jensen, 2016). The prevalence of EGIDs in the US/European Union has been increasing in recent years, and a similar finding has been reported in Japan (Fujishiro, 2011; Kinoshita, 2015; Chehade, 2021). Although eosinophils (eos) are normally present in the lamina propria except the esophagus under noninflammatory conditions, the number of eos along the GI tract is variable, and the highest concentrations are found in the cecum and appendix (Oh, 2008; Ko, 2014). They are involved in the mucosal immune system of the GI tract and have a role in host defense for healthy individuals (Lucendo, 2008). The number of eos increases in the pathogenesis of numerous inflammatory processes, including parasitic infections and allergic diseases. In these states activated eos produce and release highly bioactive inflammatory mediators like eosinophil cationic protein (ECP) and major basic protein. These cationic proteins possessing ribonuclease and antiviral activity are cytotoxic to the GI epithelium. This could trigger degranulation of mast cells and release of cytokines (eg, interleukin (IL)-1, IL-3, IL-4, IL-5, IL-13, transforming growth factors), chemokines (eg, eotaxin, Regulation upon Activation Normal T-cell Expressed and Secreted [RANTES]), lipid mediators (eg, leukotrienes, platelet activating factor), and neuromediators (eg, substance P, vasoactive intestinal polypeptide) (Khan, 2005; Rankin, 2000; Hogan, 2004).

1.1.1 Pathophysiology

Eosinophilic gastroenteritis is an uncommon and heterogeneous disease characterized by eosinophilic infiltration of the GI tract and the inflammatory process may involve the entire GI tract, presenting with a variety of GI manifestations that depend on the site affected and the layer of the GI wall involved (Klein, 1970). Additionally, many patients may have a concomitant history

of atopic conditions including asthma, allergic rhinitis or atopic dermatitis, as well as allergy to medicine, food, or pollen (Reed, 2015; Ko, 2014).

The pathogenesis of EGE is thought to be similar to that of EoE and may be due to abnormal immune responses leading to increased eos counts and inflammation in the GI tract, though the details of this immunological abnormality have yet to be fully clarified. Indeed, several basic and clinical similarities between EoE and EGE have been demonstrated (Kinoshita, 2013; Furuta, 2013; Ishimura, 2013; Kinoshita, 2012; Ishihara, 2017; Caldwell, 2014; Shoda, 2016). Microarray analyses of both EGE and EoE have shown similar findings of increased T-helper type 2 (Th2) responses in the GI mucosa. Furthermore, co-occurrence of esophageal and GI eos infiltration is not a rare condition and suggests a similar pathogenesis for both. Based on their similarities, EGE is thought to be a chronic Th2-type eos allergic reaction caused mainly by food allergens, such as also seen with EoE (Sato, 2017; Kinoshita, 2019; Sekai, 2021). Additionally, to support this knowledge, the improvement of dysphagia symptoms in patients with concomitant EoE has been reported in a clinical study of another drug in patients with EGE (Dellon, 2020; Hirano, 2020).

1.1.2 Symptoms and Diagnosis

Compared to EoE, which is localized to the esophagus, EGE is a disease that affects the entire GI tract and its symptoms differ depending on the location of the lesion. Symptoms of EGE are non-specific and various, and include abdominal pain, nausea, vomiting, early satiety, loss of appetite, abdominal cramping, bloating, and diarrhea. Abdominal pain and nausea are the most frequent presenting main symptoms in children and adults. Bleeding, anemia, protein-losing enteropathy, malabsorption, and weight loss are also observed. Gastrointestinal obstruction, intestinal rupture, peritonitis and eosinophilic ascites may occur in severe cases. As unusual complications of EGE, pancreatitis, acute bowel obstruction, duodenal ulcer or perforation have also reported (Reed, 2015; Pineton, 2011; Ko, 2014; Zhang, 2011; Zhang, 2017; Kinoshita, 2013; Kant, 2021; Japan Intractable Diseases Information Center, 2021).

The natural history of EGE remains largely unknown. Three different patterns of disease course are reported: (1) a single flare of EGE, defined by GI symptoms present for less than 6 months associated with the absence of any relapse after initial flare; (2) a recurring course of EGE, defined by at least two flares of the disease separated by a period without GI symptoms and without peripheral blood eosinophilia; (3) a chronic continuous course of the disease, defined by chronic persistent GI symptoms for more than 6 months without period of remission. It was also found that absence of spontaneous remission and high blood eos count at diagnosis was significantly associated with a high risk of clinical relapse (Zhang, 2017). It has also been reported that approximately 40% of patients with EGE are cured without relapse, while approximately 50% of patients develop recurrence and chronic persistent GI symptoms (Pineton, 2011).

In Japan, the Japan Ministry of Health, Labour and Welfare (MHLW) proposed the diagnostic criteria of EGE in “Guidelines for diagnosis and treatment of eosinophilic gastroenteritis (draft)” in 2011 (Kinoshita, 2017; Japan Intractable Diseases Information Center, 2021) as follow;

Subjects who meet criteria 1 and 2, or 1 and 3, will be diagnosed as EGE.

1. The presence of GI symptoms (abdominal pain, diarrhea, vomiting, etc.)

2. The presence of infiltration of inflammatory cells mainly consisting of eos in the mucosa shown in biopsies of the stomach, small intestine, and large intestine (eosinophilic infiltration: ≥ 20 cells/high power field (hpf), biopsy should be performed at several sites, and other inflammatory bowel diseases should be ruled out)
3. The presence of ascites, with numerous eos in the ascites

The following are used as additional diagnostic criteria as reference: a history of allergic disease such as asthma, the confirmation of eosinophilia in peripheral blood, the confirmation of thickening of the wall of the stomach and intestinal tract shown by computed tomography scan, the confirmation of edema, redness, and erosion in the stomach, small intestine, and large intestine shown by endoscopy, and/or effectiveness of glucocorticoid therapy.

1.1.3 Current Available Therapies and Standard of Care

The most widely used treatment for EGE is systemic glucocorticoid administration, but it is not approved in Japan. Prednisolone 20 to 40 mg/day is often orally administered, but there is no clear guidance on the dose, rate of dose reduction, timing of discontinuation, treatment for refractory cases, and treatments for recurrence or relapse. Systemic glucocorticoid therapy is often associated with long-term steroid side effects such as diabetes, osteoporosis, and depression because it is difficult to achieve effective remission of inflammation (Japan Intractable Diseases Information Center, 2021). Although the value of antiallergic drugs has been investigated, none of the findings obtained showed adequate effectiveness. In consideration of the disease pathogenesis, use of an elimination diet has been investigated and the effects reported in a case report and case series, with some limitations (Ko, 2014; Lucendo, 2015; Yamada, 2014).

In Japan, there is no approved drug indicated for EGIDs (EoE/EGE) as of July 2023, and the main treatment is symptomatic treatment such as systemic glucocorticoid administration and diet therapy using an elimination diet. 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 cosignaling 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). As there is still no approved drug indicated for EGE and unmet medical needs exist, new therapies with an effective and favorable safety profile are required.

1.2 Compound Background

1.2.1 Mechanism of Action

CC-93538, also known as BMS-986355 (nonproprietary name, cendakimab), is a recombinant, humanized, high-affinity neutralizing (immunoglobulin G1 kappa [IgG1κ]) monoclonal antibody (mAb). CC-93538 is highly selective for human IL-13 and was generated by humanization of a rodent anti-human IL-13 mAb, which was identified using hybridoma technology through immunization of mice with human Q110 variant recombinant IL-13. The fragment, crystallizable (Fc) region of CC-93538 is mutated at residues L240A and L241A in the heavy chain hinge/CH2 region to reduce effector function as suggested by literature reports (Hezareh, 2001; Lo, 2017). CC-93538 is produced by mammalian cell expression.

IL-13 is a cytokine that is expressed by a large number of cell types including most leukocytes, mast cells, epithelial cells, fibroblasts, and smooth muscle cells (Brightling, 2010). CC-93538 has a high affinity for wild-type IL-13 and a common variant of IL-13, Q110, which is associated with and enhances human allergic inflammation (Vladich, 2005). CC-93538 binds an IL-13 epitope, comprised of residues in helix A and helix D (Ying, 2010). This binding in turn prevents IL-13 from binding to both IL-13Rα1 and IL-13Rα2 (Ying, 2010), where IL-13 may be implicated in EGE pathogenesis (Pesek, 2020; Wechsler, 2018; 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. Two 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. The details are described in the Investigator's Brochure.

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

1.2.2.3 Phase 1 Study, RPC02-1901

Study RPC02-1901 was a Phase 1, randomized, open-label, single-dose, parallel-group study to characterize the PK of CC-93538 in healthy adult subjects following a single 360 mg IV infusion or 360 mg SC administration using the 150 mg/mL formulation. Twenty-four healthy adult subjects were randomized to receive a single CC-93538 360 mg dose either via IV infusion (N = 12) or SC injection (N = 12). Following SC administration, the absorption of CC-93538 was slow with a median t_{max} of approximately 144 hours (approximately 6 days). CC-93538 showed a long $t_{½}$ of approximately 475 to 497 hours (approximately 20 to 21 days) and a small volume of distribution of approximately 5 L. The SC bioavailability of CC-93538 was estimated to be approximately 53%. Anti-CC-93538 antibodies were detected in 10 of 24 subjects. Of those 10 subjects, 3 had pre-existing antibodies and there was no indication that the response increased after treatment. Thus, in 7 out of 24 (29%) subjects, treatment-induced ADAs were detected. Of those 7 subjects for which treatment-induced ADAs were detected, the ADA titers were low for 6 of them. However, 1 subject had titers that were higher than the others (20- to 50-fold). Despite this, there was no indication that exposure was impacted in that subject or in any of the subjects who had treatment-induced ADAs. None of the subjects who had treatment-induced ADAs had TEAEs suspected by the investigator to be related to CC-93538.

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

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

Study CC-93538-CP-001 was a Phase 1, randomized, open-label, single-dose study to evaluate the PK of CC-93538 in healthy Japanese and Caucasian adult subjects. Forty-eight subjects (24 Japanese and 24 Caucasians) received either a single 180 mg or 360 mg SC dose of CC-93538. Preliminary results show that following SC administration of either 180 mg or 360 mg CC-93538, the absorption of CC-93538 was slow with a median t_{max} of 5.4 to 7.5 days. A long $t_{½}$ 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% confidence interval (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% range. 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 a positive anti-CC-93538 antibody response, 12 TEAEs were reported; 1 of which (injection site pain) was considered by the investigator to be related to study drug. There was no indication that CC-93538 exposure was impacted in any of the subjects with positive ADAs, and ADA response did not impact the safety of CC-93538 following a single 180 mg or 360 mg SC dose. There were no deaths, SAEs, or TEAEs leading to study discontinuation. All TEAEs were mild to moderate in severity. The only TEAEs reported in 2 or more subjects included upper respiratory tract infection, cough, back pain, headache, and anemia. 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 (2 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 2 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 2 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. 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) (3 subjects from the 150 mg/mL treatment group and one subject from the 180 mg/mL treatment group). 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 [redacted] versus PFS, and to evaluate the PK of CC-93538 when administered by the [redacted] 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 [redacted] in the abdomen. In Part 2 of the study, 40 subjects were randomized 1:1 to receive CC-93538 360 mg SC by [redacted] 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 [redacted] 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 [redacted] were contained entirely within 80% to 125%, indicating the 2 devices (PFS and [redacted] are biocomparable.

In Part 2, cendakimab exposure when administered using [redacted] in upper arm or upper thigh was ~20% higher than that in abdomen. The differences were not expected to be clinically meaningful. The cendakimab exposure between upper arm and upper thigh administration were comparable.

In Part A, 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 [redacted] 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 [redacted]

Anti-drug antibodies (ADAs) were detected in 10 subjects (4 in the PFS arm and 6 in the [redacted] arm [1 subject in the [redacted] arm had existing ADAs at baseline]). ADA profiles were similar between subjects receiving CC-93538 with the PFS or [redacted] 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 [redacted]

The two presentations of CC-93538, given by PFS or [redacted] 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 weighing ≥ 40 kg and ≤ 125 kg with EoE have shown an initial IV loading dose of CC-93538 followed by administration of 180 mg or 360 mg SC weekly reduced mean esophageal eos count and improved other inflammatory parameters (see the Investigator's Brochure). In the primary efficacy endpoint analysis, the mean changes from baseline to Week 16 in mean esophageal eos count measured in the 5 most inflamed 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).

Additionally, CC-93538 360 mg SC ameliorated dysphagia symptoms. In the open-label long-term extension, treatment of subjects with the weekly 360 mg SC dose demonstrated improvements in subjects who transitioned from placebo and sustained effect in those who originally received the 180 mg or 360 mg dose in the controlled period of the study. The mean change from baseline to Week 16 in the dysphagia clinical symptom frequency and severity score (also referred to as the Dysphagia Symptom Diary [DSD] composite score), as assessed by the DSD instrument over the prior 2 weeks was -6.41, -5.31, and -13.31 in the Placebo, CC-93538 180 mg, and CC-93538 360 mg groups, respectively. No IV loading dose was used in those subjects who entered the open-label extension. The study also demonstrated the safety and tolerability of CC-93538 and showed continued clinical, endoscopic, and histologic improvements in subjects treated with 360 mg SC for up to 68 weeks of treatment and suggested that treatment was potentially effective in both steroid refractory and non-steroid refractory populations. These Phase 2 data indicate that targeting IL-13 with CC-93538 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 treatment for EoE.

As well as EoE, IL-13 is the dominant Th2 cytokine in the pathogenesis of EGE and CC-93538 is expected to act by neutralizing IL-13 and inhibiting infiltration and accumulation of eos to inflammatory sites.

Please refer to the investigator's Brochure 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

In Japan, EGE together with EoE is considered as an intractable disease designated as EGIDs (Intractable Diseases No.98). Based on opinions from medical experts of EGIDs, there is an extremely high unmet medical need for EGE in addition to EoE in Japan, and there is a strong desire for the development of new therapeutic drugs.

Given that the number of patients with EGE in other countries is smaller than that in Japan, and the development of CC-93538 is planned to prioritize EoE, no clinical study of EGE has been conducted and no multi-regional clinical trial is planned.

In consideration of the above situation, it was planned to conduct the Japan local Phase 3 study in patients with EGE (Study CC-93538-EG-001) in parallel with the global Phase 3 study in patients with EoE (Study CC-93538-EE-001) in order to meet the needs for treatment of EGE in clinical practice in Japan, and to develop the drug for the indication of EGIDs. As with EoE, EGE primarily involves eos infiltration into the GI tract, and CC-93538, an anti-IL-13 antibody, is expected to have an effect on both diseases with a similar mechanism of action.

No clinical studies of CC-93538 in patients with EGE have been conducted. However, 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 (Study RPC02-201) of 99 adult subjects with EoE, weekly administration of CC-93538 360 mg SC reduced mean esophageal eos count and improved other inflammatory and symptomatic parameters. These results support the continued development of CC-93538 as a novel treatment for EoE. The single pivotal Phase 3 study is designed to confirm and extend the findings obtained from the positive Phase 2 study with CC-93538.

1.3.2 Rationale for the Study Design

The Phase 3 program includes a multicenter, Japan-local, randomized, double-blind, placebo-controlled induction and maintenance study to evaluate the efficacy and safety of CC-93538 in adult and adolescent subjects with EGE (Study CC-93538-EG-001). In addition, 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 (Study CC-93538-EE-002) are included.

The EGE study includes a 16-week Induction Phase followed by a 32-week Maintenance Phase, and an Open-label Long-term Extension (OLE) Phase for a minimum of 2 years. A double-blind, placebo-controlled treat-through design with allowance for use of concomitant corticosteroid therapy and concomitant rescue therapy has been chosen, as it enhances subject recruitment and retainment for evaluation of relevant short-term as well as the long-term efficacy of CC-93538 in EGE. Since chronic administration of systemic steroids should be avoided as much as possible, the timing of the primary endpoint evaluation was set at 16 weeks, taking into account the timing at which the dosage of systemic steroids can be changed.

For the OLE Phase, the CC-93538 360 mg SC dose will be administered by a single injection of 2 mL provided in a 360 mg/2 mL [redacted] in Protocol Amendment 5. The results of Study CC-93538-CP-002 support the introduction of the new 360 mg/2.0 mL PFS presentation administered as a single injection in Protocol Amendment 4 (see Section 1.2.2.5). Further, Study IM042-003 Part 1 preliminary results demonstrated that the [redacted] presentation was biocomparable to the PFS presentation. The two presentations of CC-93538, given by PFS or [redacted] administered as a single dose of 360 mg, were well tolerated and had an acceptable safety profile in healthy adults. The ADA profiles were similar between subjects receiving the CC-93538 with the PFS or [redacted] with no differences in safety, tolerability, or PK. The results of Study IM042-003 support the introduction of the 360 mg/2 mL [redacted] presentation in Protocol Amendment 5.

1.3.2.1 Benefit-Risk Assessment

As few treatment options exist for patients with EGE, there is an unmet need for new pharmacotherapies targeting the pathophysiology of EGE 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, EGE, and other inflammatory conditions. The overall safety profile of CC-93538 remains consistent with the information that has been presented in the Investigator's Brochure (IB). Please refer to the IB for additional information.

While CC-93538 is a biologic immunomodulator targeting IL-13, it was well tolerated in the Phase 2 study conducted in EoE subjects, without an increased risk of serious infection. Other immunomodulatory biologics in development or marketed for type 2 inflammatory diseases with a related mechanism of action, for example, dupilumab (targeting the 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 assessments, such as a detailed assessment of medical history, will be performed. Each study visit will include an assessment for AEs, and subjects who develop an intercurrent illness between study visits are encouraged to contact the investigator, who will determine if a clinical assessment is required. The Sponsor has also developed guidance for investigators on how to manage a subject with a clinical suspicion of, or a diagnosis of, COVID-19. This includes criteria for temporarily interrupting or permanently discontinuing IP (Section 7.2.9 and Section 7.2.10), and criteria for reinitiating IP on resolution of a COVID-19 infection (Section 7.2.9). 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 specialized electronic case report form (eCRF) pages, 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, it may particularly affect individuals with underlying chronic diseases. Based on the available safety data with CC-93538, and the established safety profile of other biologic immunomodulators targeting the IL-13 pathway, the overall benefit-risk for participation in this EGE study with CC-93538 is considered favorable. The individual benefit-risk considerations regarding COVID-19 infection remain 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 is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving CC-93538 are unknown. If a participant has received a specific COVID-19 vaccination, details such as type and date of vaccine received should be recorded on the COVID-19 Vaccination Form.

1.3.3 Rationale for Dose, Schedule and Regimen Selection

In the Phase 2 EoE study (Study RPC02-201), two dose levels were evaluated: CC-93538 180 mg and 360 mg SC dosing administered every week. The study results demonstrated that the 360 mg dose was more effective on the clinical symptom endpoints, with a favorable safety profile. Therefore, the CC-93538 360 mg once weekly dose has been selected for Induction Phase (up to Week 24) of the Phase 3 EoE study (Study EE-001).

The pathogenesis of EGE is thought to be similar to that of EoE and may be due to abnormal immune responses leading to increased eosinophils counts and inflammation in the GI tract, though the details of this immunological abnormality have yet to be fully clarified. Since CC-93538 is expected to have similar effects in the process of eos accumulation in the GI mucosa in both EoE and EGE, the same dosage and administration methods as those used in Induction Phase of Study EE-001 (360 mg once weekly) were selected in the Induction Phase (up to Week 16) of the Phase 3 EGE study (Study EG-001).

Since CC-93538 is expected to be used for a long duration for the management of EoE and EGE, Study EE-001 is designed to investigate whether the same effect can be maintained in the Maintenance Phase (After Week 24) at 360 mg once weekly and 360 mg once every 2 weeks. Also, 360 mg was to be administered once every 2 weeks in addition to once weekly in the Maintenance Phase (After Week 16) of Study EG-001.

1.3.3.1 Justification of Primary Endpoints

The selection of the primary endpoint, change in mean number of peak eos per hpf in GI biopsies from baseline to Week 16, is based on the following rationales:

- The pathogenesis of EGE-containing EGIDs is clear and involves eos accumulation and infiltration in the GI tract. Medical experts have commented that in clinical practice, treatment of eosinophilic GI diseases should be performed based on the reduction of eos count at the lesion site. Therefore, medical experts have also advised that the evaluation of histologic eos count in GI tissues is meaningful and should be included as the primary endpoint of this study.
- A decrease in eos count and improvement in clinical symptoms in EGE-containing EGIDs patients were retrospectively investigated by Pesek et al. A report showed that a decrease in eos in the GI tract correlated with improvement in clinical symptoms and endoscopic and histological findings in 373 patients with EGIDs (EGE: 265 subjects, eosinophilic colitis: 108 subjects) (Pesek, 2019). Therefore, it is very likely that improvement of histological eos count in the GI tract will lead to improvement of clinical symptoms. Evaluation of eos count in the GI tract has clinical significance, and it is appropriate to set it as the primary endpoint of this study.
- Eosinophil count decreased was evaluated as the primary endpoint in both the Phase 2 study of this drug in subjects with EoE and the Phase 2 study of another drug (AK002) in subjects with EGE conducted in the US (Dellon, 2020). A statistically significant decrease in eos count was observed in the active groups compared to placebo.

1.3.4 Rationale for Choice of Comparator Compounds

The study design employs a comparison to placebo which is intended to minimize bias and to provide an accurate determination of efficacy and safety findings attributable to CC-93538 administration. In addition, there are currently no approved products for the treatment of EGE in Japan and no comparators available for subjects with EGE.

2 STUDY OBJECTIVES AND ENDPOINTS

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

Table 1: Study Objectives

Primary Objective:
The primary objective of the study is to assess the efficacy of CC-93538 versus placebo in obtaining histologic improvement based on tissue eosinophils (eos) count at Week 16.
Secondary Objective(s)
The secondary objectives are: • To assess the efficacy of CC-93538 versus placebo in reducing eosinophilic gastroenteritis (EGE)-related symptoms at Week 16 • To assess the efficacy and the persistence of effect of CC-93538 versus placebo at 48 weeks in: – Obtaining histologic improvement based on tissue eos count in EGE – Reducing EGE-related symptoms • To assess the persistence of effect of CC-93538 through administration of a less frequent dosing regimen at 48 weeks in: – Obtaining histologic improvement based on tissue eos count in EGE – Reducing EGE-related symptoms • To evaluate the safety and tolerability of CC-93538 including characterization of the immunogenicity profile throughout the study • To evaluate the efficacy and the persistence of effect of CC-93538 versus placebo for 48 weeks in reducing concomitant corticosteroid use • To evaluate the time to and frequency of EGE flare events and use of rescue therapy during the study • To assess trough concentrations of CC-93538 in subjects with EGE
[redacted]

Table 1: Study Objectives

Table 2: Study Endpoints: Induction and Maintenance Phase Endpoints Through Week 48

Endpoint	Name	Description	Timeframe
Primary	Eosinophil histologic response	Changes in mean number of peak eosinophils (eos) per high-power field (hpf) in gastrointestinal (GI) biopsies from baseline to Week 16	Week 16
Key Secondary	Clinical response: eosinophilic gastroenteritis (EGE) -related symptoms	Changes from baseline in each of 5 domain scores of the Izumo Scale (APPENDIX B) from baseline • Heartburn Symptoms domain • Gastric Pain Symptoms domain • Stomach Heaviness Symptoms domain • Constipation Symptoms domain • Diarrhea Symptoms domain Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain are Symptoms of Interest of EGE	Weeks 16 and 48
	Clinical and histologic response composite	The proportion of responders defined as subjects who achieve both clinical and histologic response: • Clinical response defined as the proportion of subjects who achieve < 4/15 in each of three Symptoms of Interest (Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain) scores of the Izumo Scale from baseline • Histologic response defined as a > 75% reduction of peak gastric and/or duodenal eos count from baseline	Weeks 16 and 48
	Safety and tolerability	Safety and tolerability evaluated by the incidence, severity and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities and the presence of anti-drug antibodies, including neutralizing antibodies when warranted	Through Week 48
Secondary	Eosinophil histologic response	Changes in mean number of peak eos per hpf in GI biopsies from baseline to Week 48	Week 48
	Eosinophil histologic response	Percent changes in mean number of peak eos per hpf in GI biopsies from baseline	Weeks 16 and 48
	Eosinophil histologic response (> 75% reduction)	The proportion of subjects achieving eosinophilic histologic response defined as a > 75% reduction of peak gastric and/or duodenal eos count from baseline, respectively	Weeks 16 and 48

Table 2: Study Endpoints: Induction and Maintenance Phase Endpoints Through Week 48

Endpoint	Name	Description	Timeframe
Secondary (continued)	Clinical responder definition	Proportion of subjects who achieve < 4/15 in each of three Symptoms of Interest scores using the Izumo Scale from baseline Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain are Symptoms of Interest of EGE	Weeks 16 and 48
	Clinical response: Eosinophilic gastrointestinal disorder (EGID) Severity Score	Changes in total score of EGID Severity Score consisting of 8 symptom/laboratory scores and 2 medical history related questions using EGID Severity Score (APPENDIX C for subjects ≥ 20 years at the time of signing the informed consent form [ICF]) or consisting of 8 symptom/laboratory scores and 3 general condition related questions (APPENDIX D for subjects from 12 to 19 years at the time of signing the ICF/assent) from baseline	Weeks 16 and 48
	Time to event	The time to event of EGE flare	Through Week 48
	Time to event	The time to event of use of rescue therapy	Through Week 48
	Time to event (subjects who use concomitant treatment only)	The time until concomitant corticosteroid use to zero (and continued by Week 48)	From Week 16 through Week 48
	Proportion of subjects with event (subjects who use concomitant treatment only)	The proportion of subjects for whom the dose of concomitant steroids is reduced to zero	Weeks 24, 32, 40, and 48
	Pharmaco-kinetics (PK)	Trough concentrations of CC-93538 through Week 48	Through Week 48
[redacted]			

Table 2: Study Endpoints: Induction and Maintenance Phase Endpoints Through Week 48

Endpoint	Name	Description	Timeframe
[redacted]			

Table 2: Study Endpoints: Induction and Maintenance Phase Endpoints Through Week 48

Endpoint	Name	Description	Timeframe
[redacted]			

Table 3: Study Endpoints: Open-label Long-term Extension Period Endpoints After Week 48

Endpoint	Name	Description	Timeframe
Secondary	Safety and tolerability	Safety and tolerability evaluated by the incidence, severity and relationship to CC-93538 of adverse events (AEs), serious adverse events (SAEs), clinical laboratory abnormalities, changes in vital signs, physical examination abnormalities and the presence of anti-drug antibodies, including neutralizing antibodies when warranted	Through the Safety Follow-up Visit
[redacted]			

Table 3: Study Endpoints: Open-label Long-term Extension Period Endpoints After Week 48

Endpoint	Name	Description	Timeframe
[redacted]			

Table 3: Study Endpoints: Open-label Long-term Extension Period Endpoints After Week 48

Endpoint	Name	Description	Timeframe
[redacted]			

Table 3: Study Endpoints: Open-label Long-term Extension Period Endpoints After Week 48

Endpoint	Name	Description	Timeframe
[redacted]			

3 OVERALL STUDY DESIGN

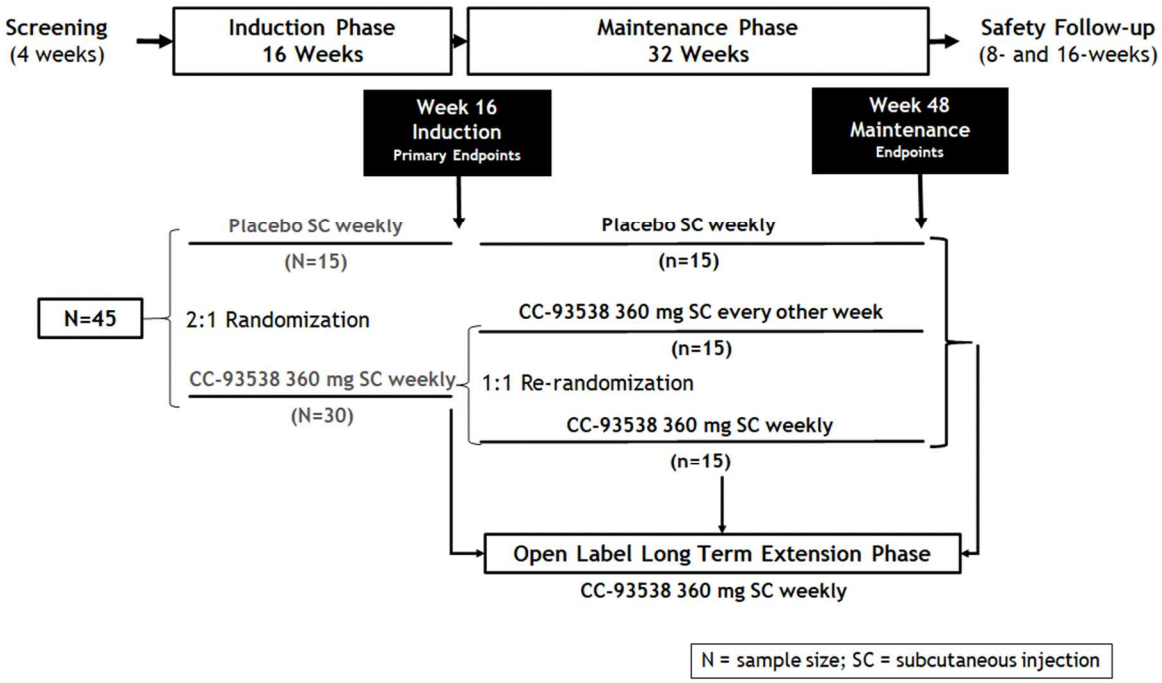
3.1 Study Design

Study CC-93538-EG-001 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled induction and maintenance study to assess the efficacy and safety of CC-93538 in adult and adolescent subjects with EGE. The study will include a 16-week Induction Phase followed by a 32-week Maintenance Phase and an Open-label Long-term Extension (OLE) Phase for a minimum of 2 years, but may extend for a longer duration. Subjects will be randomized at the beginning of the study into 2 treatment arms in a 2:1 ratio for the 16 weeks of the Induction Phase: CC-93538 360 mg SC once weekly or matching placebo. Subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized in a 1:1 ratio for the 32 weeks of the Maintenance Phase: CC-93538 360 mg SC once weekly or CC-93538 360 mg SC once every other week. Subjects who are randomized to receive matching placebo in the Induction Phase will continue to receive placebo in the Maintenance Phase.

Subjects who complete Week 16 of the Induction Phase or Week 48 of the Maintenance Phase are eligible to enter the OLE Phase. During the Maintenance Phase, subjects experiencing a severe EGE flare and/or experience worsening of EGE symptoms may also enter the OLE Phase. All subjects will receive CC-93538 360 mg SC once weekly in the OLE Phase. The OLE Phase is planned to continue for 2 years or until the marketing launch, or the subject decides to withdraw from the study, the investigator decides to withdraw the subject from the study, or the Sponsor decides to terminate the study.

An overview of the overall study design is presented in Figure 1.

Figure 1: Overall Study Schema



The safety monitoring of this study will be performed by an external, independent Data Monitoring Committee (DMC) (Section 9.9.4) in addition to routine internal review by the Safety Management Team (SMT) (Section 9.9.3).

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

3.1.1 Screening Period

Prospective subjects will be assessed during a Screening Period of up to 4 weeks to confirm initial eligibility for the study via medical history, physical examination, review of prior therapy, clinical laboratory tests, and esophagogastroduodenoscopy (EGD), for evaluation of histologic and endoscopic findings. For the EGD and informed consent only, an extension of the screening window of up to 8 weeks total may be allowed to accommodate the scheduling of this procedure after informed consent has been obtained. The screening EGD must be performed within 8 weeks (56 days) of the planned Day 1 Visit for subjects to be eligible to participate in the study. All screening procedures should be performed during the 4-week Screening Period prior to Day 1. Symptoms of EGE will be assessed by the patient-reported outcome (PRO) questionnaire (referred to as Izumo Scale [weekly], [redacted]. Izumo scale will be completed at least the 2 consecutive weeks before the IP administration on Day 1, but may be performed for consecutive weeks during the screening period. [redacted] Refer to Section 6.1 for further details.

3.1.2 Induction Phase

Following a 4-week Screening Period, subjects meeting all inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the Induction Phase. Approximately 45 subjects 12 to 75 years of age, inclusive, with a diagnosis of EGE and with symptoms of EGE will be randomized 2:1 to receive CC-93538 360 mg SC once weekly (N = approximately 30) or matching placebo (N = approximately 15), in a double-blind fashion for 16 weeks. Subjects will be required to have weekly symptom scores of ≥ 4/15 for any of Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain and /or Diarrhea Symptoms domain, as assessed by the Izumo Scale with electronic device over the 2 consecutive weeks before baseline (assessed on Day 1), and histologic evidence of EGE with ≥ 30 eos/hpf in at least 5 hpf in the stomach and/or ≥30 eos/hpf in at least 3 hpf in the duodenum. Both assessments will be conducted while on stable background therapy. Peak gastric/duodenum eos count will be confirmed by the central reader.

Subjects weighing ≥ 30 kg will be enrolled in this study. Currently, there is no administration experience of CC-93538 360 mg once weekly in subjects weighing < 40 kg. Careful and close safety monitoring (eg, for hypersensitivity reaction) should be considered for this population. For subjects weighing ≥ 30 kg and <40 kg, the first 3 weekly SC doses will be administered in the

clinic, with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation, and be monitored every 2 weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until Week 16 (ie, Week 6 [Day 43 ± 3 days], Week 10 [Day 71 ± 3 days], and Week 14 [Day 99 ± 3 days]).

Treatment assignment at baseline will be stratified by (with/without) concomitant use of corticosteroid treatment at baseline (up to 10 mg/day as the equivalent of prednisone) to ensure an equal balance in the treatment arms. Baseline assessments and procedures will be completed prior to randomization and administration of IP on Day 1. The dosage regimen of permitted anti-inflammatory therapy (including concomitant corticosteroid treatment at baseline; up to 10 mg/day as the equivalent of prednisone) must be kept stable until Week 16. Subjects with a worsening of EGE symptoms (described in Section 6.4.2.10) during the Induction Phase will be required to complete the EGE Flare Assessment Visit per the Table of Events (Table 4). The subject may continue to participate with concomitant rescue therapy as needed and will be eligible to enter the OLE Phase following completion of Week 16 of the Induction Phase, or discontinue from the study. Details are described in Section 3.1.6. All attempts should be made to complete the Induction Phase.

Clinical laboratory tests, vital signs, physical examinations [redacted] 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 assess immunogenicity), concomitant medications, and AE/SAE assessments will be performed according to the Table of Events presented in Table 4. [redacted]

3.1.3 Maintenance Phase

After completion of Week 16 of the Induction Phase, eligible subjects will continue participation and enter the Maintenance Phase if none of the conditions disqualifying subjects from eligibility have been met as described in Section 3.1.6. A placebo-controlled Maintenance Phase will allow for a determination of persistence of treatment effect and the overall long-term efficacy of CC-93538.

The Maintenance Phase treatment arms include CC-93538 360 mg SC once every week, CC-93538 360 mg SC once every other week, and matching placebo. Subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized (1:1) to CC-93538 360 mg SC once weekly or CC-93538 360 mg SC once every other week at the beginning of the Maintenance Phase, and subjects who are randomized to receive matching placebo in the Induction Phase will continue placebo in the Maintenance Phase. A double-blind fashion will be kept in the Maintenance Phase.

If the reduction of EGE-related symptoms is observed at/after Week 16 (in the Maintenance Phase), the investigator should begin tapering the dosage regimen of concomitant corticosteroid treatment after Week 16. The dose reduction should be 2.5 mg/week (as the equivalent of prednisone). If the symptoms worsen after tapering of the dosage regimen of concomitant

corticosteroid treatment, the dose can be increased until it is the same as the baseline dose at the Induction Phase.

Subjects who complete Week 48 of the Maintenance Phase have 2 options:

1. to enter the Open-label Long-term Extension Phase (Section 3.1.4)
2. to return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively, after the last dose of IP (at Week 55 and Week 63 for study completers) (Section 3.1.5)

Subjects with a worsening of EGE symptoms (described in Section 6.4.2.10) during the Maintenance Phase will be required to complete the EGE Flare Assessment Visit per the Table of Events (Table 5). The subjects will need to discontinue participation in the Maintenance Phase and may be eligible to enter the OLE Phase. Details are described in Section 3.1.6.

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

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

3.1.4 Open-label Long-term Extension Phase

Subjects who meet one of the following criteria with respect to participation in the Induction Phase and the Maintenance Phase will be given the opportunity to participate in the OLE Phase.

- Subjects who do not qualify for entry into the Maintenance Phase including:
  - Subjects who experience a severe EGE flare requiring concomitant rescue therapy during the Induction Phase will be eligible for the OLE Phase after completion of Week 16 of the Induction Phase
- Subjects who cannot complete the Maintenance Phase including
  - Subjects who experience a severe EGE flare requiring concomitant rescue therapy and/or worsening of EGE symptoms (for 2 consecutive visits [4 weeks apart] at the beginning of or during the Maintenance Phase will be eligible to enter the OLE Phase at the Early Termination (ET) Visit
- Subjects who complete Week 48 of the Maintenance Phase will be eligible for the OLE Phase after completion of Week 48 of the Maintenance Phase.

The OLE Phase baseline assessments will be obtained from either the Induction Phase Week 16 Visit assessments, the Maintenance Phase Week 48 Visit assessments, or the Maintenance Phase

EGE Flare Assessment Visit, and ET Visit assessments, as applicable. Additional OLE baseline assessments not performed at the final Induction Phase Visit (Week 16), final Maintenance Phase Visit (Week 48) or the Maintenance Phase EGE Flare Assessment Visit and ET Visit assessments should be conducted at the OLE Day 1 Visit in accordance with the Table of Events (Table 6); it is anticipated that this should occur for most subjects on the same day. Subjects will not be allowed to enroll in the OLE Phase and receive IP on OLE Day 1 if there will be a delay of > 21 days from dosing in the final Induction Visit or the final dosing in the Maintenance Phase unless discussed with the Medical Monitor (refer to Section 6.3.2). The 2 Safety Follow-up Visits are not required for subjects enrolling in the OLE Phase, after the final Induction Phase Visit, final Maintenance Phase Visit or the Maintenance Phase EGE Flare Assessment Visit and ET Visit assessments.

During the OLE Phase, all subjects will be administered CC-93538 at a dose of 360 mg SC once weekly as long as they are participating in the study, until the investigator decides to withdraw the subject, or the Sponsor decides to terminate/complete the study. Individual subject participation in the OLE Phase may be for a minimum of 2 years but may extend for a longer duration. The dosing regimen in the OLE Phase may be revised through an amendment to the study protocol once results from the Maintenance Phase are available and the most effective and safest dosing regimen is confirmed.

Depending on the EGE symptoms of subject, the investigator may decrease/increase the dose of concomitant corticosteroid treatment after OLE Visit 1 during the OLE Phase.

Subjects with a worsening of EGE symptoms (described in Section 6.4.2.10) during the OLE Phase will be required to complete the EGE Flare Assessment Visit per the Table of Events (Table 6).

Clinical laboratory tests, vital signs, physical examinations [redacted] pregnancy tests (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, [redacted] will be performed in accordance with the Table of Events (Table 6).

Subjects may discontinue from the OLE Phase at any time. Subjects who discontinue the study at or after 2 years of participation (the fourth quarter Visit in Year 2 [Week 104]) will complete an OLE-End of Treatment (EoT) Visit within 2 weeks after receiving the final dose of CC-93538, and an 8-week Interim and a 16-week Final Safety Follow-up Visit at 8 weeks 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 OLE-ET Visit (Table 6).

3.1.5 Early Termination, End of Treatment and Safety Follow-up Visits

Subjects who complete Week 48 of the Maintenance Phase and do not participate in the OLE Phase will be required to return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively, after the last dose of IP (at Week 55 and Week 63 for study completers). Subjects may discontinue from the study at any time. Subjects who discontinue the study during the Maintenance Phase will complete ET Visit and subjects who discontinue the study during the OLE Phase (and before OLE Week 104) will complete an OLE-ET Visit within 2 weeks after their final

dose of IP. In addition to the ET or the OLE-ET Visit procedures, subjects exiting the study early will also return for the Interim and the Final Safety Follow-up Visits (Section 6.3.1). However, subjects who are permanently discontinued from IP and continue study participation in order to complete safety and efficacy assessments will return for the Interim and Final Safety Follow-up Visits after their last study visit (refer to Section 6.3.1).

For subjects who discontinue the study at or after 2 years of participation (the fourth quarter visit in OLE Phase Year 2 [OLE Week 104]) will complete an OLE-EoT Visit (Section 6.2.2) within 2 weeks after their final dose of IP and an 8-week Interim and a 16-week Final Safety Follow-up Visit.

3.1.6 Worsening of EGE Symptoms and EGE flare

Subjects with a worsening of EGE symptoms (described in Section 6.4.2.10) during the study, either in the Induction Phase, Maintenance Phase, or the OLE Phase will be required to complete the EGE Flare Assessment Visit per the Table of Events (Table 4, Table 5, and Table 6). For subjects with a worsening of EGE symptoms and/or EGE flare, an EGD may be required to determine if rescue therapy is clinically indicated. The results of the gastric/duodenal eos count will be blinded to investigative sites with the possible exception of screening during the Induction Phase (see below). After randomization, a local histologic assessment of EGD biopsy samples should not be performed, unless required for safety reasons (eg, severe EGE flare, etc).

Any worsening of EGE symptoms during study participation will be documented as an EGE flare. See Section 6.4.2.10 and Section 6.2.1 for the protocol definition of EGE flare and EGE Flare Assessment Visit details, respectively.

Subjects with increased signs and symptoms of EGE are instructed to contact the investigator and/or study staff to determine if an EGE Flare Assessment Visit is warranted.

Induction Phase

Subjects experiencing a severe EGE flare and/or worsening of EGE symptoms (for 2 consecutive visits [4 weeks apart], described in Section 6.4.2.10) in the Induction Phase may continue to participate with concomitant rescue therapy as needed and will be eligible to enter the OLE Phase following completion of Week 16 of the Induction Phase. Subjects with a severe EGE flare in the Induction Phase will not qualify for entry into the Maintenance Phase.

If the gastric/duodenal eos count is required to determine the need for emergent rescue therapy during the Induction Phase, the results of the gastric/duodenal eos count will be disclosed as long as the investigator requires the result. The subject is to be discontinued from the study and will not be allowed to enter either the Maintenance Phase or the OLE Phase. All attempts should be made to complete the Induction Phase.

Subjects experiencing a mild to moderate EGE flare in the Induction Phase will continue to the Maintenance Phase of the study.

Maintenance Phase

Subjects who experience a severe EGE flare and/or worsening of EGE symptoms (for 2 consecutive visits [4 weeks apart], described in Section 6.4.2.10) at the beginning of or during the Maintenance Phase will need to discontinue participation in the Maintenance Phase and may be eligible to enter the OLE Phase at the ET Visit.

If the gastric/duodenal eos count is required to determine the need for emergent rescue therapy during the Maintenance Phase, the results of the gastric/duodenal eos count will be disclosed as long as the investigator requires the result. The subject may also be eligible to enter the OLE Phase.

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

OLE Phase

During the OLE Phase, subjects who demonstrate a persistent lack of improvement, worsening of EGE symptoms or severe EGE flare should be evaluated if continuation of study treatment is appropriate. While subjects will have the opportunity to continue participation in the OLE Phase with use of rescue therapy as needed, based on clinical judgment, the investigator should discontinue any subject if study participation no longer is in the best interest of the subject. Subjects who are discontinued from the OLE Phase will be asked to complete an OLE-ET/EoT Visit (Section 6.2.2) and the two Safety Follow-up Visits (Section 6.3.1).

3.2 Study Duration for Subjects

The maximum duration of subject participation in the Screening Period, Induction Phase and Maintenance Phase is approximately 72 weeks, including the Interim and the Final Safety Follow-up Visits. Subjects will participate for up to 4 weeks in the Screening Period (the screening EGD may be completed up to 8 weeks prior to Day 1), 16 weeks in the Induction Phase, and 32 weeks in the Maintenance Phase of the study. Subjects completing the Maintenance Phase who do not continue IP administration in the OLE Phase will complete the Interim and the Final Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration.

Subjects who enter the OLE Phase will complete the OLE baseline assessments on Day 1, excluding those obtained from either the Induction Phase Week 16 Visit, the Maintenance Phase Week 48 Visit, or the ET Visit during the Maintenance Phase, as applicable. Subjects will receive weekly doses of IP during the OLE Phase for a minimum duration of 2 years and will complete an OLE-ET Visit or an OLE-EoT Visit within 2 weeks after the final dose and an Interim and a Final Safety Follow-up Visits at 8 and 16 weeks, respectively, after the final dose. Individual subject participation in the OLE Phase may be a minimum of 2 years but may extend for a longer duration, provided the subject does not withdraw from the OLE Phase prior to Year 2 of the OLE.

Subjects may continue participation to the OLE Phase as long as they tolerate treatment and are receiving benefit from participation in the study. Participation may continue until the marketing launch (the terms “this study” in this protocol will automatically be replaced with “post-marketing clinical study” on and after the date of marketing approval in Japan), or the subject decides to

withdraw from the study, the investigator decides to withdraw the subject from the study, or the Sponsor decides to terminate the study (see Section 12.8).

3.3 End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up (the Final Safety Follow-up Visit), or the date of receipt of the last data point from the last subject that is required for primary, secondary [redacted] analysis, as prespecified in the protocol, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

The study population will consist of males and females aged 12 to 75 years (inclusive) with EGE. Forty-five adults (aged 18 to 75 years) and adolescents (aged 12 to 17 years) will be enrolled in the study.

4.2 Inclusion Criteria

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

1. Subject must be ≥ 12 years and ≤ 75 years of age and have a body weight of ≥ 30 kg at the time of signing the informed consent form (ICF).
   If a subject is < 18 years old, subject assent must be obtained and parental/legal representative consent is required.
2. Subjects who were diagnosed with EGE at least 3 months prior to study entry
3. Subject has histologic evidence of EGE defined as ≥ 30 eos/hpf in at least 5 hpf in the stomach and/or ≥ 30 eos/hpf in at least 3 hpf in the duodenum while on stable background therapy (eg, corticosteroids, however a stable dose of prednisone [up to 10 mg/day] is allowed, see Exclusion Criterion 9) for EGE. The histologic criterion for diagnosis of EGE must be confirmed by a centrally read histological assessment of an EGD specimen during the Screening Period prior to randomization.
4. Subject has weekly symptom scores of ≥ 4/15 for any of Gastric Pain Symptoms domain, Stomach Heaviness Symptom domains, and /or Diarrhea Symptoms domain as assessed by the Izumo Scale with electronic device for the 2 consecutive weeks before the IP administration on Day 1.
5. Subjects must agree to maintain a stable diet (including any food elimination diet for the treatment of food allergy or EGE) from the first Screening Visit and throughout the duration of the study, and subjects must have maintained a stable diet for at least 4 weeks prior to the first Screening Visit. Subjects must agree not to introduce any changes in their diet while participating in the study. If the subject is currently successfully treated for EGE with dietary modifications (eg, food elimination diet) and resulting in a complete response to EGE, the subject is not allowed to participate to this study.
6. Subjects currently receiving systemic corticosteroids, inhaled corticosteroids, proton pump inhibitors (PPIs), leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for indications of EGE or other than EGE, or medium potency topical corticosteroids (eg, mometasone furoate cream or lotion) for dermatologic conditions, must maintain stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens must remain stable throughout the duration of the study except for systemic corticosteroids (the dose/regimen of systemic corticosteroids must remain stable for the 16 weeks of the Induction Phase). If recently discontinued, the medication must have been discontinued at least 4 weeks prior to the first Screening Visit.
7. Female subjects of childbearing potential must agree to practice a highly effective method of contraception. Highly effective methods of contraception are those that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly.
   An FCBP is a female who: 1) has achieved menarche at some point; and 2) has not undergone

a hysterectomy, 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 follow the criteria below:

a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study and through the Final 16-week Safety Follow-up Visit. This applies even if the subject practices true abstinence* from heterosexual contact.
b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, highly effective contraception without interruption throughout the study and for 5 months after the last dose of IP. Acceptable methods of birth control in this study are the following (birth control must be effective by the time the FCBP subject is randomized into the study [eg, hormonal contraception should be initiated at least 28 days before randomization]):
   - combined hormonal (estrogen and progestogen containing) contraception, which may be oral, intravaginal, or transdermal
     Note: intravaginal and transdermal combined hormonal contraception are not approved in Japan.
   - 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.
   - 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

8. Subject is willing to receive weekly SC injections throughout the study.
9. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
10. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.

* 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.

4.3 Exclusion Criteria

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

1. Subject who has ascites requiring treatment or symptomatic ascites
2. Subject who has a history of inflammatory bowel disease (including Crohn's disease and ulcerous colitis), achalasia or esophageal surgery.
3. Subject who has a history of GI bleeding disorders and/or demonstrates presence of esophageal varices.
4. Subject who has other causes of gastric and/or duodenal eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA).
5. 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 [HES], Mendelian disorder associated with EGE, or cardiovascular condition, or neurologic or psychiatric illness that compromises the prospective subject's ability to accurately document symptoms of EGE).
   - Diagnosis of HES is based on standard criteria (blood eosinophils >1500/μL with involvement of either the heart, nervous system, and/or bone marrow).
6. 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, upper or lower GI bleed, inflammatory bowel disease, [redacted], etc).
7. Subject has a diagnosis of celiac disease or active Helicobacter pylori infection as determined by screening EGD or a history of celiac disease diagnosed by prior EGD.
8. Subject demonstrates evidence of immunosuppression or is receiving systemic immunosuppressive or immunomodulating drugs with the exception of corticosteroids allowed as background or rescue therapy (eg, [redacted] anti-immunoglobulin E [IgE] antibodies, α4β7 integrin inhibitor antibodies, or any other monoclonal antibody, methotrexate, cyclosporine, azathioprine, mercaptopurine, interferon alpha [IFNα], tumor necrosis factor alpha [TNFα] inhibitors, etc) within 5 drug half-lives prior to the first Screening Visit. Any use of these medications will be prohibited during the study.
9. Subject who uses systemic corticosteroids exceeding the equivalent of up to 10 mg/day of prednisone within 4 weeks prior to the first Screening Visit.
10. Subject is currently receiving a high potency topical corticosteroid (eg, augmented betamethasone dipropionate, clobetasol propionate, etc) for dermatologic use. Prospective subjects must not have received a high potency topical corticosteroid for dermatologic use within 8 weeks of the first Screening Visit. Any use will be prohibited during the study.
11. Subject has received oral or sublingual immunotherapy within 6 months of the first Screening Visit; any use will be prohibited during the study. Subjects receiving SC immunotherapy may participate but must be on stable doses for at least 3 months prior to the first Screening Visit and during the study.

12. Subject is receiving concurrent treatment with another IP, including through participation in an interventional trial for COVID-19. Prospective subjects may not participate in a concurrent IP study or have received an IP within 5 drug half-lives prior to signing the ICF/assent for this study. Further, for subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the impact of the vaccine is stabilized, as determined by discussion between the investigator and the Clinical Trial Physician.
13. Subject has received a live (including attenuated) vaccine within 1 month prior to the first Screening Visit or anticipates the need to be vaccinated with a live (including 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.
14. Subject has previously received CC-93538 treatment (formerly known as RPC4046 and ABT-308) through participation in any other CC-93538 clinical study.
15. Subject has liver function impairment or persisting elevations of aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) that are 2 times the upper limit of normal (ULN), or total bilirubin 1.5 times the ULN. Subjects with elevations in total bilirubin that are due to Gilbert Syndrome and that are not clinically meaningful may participate.
16. Subject has an active parasitic/helminthic infection or a suspected parasitic/helminthic infection. Subjects with suspected infections may participate if clinical and laboratory assessments, if needed, rule out active infection prior to randomization.
17. Subject has an ongoing infection (eg, hepatitis B or C, human immunodeficiency virus [HIV], or tuberculosis as defined by standard medical guidelines and as outlined in Section 6.1).
18. Severe infection within 4 weeks prior to screening
    - Additionally, in the case of prior SARS-CoV-2 infection, symptoms must have completely resolved, and based on investigator assessment in consultation with the Clinical Trial Physician, there are no sequelae that would place the participant at a higher risk of receiving investigational treatment
19. Subject has known hereditary fructose intolerance (HFI).
20. Subject is pregnant or lactating.
21. Subject has a history of idiopathic anaphylaxis or a major immunologic reaction (such as anaphylactic reaction, anaphylactoid reaction, or serum sickness) to an Immunoglobulin G (IgG) containing agent.
    Note: a subject who has a known hypersensitivity to any ingredient in the IP is also excluded.
22. Subject has a history of cancer or lymphoproliferative disease, other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or adequately treated cervical carcinoma in situ, within 5 years of screening.
23. Subject has a history of alcohol or drug abuse diagnosed within 5 years prior to initiation of screening.

24. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
25. 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.
26. Subject has any condition that confounds the ability to interpret data from the study.

5 TABLES OF EVENTS

Table 4: Table of Events for the Induction Phase

Study Procedures	Screen-ing[a]	Induction Phase Treatment Period								EGE Flare Assessment Visit [e]	ET Visit [f]	Interim 8-week Safety Follow-up Visit [g]	Final 16-week Safety Follow-up Visit [g]
Visit Label		Visit 1[b]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 [c, d]				
Visit Week (Window)	Day -28 to -1	Day 1	Week 1 (Day 8±3d)	Week 2 (Day 15±3d)	Week 3 (Day 22±3d) [h]	Week 4 (Day 29±3d) [h]	Week 8 (Day 57±3d) [h]	Week 12 (Day 85±3d) [h]	Week 16 (Day 113±3d) [h]			Week 23 (Day 162±7d)	Week 31 (Day 218±7d)
Informed consent/assent	X	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/ exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	-	-
Demographics/base-line characteristics	X	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-
Prior therapy	X	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant therapy	X	X	(X)[h]	X	(X)[h]	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	(X)[h]	X	(X)[h]	X	X [h]	X [h]	X [h]	X	X	X	X
Hematology and chemistry (pre-dose) [i, j]	X	X	-	-	-	X	X	X	X	X	X	X	X
Coagulation panel	X	-	-	-	-	-	-	-	-	-	-	-	-
Urinalysis (pre-dose) [i]	X	X	-	-	-	X	-	-	X	X	X	X	X
Testing for hepatitis B and C and HIV	X	-	-	-	-	-	-	-	-	-	-	-	-
TB assessment	X	-	-	-	-	-	-	-	-	-	-	-	-

Table 4: Table of Events for the Induction Phase

Study Procedures	Screening[a]	Induction Phase Treatment Period								EGE Flare Assessment Visit [e]	ET Visit [f]	Interim 8-week Safety Follow-up Visit [g]	Final 16-week Safety Follow-up Visit [g]
Visit Label		**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 [c, d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 1 (Day 8±3d)**	**Week 2 (Day 15±3d)**	**Week 3 (Day 22±3d) [h]**	**Week 4 (Day 29±3d) [h]**	**Week 8 (Day 57±3d) [h]**	**Week 12 (Day 85±3d) [h]**	**Week 16 (Day 113±3d) [h]**			**Week 23 (Day 162±7d)**	**Week 31 (Day 218±7d)**
Pregnancy test (FCBP only) [k]	X	X	-	-	-	X	X	X	X	-	X	X	X
Physical examination [l]	X	X	-	-	-	X	X	X	X	-	X	X	X
Height (cm)	X	-	-	-	-	-	(X)[m]	-	(X)[m]	(X) [m]	(X)[m]	(X)[m]	(X)[m]
Weight (kg)	X	X	-	X	-	X	X	X	X	X	X	X	X
Vital signs	X	X	-	X	-	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	-	-	-	-	-	-	-	-	-	-	-	-
Serum antibodies to CC-93538 [i]	-	X	-	-	-	X	X	-	X	-	X	X	X
Serum CC-93538 PK assessment [i]	-	X	-	X	-	X	X	X	X	-	X	X	X
[redacted]													
Izumo Scale [q]	X	X	X	X	X	X	X	X	X	-	X	X	X

Table 4: Table of Events for the Induction Phase

Study Procedures	Screen-ing[a]	Induction Phase Treatment Period								EGE Flare Assessment Visit [e]	ET Visit [f]	Interim 8-week Safety Follow-up Visit [g]	Final 16-week Safety Follow-up Visit [g]
Visit Label		**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 [c, d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 1 (Day 8±3d)**	**Week 2 (Day 15±3d)**	**Week 3 (Day 22±3d) [h]**	**Week 4 (Day 29±3d) [h]**	**Week 8 (Day 57±3d) [h]**	**Week 12 (Day 85±3d) [h]**	**Week 16 (Day 113±3d) [h]**			**Week 23 (Day 162±7d)**	**Week 31 (Day 218±7d)**
EGID Severity Score [r]	-	X	-	-	-	-	X	-	X	X	X	X	X
[redacted]													

Table 4: Table of Events for the Induction Phase

Study Procedures	Screen-ing[a]	Induction Phase Treatment Period								EGE Flare Assessment Visit [e]	ET Visit [f]	Interim 8-week Safety Follow-up Visit [g]	Final 16-week Safety Follow-up Visit [g]
Visit Label		Visit 1[b]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 [c, d]				
Visit Week (Window)	Day -28 to -1	Day 1	Week 1 (Day 8±3d)	Week 2 (Day 15±3d)	Week 3 (Day 22±3d) [h]	Week 4 (Day 29±3d) [h]	Week 8 (Day 57±3d) [h]	Week 12 (Day 85±3d) [h]	Week 16 (Day 113±3d) [h]			Week 23 (Day 162±7d)	Week 31 (Day 218±7d)
[redacted]													
EGD with tissue biopsies [v]	X	-	-	-	-	-	-	-	X	X [w]	X [x]	-	-
[redacted]													

Table 4: Table of Events for the Induction Phase

Study Procedures	Screen-ing[a]	Induction Phase Treatment Period								EGE Flare Assessment Visit [e]	ET Visit [f]	Interim 8-week Safety Follow-up Visit [g]	Final 16-week Safety Follow-up Visit [g]
Visit Label		**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8 [c, d]**				
Visit Week (Window)	**Day -28 to -1**	**Day 1**	**Week 1 (Day 8±3d)**	**Week 2 (Day 15±3d)**	**Week 3 (Day 22±3d) [h]**	**Week 4 (Day 29±3d) [h]**	**Week 8 (Day 57±3d) [h]**	**Week 12 (Day 85±3d) [h]**	**Week 16 (Day 113±3d) [h]**			**Week 23 (Day 162±7d)**	**Week 31 (Day 218±7d)**
Entry to Maintenance Phase [y]	-	-	-	-	-	-	-	-	X [z]	-	-	-	-
Randomization via IWRS	-	X	-	-	-	-	-	-	-	-	-	-	-
IP administration [aa]	-	X	X[h]	X[h]	X[h]	X	X	X	X	-	-	-	-

Abbreviations: AE = adverse event; [redacted] COVID-19: = Coronavirus disease 2019; d = day; ECG = electrocardiogram; [redacted] EGD = esophagogastroduodenoscopy; EGE = eosinophilic gastroenteritis; EGID = eosinophilic gastrointestinal disorder; [redacted] ePRO = electronic patient-reported outcome; [redacted] ET = Early Termination; FCBP = female of childbearing potential; [redacted] HIV = human immunodeficiency virus; [redacted] IP = investigational product; IWRS = Interactive Web Response System; [redacted] PK = pharmacokinetic(s); PRO = patient-reported outcome; SAE = serious adverse event; [redacted] TB = tuberculosis; [redacted]

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

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

c. For subjects continuing in the Maintenance Phase, Visit 8 (Week 16) of the Induction Phase will also be the first visit in the Maintenance Phase or the Open-label Long-term Extension Phase. See Table 5 and Table 6 for the Table of Events for the Maintenance Phase or Open-label Long-term Extension Phase.

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

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

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

g. Subjects who complete the Induction Phase and do not enter either the Maintenance Phase or OLE Phase will be asked to complete the Interim 8-week Safety Follow-up Visit (8 weeks after final IP administration; at Week 23 for subjects who complete the Induction Phase) and the Final 16-week Safety Follow-up Visit (16 weeks after final IP administration; at Week 31 for subjects who complete the Induction Phase) for the assessment of safety and clinical status. For subjects exiting the study before completing the Induction Phase, these visits should occur at 8 and 16 weeks following the last dose of IP (ie, visits may occur before Weeks 23 and 31). However, subjects who are permanently discontinued from IP and continue study participation will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 16 or the ET Visit).

h. Collection of concomitant therapy and confirmation of AE/SAE should be performed for subjects weighing from 30 to 40 kg at Visit 2 and Visit 4. If necessary, additional clinical laboratory tests may be performed. Also, the first 3 weekly SC doses will be administered in the clinic with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation and be monitored every 2 weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until Week 16 (ie, Week 6 [Day 43 ± 3 days], Week 10 [Day 71 ± 3 days], and Week 14 [Day 99 ± 3 days]).

i. Pre-dose collection, except for both Safety Follow-up Visits (if applicable), the ET Visit (if applicable), and the EGE Flare Assessment Visit (if applicable).

j. Fasting lipid panel and fasting glucose (instead of random glucose) will only be conducted at Day 1, Week 16, and the ET Visit (if applicable).

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

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

m. For only subjects aged from 12 to 19 years at the time of signing the ICF/assent, height will be measured at Week 8, Week 16, the EGE Flare Assessment Visit, both Safety Follow-up Visits and ET Visit in which the EGID severity scoring is scheduled.

[redacted]

q. The Izumo Scale is to be completed during the Screening Period for at least the 2 consecutive weeks before the IP administration on Day 1 and weekly (at the same time as much as possible) from Day 1 through Week 16 using a handheld device (ePRO instrument). For subjects who are required to complete the Safety Follow-up Visits, the Izumo Scale will also be assessed for at least the prior week at each of the 2 Safety Follow-up Visits. The ePRO instrument will be distributed to subjects at the Screening Visit. Subjects will not be able to complete a questionnaire more than 3 days before/after it is due and will not be able to go back and make any corrections or changes to the data originally entered.

r. The height obtained at the most recent visit can be used to calculate the EGID severity score for subjects from 12 to 19 years at the time of signing the ICF/assent.

[redacted]

[redacted]

v. Esophagogastroduodenoscopy (EGD) biopsies [redacted]. It is recommended to avoid the screening EGD to perform during the last 2 weeks of screening just prior to Day 1.

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

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

y. The investigator will confirm the subject's suitability for entry to the Maintenance Phase according to protocol requirements detailed in Section 6.4.2.11.

z. If a subject meets the rescue criteria detailed in Section 6.4.2.10, the subject can enter the OLE Phase.

aa. Once weekly IP administration (CC-93538 or placebo: subcutaneous [SC] doses on Day 1 followed by SC doses weekly from Week 1 through Week 15 [ie, a total of 16 weekly SC doses inclusive of the Day 1 dose]). The first 3 weekly SC doses will be required to be given in the clinic, and subjects will remain in the clinic for at least 30 minutes following dosing for observation. Additionally, the investigator will review the importance of IP compliance and evaluate compliance for each subject in accordance with the protocol.

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period									EGE Flare Assessment Visit [b]	ET Visit [c]	Interim 8-week Safety Follow-up Visit [d]	Final 16-week Safety Follow-up Visit [d]
Visit Label	**Visit 8 [a]**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**				
Visit Week (Window)	**Week 16 (Day 113±3d)**	**Week 20 (Day 141±3d)**	**Week 24 (Day 169±3d)**	**Week 28 (Day 197±3d)**	**Week 32 (Day 225±3d)**	**Week 36 (Day 253±3d)**	**Week 40 (Day 281±3d)**	**Week 44 (Day 309±3d)**	**Week 48 (Day 337±3d)**			**Week 55 (Day 386±7d)**	**Week 63 (Day 442±7d)**
Confirm eligibility	X	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry [e, f]	X	-	X	-	X	-	X	-	X	X	X	X	X
Urinalysis [e]	X	-	-	-	-	-	-	-	X	X	X	X	X
Urine pregnancy test (FCBP only) [g]	X	X	X	X	X	X	X	X	X	-	X	X	X
Physical examination [h]	X	-	-	-	X	-	-	-	X	-	X	X	X
Height (cm)	(X)[i]	-	-	-	(X) [i]	-	-	-	(X)[i]	(X)[i]	(X) [i]	(X)[i]	(X)[i]
Weight (kg)	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum antibodies to CC-93538 [e]	X	X	X	X	X	-	-	-	X	-	X	X	X
Serum CC-93538 PK assessment [e]	X	X	X	X	X	X	X	-	X	-	X	X	X

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period									EGE Flare Assessment Visit [b]	ET Visit [c]	Interim 8-week Safety Follow-up Visit [d]	Final 16-week Safety Follow-up Visit [d]
Visit Label	Visit 8 [a]	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16				
Visit Week (Window)	Week 16 (Day 113±3d)	Week 20 (Day 141±3d)	Week 24 (Day 169±3d)	Week 28 (Day 197±3d)	Week 32 (Day 225±3d)	Week 36 (Day 253±3d)	Week 40 (Day 281±3d)	Week 44 (Day 309±3d)	Week 48 (Day 337±3d)			Week 55 (Day 386±7d)	Week 63 (Day 442±7d)
[redacted]													
Izumo Scale [l]	X	X	X	X	X	X	X	X	X	-	X	X	X
EGID Severity Score [m]	X	-	-	-	X	-	-	-	X	X	X	X	X
[redacted]													

Table 5: Table of Events for the Maintenance Phase

Study Procedures	Maintenance Phase Treatment Period									EGE Flare Assessment Visit [b]	ET Visit [c]	Interim 8-week Safety Follow-up Visit [d]	Final 16-week Safety Follow-up Visit [d]
Visit Label	Visit 8 [a]	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15	Visit 16				
Visit Week (Window)	Week 16 (Day 113±3d)	Week 20 (Day 141±3d)	Week 24 (Day 169±3d)	Week 28 (Day 197±3d)	Week 32 (Day 225±3d)	Week 36 (Day 253±3d)	Week 40 (Day 281±3d)	Week 44 (Day 309±3d)	Week 48 (Day 337±3d)			Week 55 (Day 386±7d)	Week 63 (Day 442±7d)
[redacted]													
EGD with tissue biopsies [p]	X	-	-	-	-	-	-	-	X	X [q]	X [r]	-	-
[redacted]													
Entry to OLE Phase	-	-	-	-	-	-	-	-	X [s]	-	(X) [s]	-	-
Re randomization via IWRS	X [t]	-	-	-	-	-	-	-	-	-	-	-	-
IP administration [u]	X	X	X	X	X	X	X	X	-	-	-	-	-

Abbreviations: AE = adverse event; [redacted] COVID-19: = Coronavirus disease 2019; d = day; ECG = electrocardiogram; [redacted] EGD = esophagogastroduodenoscopy; EGE = eosinophilic gastroenteritis; EGID = eosinophilic gastrointestinal disorder; [redacted] ePRO = electronic patient-reported outcome; [redacted] ET = Early Termination; FCBP = female of childbearing potential; [redacted] HIV = human immunodeficiency virus; [redacted] IP = investigational product; IWRS = Interactive Web Response System; OLE = Open-label Long-term Extension; [redacted] PK = pharmacokinetic(s); PRO = electronic patient-reported outcome; SAE = serious adverse event; [redacted]

[redacted]

a. The assessments performed at the Induction Phase Week 16 Visit will also serve as the data for the first visit of the Maintenance Phase (Maintenance Phase Week 16 is equivalent to Induction Phase Week 16) and do not need to be repeated specifically for the Maintenance Phase. If the first visit of the Maintenance Phase does not occur at the Induction Week 16 Visit, an assessment of concomitant medications and AEs/SAEs will be performed, and a urine pregnancy test (FCBP only) will be performed only if it has been more than 30 days since the last test. A + 4 day allowance (in addition to the Visit 8 window of ± 3 days) for the scheduling of the EGD and investigator assessment of subject suitability for entry to Maintenance may be used if needed. All assessments are to be performed prior to IP administration. Subjects should begin the Maintenance Phase within ≤ 14 days from the final dosing in the Induction Phase.
b. An EGE Flare Assessment Visit should be scheduled as close as possible to the time that an EGE flare is suspected.
c. Subjects who prematurely discontinue the study during the Maintenance Phase will be asked to complete an Early Termination Visit and then an Interim and a Final Safety Follow-up Visit at 8 weeks and at 16 weeks, respectively, after final IP administration for the assessment of safety and clinical status. Early Termination procedures performed at the EGE Flare Assessment Visit do not need to be repeated for subjects who are discontinuing the study prematurely due to an EGE flare.
d. Subjects who complete the Maintenance Phase and do not continue IP administration (in the OLE Phase) will be asked to complete the Interim 8-week Safety Follow-up Visit (8 weeks after final IP administration; at Week 55 for subjects who complete the Maintenance Phase) and the Final 16-week Safety Follow-up Visit (16 weeks following final IP administration; at Week 63 for subjects who complete the Maintenance Phase) for assessment of safety and clinical status. For subjects exiting the study before completing the Maintenance Phase, these visits should occur at 8 and 16 weeks following the last dose of IP (ie, visits may occur before Week 55 and 63). However, subjects who are permanently discontinued from IP and continue study participation will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 48 or the ET Visit).
e. Pre-dose collection except for both Safety Follow-up Visits (if applicable), the ET Visit (if applicable), and the EGE Flare Assessment Visit (if applicable).
f. Fasting lipid panel and fasting glucose (instead of random glucose) will only be conducted at Week 16, Week 48, and the ET Visit (if applicable).
g. For females of childbearing potential (FCBP), urine pregnancy tests are required. In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At each study visit, the investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.
h. Complete physical examination to be performed at Maintenance Phase Week 16, Week 48, both Safety Follow-up Visits (if applicable) and at Early Termination (if applicable). Abbreviated physical examination to be conducted at Week 32.
i. For only subjects aged from 12 to 19 years at the time of signing the ICF/assent), height will be measured at Week 16, Week 32, Week 48, the EGE Flare Assessment Visit, both Safety Follow-up Visits, and ET Visit in which the EGID severity scoring is scheduled.

[redacted]

l. The Izumo Scale is to be completed weekly (at the same time as much as possible) from Week 16 through Week 48 using a handheld device (ePRO instrument). For subjects who are required to complete the Safety Follow-up Visits, the Izumo Scale will also be assessed for at least the prior week at each of the 2 Safety

Follow-up Visits. Subjects will not be able to complete a questionnaire more than 3 days before/after it is due and will not be able to go back and make any corrections or changes to the data originally entered.

m. The height obtained at the most recent visit can be used to calculate the EGID severity score for subjects from 12 to 19 years at the time of signing the ICF/assent.

[redacted]

p. Esophagogastroduodenoscopy (EGD) biopsies [redacted].

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

r. EGD is not required at Early Termination Visits that occur before Week 24 of the Maintenance Phase.

s. If a subject meets the rescue criteria detailed in Section 6.4.2.10, the subject can enter the OLE Phase. A subject may be eligible for entry to the OLE Phase during the Maintenance Phase.

t. All subjects should be re-randomized via IWRS. However only subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized (1:1) to CC-93538 360 mg SC once weekly or CC-93538 360 mg SC once every other week and subjects who are randomized to receive matching placebo in the Induction Phase will continue placebo in the Maintenance Phase.

u. Subjects continuing participation in the Maintenance Phase will be given their first dose of IP at the first visit of the Maintenance Phase (ie, the Week 16 Induction Visit for most subjects). Subjects will then receive weekly doses through Week 47 (ie, a total of 32 doses of IP). For a subject who chooses to proceed to the OLE Phase, when a subject's Week 48 visit and the first visit of the OLE Phase do not occur on the same day, an extra IP will not be dispensed, and IP administration will be skipped until entering the OLE Phase.

Table 6: Table of Events for the Open-label Long-term Extension (OLE)

Study Procedures	Base-line [a]	Open-label Long-term Extension Period Year 1						Open-label Long-term Extension Period Year 2 and Beyond [b]				[redacted]	EGE Flare Assess-ment Visit[c]	OLE-ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label	OLE Visit 1[a, e]	OLE Visit 2[e]	OLE Visit 3[e]	OLE Visit 4[e]	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 Q1 (Year x +Wk 13 [±14d])	Mid-point of Year (Year x + Wk 26 [±14d])	End of Q3 (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)
Confirm eligibility	X	-	-	-	-	-	-	-	-	-	-		-	-	-	-
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Hematology and chemistry [f]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Urinalysis [f] (pre dose)	X	X	-	-	X	-	X	-	X	-	X		X	X	X	X
Urine 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
[redacted]																

Table 6: Table of Events for the Open-label Long-term Extension (OLE)

Study Procedures	Base-line [a]	Open-label Long-term Extension Period Year 1						Open-label Long-term Extension Period Year 2 and Beyond [b]				[redacted]	EGE Flare Assess-ment Visit[c]	OLE-ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label	**OLE Visit 1[a, e]**	**OLE Visit 2[e]**	**OLE Visit 3[e]**	**OLE Visit 4[e]**	**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 Q1 (Year x +Wk 13 [±14d])**	**Mid-point of Year (Year x + Wk 26 [±14d])**	**End of Q3 (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)**
Vital signs	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Serum antibodies to CC-93538 [f, j]	X	X	X	X	X	X	X	X	X	X	X		-	X	X	X
[redacted]																

Table 6: Table of Events for the Open-label Long-term Extension (OLE)

Study Procedures	Base-line [a]	Open-label Long-term Extension Period Year 1						Open-label Long-term Extension Period Year 2 and Beyond [b]				[redacted]	EGE Flare Assess-ment Visit[c]	OLE-ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label	OLE Visit 1[a, e]	OLE Visit 2[e]	OLE Visit 3[e]	OLE Visit 4[e]	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 Q1 (Year x +Wk 13 [±14d])	Mid-point of Year (Year x + Wk 26 [±14d])	End of Q3 (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)
[redacted]																

Table 6: Table of Events for the Open-label Long-term Extension (OLE)

Study Procedures	Base-line [a]	Open-label Long-term Extension Period Year 1						Open-label Long-term Extension Period Year 2 and Beyond [b]				[redacted]	EGE Flare Assess-ment Visit[c]	OLE-ET/ EoT Visit[d]	Interim 8-week Safety Follow-up Visit	Final 16-week Safety Follow-up Visit
Visit Label	OLE Visit 1[a, e]	OLE Visit 2[e]	OLE Visit 3[e]	OLE Visit 4[e]	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 Q1 (Year x +Wk 13 [±14d])	Mid-point of Year (Year x + Wk 26 [±14d])	End of Q3 (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)
[redacted]																
CC-93538 administra-tion [x]	X	X	X	X	X	X	X	X	X	X	X		-	-	-	-

Abbreviations: AE = adverse event; [redacted] COVID-19: = Coronavirus disease 2019; d = day; [redacted] EGD = esophagogastroduodenoscopy; EGE = eosinophilic gastroenteritis; EGID = eosinophilic gastrointestinal disorder; [redacted] EoT = End of Treatment; ET = Early Termination; FCBP = female of childbearing potential; [redacted] IP = investigational product; OLE = Open-label Long-term Extension; [redacted] ; Q = Quarter; SAE = serious adverse event; [redacted] Wk = Week

[a] All Open-label Long-term Extension (OLE) Day 1 study procedures/assessments will serve as baseline assessments and will be completed prior to dosing. The OLE Day 1/Baseline assessments will include the Induction Phase Week 16 Visit assessments, Maintenance Phase Week 48 Visit assessments, or Maintenance Phase EGE Flare Assessment Visit and ET Visit assessment, as applicable. Additional OLE baseline assessments not performed at the final Induction Phase Visit (Week 16), Maintenance Phase Visit (Week 48), or Maintenance Phase EGE Flare Assessment Visit and ET Visit assessment 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 6.3.2. OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the Induction Phase Week 16 Visit, Maintenance Week 48 Visit, Maintenance Phase EGE Flare Assessment Visit and ET Visit or OLE Day 1. Subjects will not be allowed to enroll in the OLE Phase and receive CC-93538 on Day 1 if there will be a delay of > 21 days from dosing in the final Induction Phase Visit or the final dosing in the Maintenance Phase unless discussed with the Medical Monitor (refer to Section 6.3.2).

[b] After completion of Week 48 (OLE Visit 7) plus an additional 4 weeks in the OLE Phase (that is, after Week 52 of the OLE Phase), subjects will continue on into the second year of the OLE Phase (OLE Year 2 and beyond). During OLE Year 2 and beyond, subjects will attend study visits every 13 weeks (± 14 days) for a total of four 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 included in the Quarterly 1 and 3 Visits.

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

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

[e] If subject weighing ≥ 30 kg and <40 kg enters the OLE Phase from Week 16 of the Induction Phase or during the Maintenance Phase, the first 3 weekly SC doses will be administered in the clinic with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation and will be monitored every 2 weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until OLE Visit 4 (OLE Week 16) (ie, OLE Week 6 [Day 43 ± 3 days], OLE Week 10 [Day 71 ± 3 days], OLE Week 12 [Day 85 ± 3 days], and OLE Week 14 [Day 99 ± 3 days])

[f] Pre-dose assessment, except for the OLE-ET/EoT Visit, 2 Safety Follow-up Visits and the EGE Flare Assessment Visit (if applicable).

[g] For females of childbearing potential (FCBPs), urine (or serum) pregnancy test will be performed at OLE Day 1/Baseline and 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 each study visit, the investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.

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

[i] [redacted] OLE Week 24, OLE Week 48, OLE Q4 Visits (OLE Year 2 and beyond), the EGE Flare Assessment Visit and OLE-ET/EoT Visit in which the EGID severity scoring is scheduled.

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

[redacted]

[x] All subjects will receive weekly open-label CC-93538 360 mg during the OLE Phase. Subjects will be given their first dose of CC-93538 at the OLE Day 1 Visit (which could be the same day as the Induction Phase Week 16, the Maintenance Phase Week 48, or ET Visit during the Maintenance Phase). Subjects will then receive weekly doses throughout the OLE Phase for as long as the study is active; participation may continue until the subject decides to withdraw from the study, the investigator decides to withdraw the subject from the study, or the Sponsor decides to terminate/complete 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 single 2 mL weekly SC injection using the 360 mg/2 mL [redacted] presentation, after the new 360 mg/2 mL [redacted] presentation is introduced into the OLE Phase for subjects who did not begin dosing with

the 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 Administration Visit.

6 PROCEDURES

Assessments and procedures for the Screening Period and the Induction Phase are outlined in Table 4. Assessments and procedures for the Maintenance Phase are outlined in Table 5. For the Follow-up Period (Safety Follow-up Visits), assessments and procedures are included in both Table 4 and Table 5. Assessments and procedures for the Open-label Long-term Extension Phase are outlined in Table 6. Study assessments and procedures are also described in Section 6.1, Section 6.2, and Section 6.3. The day of administration of the first dose of IP is defined as Day 1 (pre-dose/baseline).

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

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

- EGE clinical symptom assessment instruments and PROs
- Spontaneous or solicited AE reporting
- Vital signs
- Physical examination
- Clinical laboratory tests, including blood sampling for the assessment of serum CC-93538 levels, ADA, [redacted]
- 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.

The Izumo Scale will be completed weekly during the Screening, the Induction, the Maintenance and the OLE Phases, and for those subjects who are required to complete the Safety Follow-up Visits (Section 6.3.1), the Izumo Scale will be assessed at least for the prior week at each of the 2 Safety Follow-up Visits.

[redacted]

For the purposes of this study, adolescents are defined as subjects aged 12 to 17 years at the time of signing the ICF/assent form in Study CC-93538-EG-001 and adults are defined as subjects aged

18 to 75 years at the time of signing the ICF. 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 completed by adult subjects (The EGID Severity Score is an exception, different score scales are used for subjects from 12 to 19 years and subjects ≥ 20 years at the time of signing the ICF/assent, respectively).

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

6.1 Screening Period

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

Screening procedures, as specified in the Table of Events detailed in Table 4, will be performed for all subjects to determine study eligibility. All screening procedures must be completed within 4 weeks prior to receiving the first dose of IP. If there are issues with scheduling the screening EGD procedure, the screening window for informed consent and the EGD procedure may be extended up to 8 weeks prior to the first dose of IP. However, the EGD may not be performed during the last 2 weeks of screening at the same time the electronic PRO (ePRO) will be evaluated for the baseline timepoint. In addition, a preliminary assessment of inclusion/exclusion criteria, including the intensity of EGE symptoms, should be performed by the investigator before scheduling the EGD procedure for subjects. For FCBP subjects who initiate treatment with birth control during screening, birth control must be effective by the time the FCBP subject is randomized into the study (eg, hormonal contraception should be initiated at least 28 days before randomization). If necessary, the randomization/Day 1 Visit may be delayed up to a maximum of 28 days to achieve the minimum treatment duration. If the Day 1 Visit is delayed, the Medical Monitor should be contacted to confirm if any screening assessments (eg, safety laboratories, etc.) need to be repeated prior to randomization. All other screening assessments and procedures are to be performed by the Principal Investigator or a qualified designee. The ePRO instruments including the Izumo Scale, [redacted] will be distributed to subjects at the Screening Visit.

After completion of a training module, weekly assessments may be performed starting prior to scheduled Day 1 (baseline) for consecutive weeks during the screening period (ie, the Izumo Scale data collections during screening period are 5 times at maximum [on Day-28, Day-21, Day -14, Day -7, and Day 1]). Subjects will not be able to complete a questionnaire more than 3 days before/after it is due. Subjects are required to have completed for at least the prior 2 consecutive weeks of the Izumo Scale data collection on Day 1 (ie, for the final 2 weeks of screening preceding Day 1 that are assessed on Day -7 and Day 1) in order to be enrolled in the study.

It is expected that [redacted]. A telephone call may be made to subjects as a reminder to complete [redacted]

[redacted]. Telephone calls may take place just prior to the beginning of the final [redacted] and [redacted] which serves as the study baseline.

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

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

The following evaluations will be performed at screening as specified in the Table of Events (Table 4), after informed consent/assent has been obtained:

- Assessment of inclusion/exclusion criteria
- Demographics and baseline characteristics
- Medical history
- Prior therapy and concomitant therapy including details of the concomitant use of steroid. The use of concomitant medication and procedures will be monitored throughout the study. Refer to Section 8 for prohibited concomitant therapies and permitted concomitant therapies including stable dose requirements and other restrictions.
- Adverse event assessment begins when the subject signs the informed consent/assent form. Throughout the course of the study, every effort must be made to remain alert to possible AEs or SAEs. Once subjects consent, AEs/SAEs will be recorded at each study visit. Refer to Section 10 for definitions of AEs/SAEs, monitoring, and reporting. In addition, device (ie, PFS) failures or malfunctions should be captured, and device related AEs should also be collected.
- Hematology, chemistry, coagulation panel, and urinalysis (central laboratory). The following safety laboratory tests will be performed to assess the safety profile of CC-93538:
  - Hematology: red blood cell (RBC) count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin (hgb), hematocrit (hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC)
  - Blood chemistry: indices included at all required chemistry time points are sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose (random, at time points not requiring fasting), albumin, alkaline phosphatase, creatinine, creatine phosphokinase (CPK), ALT/SGPT, AST/SGOT, gamma glutamyltransferase (GGT), amylase, total bilirubin, direct bilirubin and C-reactive protein (CRP); in addition, fasting lipid panel (total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein) and fasting glucose (instead of random glucose) will be performed only at Day 1, Week 16, Week 48, and the ET Visit (if applicable)
  - Coagulation: prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)

  - Urinalysis: leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
  - The coagulation panel will only be conducted at screening. The hematology, chemistry, and urinalysis will be performed pre-dose (except for the Safety Follow-up Visit, ET Visit, and the EGE Flare Assessment Visit if applicable) at screening and the additional time points outlined in the Table of Events (Table 4, Table 5 and Table 6).
- Testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV (central laboratory) will be performed at screening only.
  - HBV: Hepatitis B surface antigen (HBsAg) screening test and hepatitis B core antibody (HBcAb) test will be performed. Subjects who test positive for HBsAg will be excluded from the study. For subjects who test positive only for HBcAb, an HBV deoxyribonucleic acid (DNA) test must be performed. If the HBV DNA test is positive, the subject will be excluded from the study. If the HBV DNA test is negative, the subject will be eligible for this study.
  - HCV: HCV antibody (anti-HCV IgG) test will be performed. Subjects testing positive for HCV antibody and have a positive confirmatory test (HCV ribonucleic acid [RNA]) will be excluded from the study. Subjects with evidence of cleared HCV infection (eg, HCV antibody positive subjects who are negative for HCV RNA) and who have not received anti-HCV therapy for at least 12 weeks will be eligible for participation.
  - HIV: An HIV antibody test will be performed. Subjects testing positive for HIV will be excluded from the study.
- Testing for tuberculosis (TB) will be performed at screening only. Active TB must be ruled out according to local medical practices. Latent TB must be assessed with a TB skin test, QuantiFERON Gold test, or other interferon gamma release assay (IGRA) (eg, T-SPOT). Subjects with latent TB must have documentation of completed prophylactic treatment by local standard of care. Subjects with an indeterminate test result using any IGRA test must be discussed for eligibility on a case by case basis by the Sponsor's Medical Monitor or designee. Subjects with latent TB who were only partially treated or who are currently receiving prophylactic treatment will not be eligible for randomization.
- Serum pregnancy test (only for FCBP). A test for the β-subunit of serum human chorionic gonadotropin (β-hCG) must be performed at screening in females of childbearing potential. Urine (or serum) β-hCG will be performed at Day 1 and at the time points outlined in the Table of Events (Table 4, Table 5 and Table 6). In the event of a positive urine test, the subject is not to be dosed, and confirmation with a serum pregnancy test should be performed. At screening and at each subsequent study visit, the investigator will counsel FCBP subjects on pregnancy precautions for the duration of the study.
- Physical examination: A complete physical examination (including evaluation of heart, lung, head and neck, abdomen, neurological assessment, and extremities) or an abbreviated (interim/brief) physical examination (including areas with previously noted abnormalities and/or that are associated with any new complaints from the subject) will be performed according to the Table of Events (Table 4, Table 5 and Table 6).
- Height (in centimeters) and weight (in kilograms)
- Vital signs: Heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be assessed at each visit. Blood pressure and pulse will be assessed in a sitting position

and once the subject is at rest. An automated validated device may be used, if available. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

- Electrocardiogram (ECG): Single 12-lead ECG will be conducted only at the Screening Visit when the subject is at rest and may be repeated to confirm any abnormal findings.
- Weekly Izumo Scale questionnaire (Section 6.4.2.1) (at least on Day -7 and Day 1) (APPENDIX B)
- EGD with tissue biopsies (Section 6.4.1)
  - Note that [redacted] 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

6.1.1 Additional Information Regarding Safety Laboratory Assessments

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

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

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

6.1.2 Screening Failures and Rescreening of Potential Subjects

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

6.1.2.1 Retesting of Subjects who Develop COVID-19 During the Screening Period

Molecular testing for asymptomatic COVID-19 infection is not required in this study. However, where local requirements or institutional practice are more restrictive, asymptomatic COVID-19 screening may be performed locally, to ensure compliance with current local guidance. In addition, some subjects may develop suspected or confirmed symptomatic COVID-19 infection, or it may be discovered that subjects have asymptomatic COVID-19 infection during the Screening Period. In such cases, subjects may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

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

6.2 Induction Phase and Maintenance Phase

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

- Screening laboratory tests will be used to determine eligibility for randomization with the exception of pregnancy tests, which will need to be confirmed by the Day 1 test results.
- A urine (or serum) pregnancy test must be performed for all FCBP on Day 1 and the results reviewed prior to randomization. A negative pregnancy test result must be obtained prior to randomization. If the urine pregnancy test result is positive but this is believed to be a false positive, the site may perform a stat serum pregnancy test at the local laboratory to confirm pregnancy status.
- Baseline laboratory tests will be performed on Day 1 for comparison with follow-up tests. However, the results of these tests will not be available prior to randomization on Day 1.
- The following instruments will be administered prior to dosing on Day 1 to serve as the baseline assessment:
  - Weekly Izumo Scale questionnaire (Section 6.1 and 6.4.2.1) (APPENDIX B)
  - EGID Severity Score (Section 6.4.2.2) (APPENDIX C and APPENDIX D)
  - [redacted]

After eligibility has been confirmed and baseline assessments have been completed, eligible subjects will be randomized to treatment on Day 1. The first 3 weekly SC doses will be administered in the clinic. Subjects will remain in the clinic for at least 30 minutes following dosing for observation. Subsequent visits, assessments and procedures will be performed as per the Table of Events (Table 4 for the Induction Phase and Table 5 for the Maintenance Phase). For subjects weighing ≥ 30 kg and <40 kg, the first 3 weekly SC doses will be administered in the clinic with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation and be monitored every two weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until Week 16 (ie, Week 6 [Day 43 ± 3 days], Week 10 [Day 71 ± 3 days], and Week 14 [Day 99 ± 3 days]).

Dosage regimen of permitted anti-inflammatory therapy (including concomitant corticosteroid treatment; the equivalent of up to 10 mg/day of prednisone) must be kept stable until Week 16. Subjects who do not require concomitant treatment are also eligible for this study.

If the reduction of EGE-related symptoms is observed at/after Week 16, the investigator should begin tapering the dosage regimen of concomitant corticosteroids treatment after Week 16. The dose reduction should be 2.5 mg / week (as the equivalent of prednisone). If the symptoms worsen after tapering of the dosage regimen of concomitant corticosteroid treatment, the dose can be increased until the baseline dosage at the Induction Phase.

For the Maintenance Phase, eligible subjects will be re-randomized to treatment on Week 16. The assessments performed at the Week 16 Visit (Visit 8) of the Induction Phase will also serve as the data for the Maintenance Phase Week 16 Visit (Visit 8) and do not need to be repeated specifically for the Maintenance Phase. If the Maintenance Phase Week 16 Visit, the first day of the Maintenance Phase, does not occur at the Induction Phase Week 16 Visit (Visit 8), an assessment of concomitant medications and AEs/SAEs will be performed, and a urine pregnancy test (in FCBP only) will be conducted if it has been more than 30 days since the last test. The investigator will confirm subjects meet the criteria to enter the Maintenance Phase according to Section 6.4.2.11. A + 4-day allowance (in addition to the Visit 8 window of ± 3 days) for the scheduling of the EGD and investigator assessment of subject suitability for entry to the Maintenance Phase is available

if needed. Subjects should begin the Maintenance Phase within ≤ 14 days from the final dosing in the Induction Phase.

If subjects are out of window for their Week 16 dose due to use of the additional +4 day window for the EGD, subjects should skip the Week 16 dose and take the Week 17 dose which will be their first Maintenance Phase dose.

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

- Confirm eligibility (for the Maintenance Phase): If the results of the gastric/duodenal eos count will be disclosed during the Induction Phase, the subject is to be discontinued from the study and will not be allowed to enter the Maintenance Phase.
- Assessment of inclusion/exclusion criteria to confirm eligibility (Day 1 only)
- Concomitant therapy
- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis
- Urine pregnancy test (only for FCBP)
- Physical examination
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- Pharmacogenetic assessment, if applicable per government and local regulations, will be collected one time at Day 1 in subjects who provide consent (note, the sample may be obtained at any subsequent Induction Phase visit
- Weekly Izumo Scale questionnaire (APPENDIX B)
- EGID Severity Score (APPENDIX C and APPENDIX D)

[redacted]

- EGD with tissue biopsies

[redacted]

- Randomization via IWRS (Day 1 and Week 16)
- Entry to the Maintenance Phase assessment (only at Induction Phase Week 16)
- Entry to the OLE Phase assessment (at Induction Phase Week 16, during the Maintenance Phase or at Maintenance Phase Week 48)
- IP administration

Telephone call reminders may take place before the 28-day collection for the daily assessment period preceding the Week 16, Week 32 and Week 48 endpoint assessments (ie, just prior to Weeks 12, 28 and 44) and before the collection period preceding the 2 Safety Follow-up Visits, if applicable. A telephone contact may be made at other time points as part of ongoing surveillance.

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

6.2.1 EGE Flare Assessment Visit

Subjects with a worsening of EGE symptoms during the study, either in the Induction Phase or Maintenance Phase will be required to complete the EGE Flare Assessment Visit as shown in the Table of Events (Table 4, Table 5 and Table 6). Subjects with increased signs and symptoms of EGE are instructed to contact the investigator and/or study staff to determine if an EGE Flare Assessment Visit is warranted. An EGE Flare Assessment Visit should be scheduled as close as possible to the time that an EGE flare is suspected.

Any worsening of EGE symptoms during study participation will be documented as an EGE flare. See Section 6.4.2.10 for the protocol definition of EGE flare and EGE Flare Assessment Visit details.

In the event that subjects discontinue the study prematurely due to an EGE flare, the ET Visit or the OLE-ET/EoT Visit will also be completed, but procedures performed at the EGE Flare Assessment Visit do not need to be repeated for the ET visit or the OLE-ET/EoT Visit.

If subjects had an EGD performed for an EGE flare assessment during the Induction (prior to Week 16) or Maintenance (prior to Week 48) Phases, an EGD will also be performed at Week 16 or Week 48, respectively. However, an exception will be made if in the investigator's judgment the EGE flare assessment occurred too close to Week 16 or Week 48 such that it is considered unsafe to perform another EGD within this short interval. In these cases, a discussion with the Medical Monitor will take place well in advance of the Week 16 or Week 48 Visit.

The following evaluations will be performed as specified in Table 4, Table 5, and Table 6:

- Concomitant therapy

- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis*
- [redacted]
- Vital signs
- EGID Severity Score (APPENDIX C and APPENDIX D)
- [redacted]
- EGD with tissue biopsies**
- [redacted]

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

6.2.2 Early Termination Visit

For subjects who discontinue the Induction Phase and the Maintenance Phase of the study prematurely for any reason (ie, subjects who do not complete Week 48) or enter the OLE Phase during the Maintenance Phase (if a subject meets the rescue criteria detailed in Section 6.4.2.10, the subject can enter the OLE Phase), every attempt should be made to complete the assessments detailed in the ET Visit conducted as close as possible to the time of study discontinuation or of the visit determining entrance to the OLE Phase from the Maintenance Phase. The ET Visit should be completed within 2 weeks after the final CC-93538 dose. If study discontinuation or the visit determining entrance to the OLE Phase from the Maintenance Phase occurs at the regularly scheduled visit (eg, Induction Phase Week 12 or Maintenance Phase Week 32), the ET Visit and all corresponding ET Visit procedures should be conducted (Table 4 and Table 5). In addition, subjects who discontinue the study should return for the Safety Follow-up Visit (Section 6.3.1). Subjects who complete the Induction Phase Week 16 Visit but do not continue in the Maintenance Phase or the OLE Phase should complete the Week 16/ET Visit and return for the Interim 8-week and Final 16-week Safety Follow-up Visits at Week 23 and Week 31, respectively (Section 6.3.1). Subjects who complete the Induction Phase and enter the OLE Phase should complete the Week 16/ET Visit; these subjects do not need to return for the 2 Safety Follow-up Visits. Assessments conducted at the Week 16 Visit do not need to be repeated. Subjects who do not complete

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

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

Maintenance Phase Week 48 but enter the OLE Phase (Section 3.1.6) do not need to return for the 2 Safety Follow-up Visits. Subjects who complete the Maintenance Phase Week 48 but do not continue in the OLE Phase should return for the Interim 8-week and Final 16-week Safety Follow-up Visits at Week 55 and Week 63, respectively. For subjects who are discontinuing the study prematurely due to an EGE flare, ET procedures performed at the EGE Flare Assessment Visit do not need to be repeated.

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

- Concomitant therapy
- Assessment of AEs/SAEs (monitored through 16 weeks after the last dose of IP or the Final Safety Follow-up Visit, whichever is longer)
- Hematology, chemistry, and urinalysis
- Pregnancy test (only for FCBP)
- Physical examination
- [redacted]
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- [redacted]
- Weekly Izumo Scale questionnaire (APPENDIX B)
- EGID Severity Score (APPENDIX C and APPENDIX D)
- [redacted]
- EGD with tissue biopsies*

* Note that EGD is not required for ET Visits occurring before Week 8 in the Induction Phase or before Week 24 in the Maintenance Phase.

[redacted]

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

6.3 Follow-up Period

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

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

In the Induction Phase, subjects who discontinue from the study prior to completing Week 16, or subjects who complete Week 16 and do not enter the Maintenance Phase or the OLE Phase will return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively, after final IP administration (at Week 23 and Week 31 for subjects completing the Induction Phase) for the assessment of safety and clinical status after exiting the study. However, subjects who are permanently discontinued from IP and continue study participation in order to complete safety and efficacy assessments in the phase of the study that permanent discontinuation from IP occurs (according to Section 11.1) will return for the Interim and Final Safety Follow-up Visits 8 and 16 weeks after their last study visit instead of their last dose of IP (eg, Week 16 or the ET Visit). Assessments should be performed in accordance with the Table of Events (Table 4). Subjects who continue participation in the Maintenance Phase or the OLE Phase will not return for the 2 Safety Follow-up Visits.

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

In the OLE Phase (Section 6.3.2), all subjects should return for an Interim and a Final Safety Follow-up Visit at 8 and 16 weeks, respectively after final IP administration. Assessments to be performed are presented in the Table of Events (Table 6).

The following evaluations will be performed as specified in Table 4, Table 5 and Table 6:

- Concomitant therapy
- Assessment of AEs/SAEs (monitored through 16 weeks after the last dose of IP or the Final Safety Follow-up Visit, whichever is longer)
- Hematology, chemistry, and urinalysis

- Pregnancy test (only for FCBP)
- Physical examination
- [redacted]
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- Weekly Izumo Scale questionnaire at least for the prior week (7 days) period preceding each of the 2 Safety Follow-up Visits (for Safety Follow-up of the Induction Phase and the Maintenance Phase)
- EGID Severity Score (for Safety Follow-up of the Induction Phase and the Maintenance Phase)
- [redacted]
- [redacted]
- [redacted]

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

6.3.2 Open-label Long-term Extension (OLE) Phase

The OLE Day 1/Baseline assessments shown in Table 6 will be completed prior to the first dose of CC-93538 in the OLE Phase. OLE Day 1/Baseline refers to any visit during which OLE baseline assessments are obtained, including the following visits from: Induction Phase Week 16 Visit or the Maintenance Phase Week 48 Visit, or the ET Visit during the Maintenance Phase. Transition to the OLE Phase should occur for most subjects on the same day as the Induction Phase Week 16 Visit, the Maintenance Phase Week 48 Visit or the ET Visit during the Maintenance Phase. Subjects entering the OLE Phase will not complete the Safety Follow-up Visits after the Induction Phase or the Maintenance Phase. Subjects will not be eligible to enroll in the OLE Phase and receive CC-93538 on OLE Day 1 if there will be a delay of > 21 days from dosing in the final Induction Visit or the final dosing in the Maintenance Phase. The investigator will review all available information to confirm that the subject continues to meet all study enrollment criteria and complete the additional Day 1 activities for confirmation of eligibility.

The following evaluations/activities will be performed as specified in Table 6:

- Confirm eligibility: If the results of the gastric/duodenal eos count will be disclosed during the Induction Phase, the subject is to be discontinued from the study and will not be allowed to enter the OLE Phase.
- The OLE baseline assessments will include those conducted for the Induction Phase Week 16 Visit, Maintenance Phase Week 48 Visit or Maintenance Phase ET Visit, as applicable. Additional OLE baseline assessments not performed at the final Induction Phase Visit (Week

16), Maintenance Phase Visit (Week 48), or Maintenance Phase ET Visit 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 schedule of events (Table 6). Subjects will not be allowed to enroll in the OLE study and receive CC-93538 on Day 1 if there will be a delay of > 21 days from final dosing in the Induction Phase or the Maintenance Phase unless discussed with the Medical Monitor.

- The EGD procedure should not be repeated at the OLE Day 1 Visit, as long as this assessment was conducted at the final Induction Phase Visit (Week 16), Maintenance Phase Visit (Week 48), or Maintenance Phase ET Visit.
- If OLE Day 1 is not on the same day as the final Induction Phase (Week 16), Maintenance Phase (Week 48) Visit or ET Visit during the Maintenance Phase, a urine (or serum) β-hCG pregnancy test (FCBP only) must be performed on OLE Day 1 and the results reviewed on OLE Day 1 prior to the first open-label OLE CC-93538 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.
- If subjects had an EGD performed for an EGE flare assessment during the Induction (prior to Week 16) or Maintenance (prior to Week 48) Phases, an EGD will also be performed at Week 16 or Week 48, respectively. However, an exception will be made if in the investigator's judgment the EGE flare assessment occurred too close to Week 16 or Week 48 such that it is considered unsafe to perform another EGD within this short interval. In these cases, a discussion with the Medical Monitor will take place well in advance of the OLE Day 1 Visit.

After baseline assessments have been completed, eligible subjects will receive CC-93538 360 mg in an open-label manner. The first 3 SC weekly doses will be administered in the clinic. Subjects will remain in the clinic for at least 30 minutes following dosing for observation.

If a subject weighing ≥ 30 kg and < 40 kg enters the OLE Phase from Week 16 of the Induction Phase or during Maintenance Phase, the first 3 weekly SC doses will be administered in the clinic with confirmation of concomitant medications and AEs, and those subjects will remain in the clinic for at least 1 hour following dosing for observation and be monitored every 2 weeks by the site staff by telephone (but not limited to telephone) between regularly scheduled visits until OLE Week 16 (ie, OLE Week 6 [Day 43 ± 3 days], OLE Week 10 [Day 71 ± 3 days], OLE Week 12 [Day 85 ± 3 days], and OLE Week 14 [Day 99 ± 3 days]).

Subsequent visits, assessments and procedures will be performed as shown in Table 6.

Following OLE Day 1, in the first year of the OLE Phase (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 Phase (that is, after Week 52 in the OLE Phase), 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 four 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 included 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 evaluations will be performed during the OLE Phase as specified in the Table 6:

- Concomitant therapy
- Assessment of AEs/SAEs (monitored through 16 weeks after the last dose of IP or the Final Safety Follow-up Visit, whichever is longer). Refer to Section 10 for definitions of AEs/SAEs, monitoring, and reporting. In addition, [redacted]/PFS device failures or malfunctions should be captured, and device-related AEs should also be collected.
- Hematology, chemistry, and urinalysis
- Pregnancy test (only for FCBP)
- Physical examination
- [redacted]
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- [redacted]
- Weekly Izumo Scale questionnaire
- EGID Severity Score
- [redacted]

[redacted]

- EGD with tissue biopsies*

[redacted]

- CC-93538 administration

Telephone call reminders may take place before the 28-day collection period for daily assessment preceding the OLE Week 24, OLE Week 36 and OLE Week 48 endpoint assessments (ie, just prior to OLE Weeks 20, 32 and 44), if applicable. A telephone contact may be made at other time points as part of ongoing surveillance.

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

[redacted]

6.3.2.2 OLE - Early Termination Visit/End of Treatment: Visit

For subjects who discontinue the OLE Phase of the study for any reason, the assessments detailed in the OLE-ET Visit/EoT Visit should be completed within 2 weeks after the final CC-93538 dose (Table 6). The OLE-ET Visit will be completed if discontinuation occurs before the Quarterly 4 Visit at the end of OLE Year 2 (OLE Week 104); the OLE-EoT Visit will be completed if discontinuation occurs at or after the Quarterly 4 Visit at the end of OLE Year 2 (OLE Week 104). If the OLE-EoT Visit occurs at the scheduled Quarterly 4 Visit at the end of OLE Year 2 (OLE Week 104), the subject will complete all assessments required for each of the 2 visits collectively

* Note EGD is required for ET Visits occurring at or before OLE 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.

(ie, assessments do not need to be repeated). In addition, these subjects should return for the Interim and Final Safety Follow-up Visits (Section 6.3.1).

The following evaluations will be performed as specified in the Table 6:

- Concomitant therapy
- Assessment of AEs/SAEs
- Hematology, chemistry, and urinalysis
- Urine pregnancy test (only for FCBP)
- Physical examination
- [redacted]
- Vital signs
- Serum antibodies to CC-93538
- Serum CC-93538 PK assessment
- [redacted]
- Weekly Izumo Scale questionnaire (Section 6.4.2.1) (only if the visit occurs before or at the OLE Week 48)
- EGID Severity Score (only if the visit occurs before or at the OLE Week 48)
- [redacted]
- EGD with tissue biopsies*
- [redacted]

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

* Note EGD is required for ET Visits occurring at or before OLE 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.

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 eos count will be read blinded to treatment allocation at a centralized reading facility. Biopsy specimens will be sent to the centralized reading facility, and with the exception of screening, results of the centrally read gastric/duodenal eos count will be blinded to investigative sites during the Induction Phase and the Maintenance Phase. For the OLE Phase, biopsy results on OLE Day 1/Baseline EGD only will be read blinded to treatment allocation and results will also be blinded to investigative sites since this will be same with the EGD conducted either at Week 16 of Induction Phase, during the Maintenance Phase or at Week 48 of Maintenance Phase. A local histologic assessment of EGD biopsy samples should not be performed during the Induction Phase and the Maintenance Phase, unless required for safety reasons (eg, severe EGE 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 processing, storage, and shipping will be provided in a separate Study Laboratory Manual.

Endoscopic procedures will be performed as follows:

- EGD will be performed at the time points specified in the Table of Events (Table 4, Table 5 and Table 6).
  Note that [redacted] 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.
- Gastric/duodenal biopsies should be obtained from the following:

  Stomach

  - A set of 4 specimens from separate areas of the gastric antrum (2 to 5 cm proximal to the pylorus)
  - A set of 4 specimens from separate areas of the gastric corpus (two from the proximal lesser curvature and two from the greater curvature)
  - Up to 1 extra specimen may be collected if there are any additional areas of interest at the judgement of the investigator (if required)
  - [redacted]

    A count of ≥ 30 eos/hpf in at least 5 hpfs will be considered diagnostic of EG.

    Duodenum

  - 4 fragments of duodenal mucosa from the second and third part of the duodenum.
  - Up to 1 extra specimen may be collected if there are any additional areas of interest at the judgement of the investigator (if required)

– [redacted]

A count of ≥ 30 eos/hpf in at least 3 hpfs will be considered diagnostic of EGE.

- All subsequent biopsies should be obtained from the same levels as the screening biopsies (ie, stomach and duodenum) maintaining consistency throughout the study.
- Biopsy samples must be obtained ideally from the areas with the most prominent visible abnormalities. For example, if 2-bite biopsies are being obtained, a minimum total of 26 biopsy fragments (from 2 separate 2-bite biopsies) would be obtained from each level.
- The screening EGD must be performed within 8 weeks prior to Day 1. The investigator must document all treatments received at the time of the EGD and biopsy (for any indication) through Day 1, and the subject must not have received any new treatment that might affect EGE since the time of EGD according to protocol requirements (see Section 8). Subjects should not undergo the screening EGD during the 14-day period just prior to baseline when the final 2 weeks of the screening the Izumo Scale is collected.
- Histologic analysis of the gastric/duodenal biopsy samples for any study-specific assessments will be performed by a central laboratory including enumeration of eos count (peak eos count/hpf) and by analysis of Hematoxylin and eosin (H&E) stained biopsies and gastric biopsies will be graded using the Sydney System on inflammation, metaplasia, atrophy, and reactive gastropathy. The Marsh Scale Classification will be used to grade duodenal samples.
- Histologic analysis includes confirmation of absence of *H. pylori* for gastric biopsies. A highly sensitive monoclonal immunohistochemical stain will be used. If negative, then the subject can participate in the study.

[redacted]

6.4.2 Clinical Symptoms of EGE

6.4.2.1 Izumo Scale Questionnaire

An electronic version of the PRO questionnaire (APPENDIX B) will be completed weekly by the subject throughout the study. The Izumo Scale questionnaire assesses the comprehensive 5 different GI symptom domains during the past week and consists with 15 weekly questions (3 questions per 1 domain):

- Heartburn Symptoms domain (Questions 1 through 3)
- Gastric Pain Symptoms domain (Questions 4 through 6)
- Stomach Heaviness Symptoms domain (Questions 7 through 9)
- Constipation Symptoms domain (Question 10 through 12)
- Diarrhea Symptoms domain (Questions 13 through 15)

Each question is scored on a scale of "0 = No trouble at all" to "5 = Can't stand it," and one symptom domain is scored from 0 to 15, with higher values indicating greater symptom severity. Total score is the sum of 5 domains and ranges from 0 to 75.

Three of these 5 domains (Gastric Pain Symptoms domain [Questions 4 through 6], Stomach Heaviness Symptoms domain [Questions 7 through 9] and Diarrhea Symptoms domain [Questions 13 through 15]) are Symptoms of Interest for EGE.

The Izumo Scale Questionnaire was developed in order to evaluate the overall gastrointestinal symptoms and in Japanese as original language (Furuta, 2009). This is written in easy-to-understand terms in Japanese, and has verified the usefulness by measuring the correlation with Gastrointestinal Symptom Rating Scale (Svedlund, 1988, Dimenäs, 1995) and the Visual analog scale (VAS) of each symptom in Japanese patients with Functional gastrointestinal disorders (FGIDs) whose symptoms are similar to EGE.

On investigation of 170 Japanese patients with gastrointestinal symptoms, the average scores of Symptoms of Interest (Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain) on patients with interference with daily activities were 6.17/15, 5.72/15, and 7.36/15, respectively. On the other hand, the average scores of Symptoms of Interest on patients without interference with daily activities were 1.96/15, 2.37/15, and 2.25/15 (Furuta, 2009). Based on this knowledge, 4/15 for each three domains is set as the threshold for inclusion criteria and clinical responder in this study.

Subjects will complete the Izumo Scale questionnaire weekly during the Screening Period via a handheld device for at least the 2 consecutive weeks before the IP administration on Day 1 (ie, for the final 2 weeks of screening preceding Day 1 that are assessed on Day -7 and Day 1). Every effort should be made to enhance subject adherence to the Izumo Scale Questionnaire completion and limit the amount of missing data, which is critical to ensure interpretability of the Izumo Scale assessment in this study. For example, ePRO instrument's reminder alarms will allow subjects to select the timing for their alarm within a standardized window (at the same time as much as possible) of weekly completion of questionnaire, and ongoing surveillance of weekly completion data will also occur in order to correct any issues as close to real time as possible.

Subjects will not be able to complete a questionnaire more than 3 days before/after it is due and will not be able to go back and make any corrections or changes to the data originally entered. This information will be automatically captured and maintained in the ePRO system of the electronic data capture system (EDC).

The Izumo Scale Questionnaire will be administered at the same time weekly as much as possible via an ePRO instruments from Day 1 through Week 48 (through the duration of the Induction and Maintenance Phases) of the study, through the ET Visit (if applicable), and first year of the OLE Phase and at least for the prior week period (7 days) preceding each of the 2 Safety Follow-up Visits (if applicable) according to the Table of Events (Table 4, Table 5, and Table 6).

6.4.2.2 EGID Severity Score

Japanese Society of Pediatric Allergy and Clinical Immunology published guidelines of "Eosinophilic Gastrointestinal Disease Clinical Practice Guidelines for Infants and Adults" in 2020. EGID Severity Score has been proposed as the severity classification to define the criteria for designated intractable diseases in Japan and is included in this guideline (Eosinophilic Gastrointestinal Disease Study Group, Ministry of Health, Labour and Welfare, 2021).

There are 2 forms of EGID Severity Score; for patients ≥ 20 years old (APPENDIX C) and for patients from 2 to 19 years old (APPENDIX D).

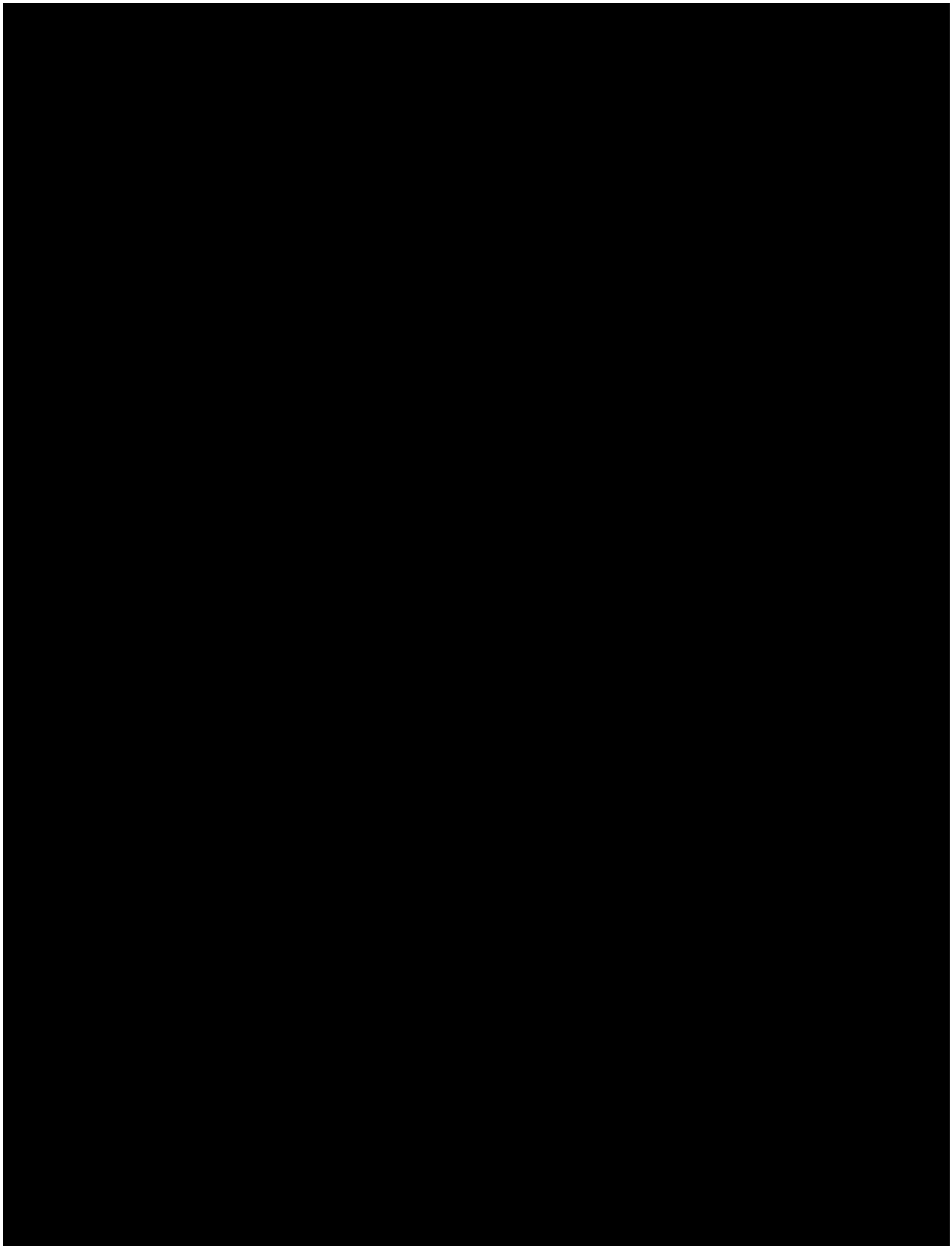
The EGID scoring tables used in this study refer to the ones shown in "Eosinophilic Gastro-Intestinal Disorder" disclosed by Japan Intractable Diseases Information Center.

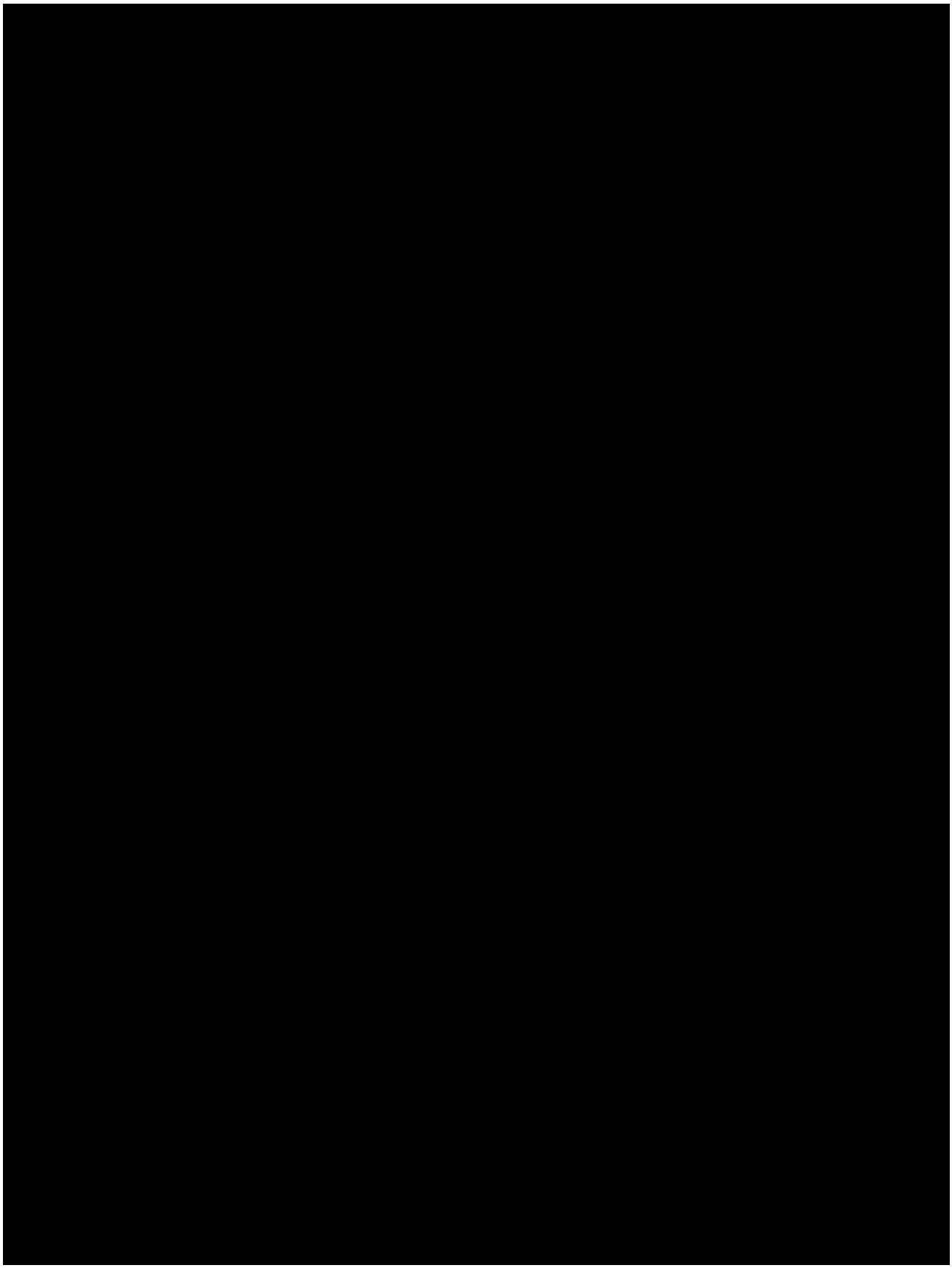
The EGID Severity Scores are assessed by the investigator. The EGID Severity Score for patients ≥ 20 years old assess the intensity and the frequency of 6 different symptoms (vomiting, dysphagia, anorexia, abdominal pain, diarrhea, bloody stool), 2 clinical laboratory tests (albumin, eos ratio of peripheral blood cells) and 2 medical history items (history of surgery and use of systemic corticosteroid or immunosuppressives). The score ranges from 0 to 82 and the higher the score, the greater the severity. A score of ≥ 40 is considered as severe, a score of 15 to 39 as moderate and a score of ≤ 14 score as mild.

The EGID Severity Score for patients from 2 to 19 years old also assesses 6 different symptoms (vomiting, dysphagia, anorexia, abdominal pain, diarrhea, bloody stool), 2 clinical laboratory tests (albumin, eos ratio of peripheral blood cells) and general condition, [redacted]. The score ranges from 0 to 100 and the higher the score, the greater the severity. A score of ≥ 40 is considered as severe, a score of 15 to 39 as moderate and ≤ 14 score as mild.

The EGID Severity Score will be assessed according to the time points detailed in the Table of Events (Table 4, Table 5, and Table 6).

[redacted]





[redacted]

6.4.2.10 Worsening of EGE Symptoms, EGE Flare, and the EGE Flare Assessment Visit

Subjects with a worsening of EGE symptoms during the study, either in the Induction Phase, Maintenance Phase, or the OLE Phase will be required to complete the EGE Flare Assessment Visit as shown in the Table of Events (Table 4, Table 5, and Table 6). Subjects with increased signs and symptoms of EGE are instructed to contact the investigator and/or study staff to determine if an EGE Flare Assessment Visit is warranted.

- Worsening of EGE symptoms is defined as continuous worsening of symptoms for 2 consecutive visits (4 weeks apart) compared to baseline, measured by the weekly Izumo Scale score (≥ 4 weeks of no change from baseline or ≥ 4 weeks of worsening from baseline).

An EGE Flare Assessment Visit including safety and efficacy evaluations can occur at any time during the study. An EGD may be required at the EGE Flare Assessment Visit to determine if use of rescue therapy is clinically indicated. Alternatively, if endoscopy is conducted as an intervention during an emergency department visit or hospitalization for a worsening of EGE symptoms or flare, medical record source data including details of the endoscopic procedure should be collected for the EGE Flare Assessment Visit EGD requirement. In addition, all attempts should be made to collect biopsy samples, and these samples should be sent to the central reader for histologic analysis. The results of the centrally read gastric/duodenal eos count will be blinded to investigative sites with the exception of screening during the Induction Phase and the Maintenance Phase. If the results of the gastric/duodenal eos count are required to determine the need for emergent rescue therapy, the results of the gastric/duodenal eos count will be disclosed as long as the investigator requires the result. If the results of the gastric/duodenal eos count will be disclosed in the Induction Phase, the subject is to be discontinued from the study and will not be allowed to enter either the Maintenance Phase or the OLE Phase. (See Section 3.1.6.)

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

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

- A severe EGE flare is defined as any worsening of EGE symptoms including a high intensity episode resulting in an emergency department visit or hospitalization, with need for rescue therapy (eg, including but not limited to concomitant corticosteroid therapy over the baseline dose), or a worsening of EGE symptoms for 2 consecutive visits (4 weeks apart) resulting in the need for rescue therapy.
- A mild to moderate EGE flare is defined as any worsening of EGE symptoms without the need for rescue therapy. Concomitant use of systemic corticosteroid therapy with or under the baseline dose of concomitant corticosteroid treatment is not considered as rescue therapy.

During the OLE Phase, subjects who demonstrate a persistent lack of improvement or worsening of EGE 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.

The ET visit or the OLE-ET/EoT procedures performed at the EGE Flare Assessment Visit do not need to be repeated for subjects who discontinue the study prematurely due to an EGE flare.

Subjects who are discontinued from the Induction Phase, the Maintenance Phase or the OLE Phase will be asked to complete an ET visit or an OLE-ET/EoT Visit (Section 6.2.2 and Section 6.3.2.2) and the 2 Safety Follow-up Visits (Section 6.3.1).

6.4.2.11 Entry to Maintenance Phase

Following completion of Week 16 of the Induction Phase, subjects will be eligible for entry into the Maintenance Phase if none of the conditions listed below are met, and based on investigator clinical judgement, it is in the best interest of the subject to continue study participation. Subjects who do not qualify for entry to the Maintenance Phase will be eligible for participation in the OLE Phase, unless permanent discontinuation from IP has occurred. The following are conditions that will exclude subjects from entry to the Maintenance Phase:

- Subjects with a severe EGE flare as described in Section 6.4.2.10
- Subjects who demonstrate a worsening of EGE symptoms prior to Week 16 (continuous worsening of symptoms for 2 consecutive visits [4 weeks apart]) at Week 16, as described in Section 6.4.2.10
- Subjects who demonstrate any other significant findings that, in the opinion of the investigator, could potentially disqualify a subject from entering the Maintenance Phase must be assessed in conjunction with the Medical Monitor to determine, if the subject is eligible for participation in the OLE Phase, when a subject wants or the investigator considers it appropriate
- Subjects who are permanently discontinued from IP during the Induction Phase (before or at Week 16), and these subjects will not be eligible for participation in the OLE Phase (see Section 11.1)
- In addition, for subjects who meet the following condition during the first 16 weeks of treatment (and without a severe EGE flare), a discussion with the Medical Monitor will be required before entry into the Maintenance Phase:
  - Subjects with any protocol-prohibited use of or change to diet (eg, steroids over baseline dose, food elimination) or medication which will impact efficacy assessment for CC-93538 (as determined through consultation with the Medical Monitor) will be excluded from entry to the Maintenance Phase

By contrast, subjects requiring concomitant systemic corticosteroids for an indication other than EGE may be eligible for entry to the Maintenance Phase if the duration of therapy is no more than 10 days and use does not occur within the 6 weeks preceding Induction Phase Week 16.

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

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

6.4.2.12 Entry to Open-label Long-term Extension

Following completion of Week 48 of the Maintenance Phase, subjects will be eligible for entry into the OLE Phase based on investigator clinical judgement, that it is in the best interest of the subject to continue study participation. Subjects who do not qualify for entry to the OLE Phase will return to complete the 2 Safety Follow up Visits.

As described in Section 3.1.6. a subject may be eligible for entry to the OLE Phase at Induction Phase Week 16 and during the Maintenance Phase.

6.5 Anti-drug Antibody Assessments

Serum samples to assess blood levels of antibodies to CC-93538 will be obtained pre-dose (except for the ET visit or the OLE-ET/EoT Visit and 2 Safety Follow-up Visits, if applicable) at the time points outlined in the Table of Events (Table 4, Table 5, and Table 6).

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

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

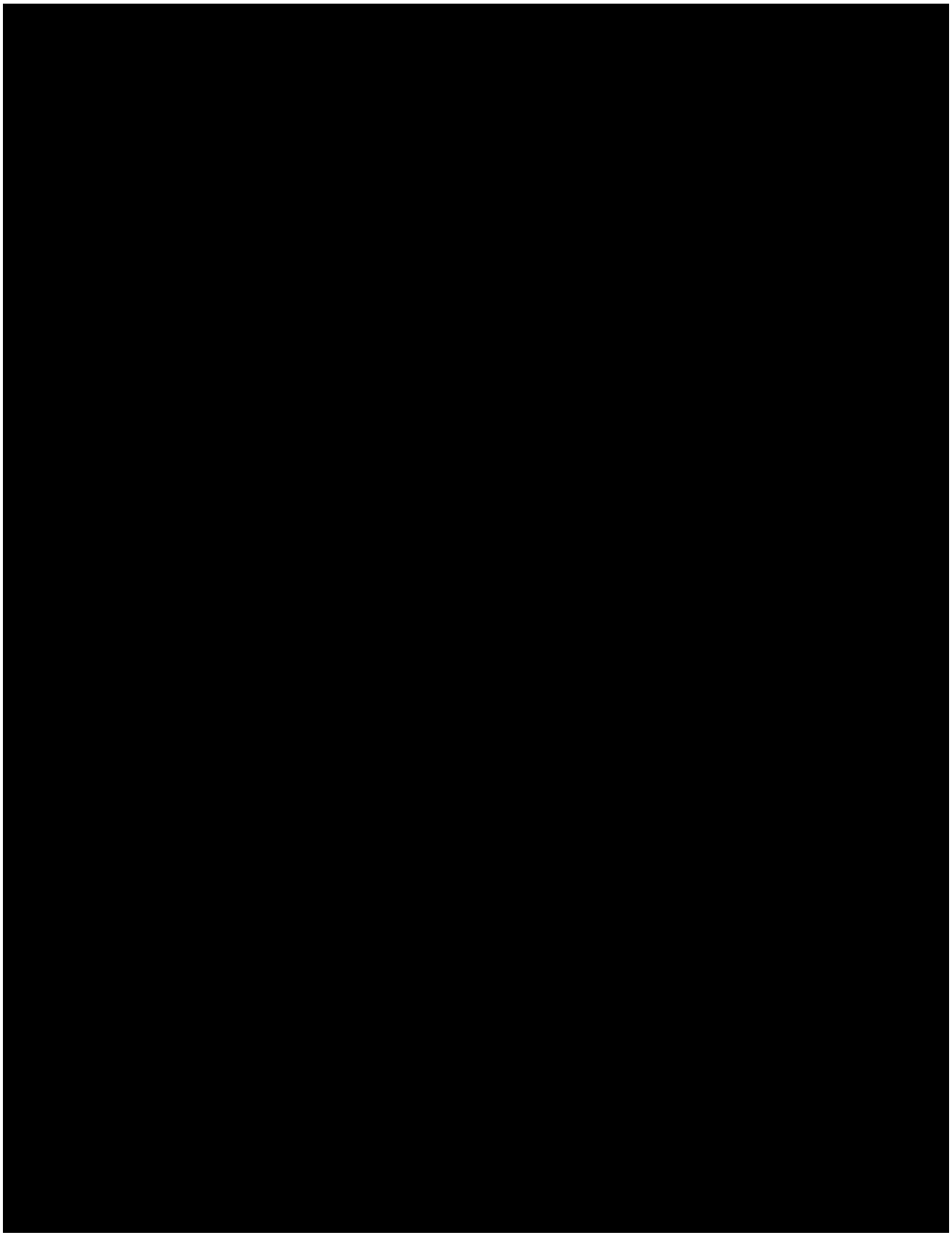
Further analysis on samples that are positive for ADA may be performed, including assessment of neutralizing antibodies when warranted. Samples will be stored for up to 5 years after study completion.

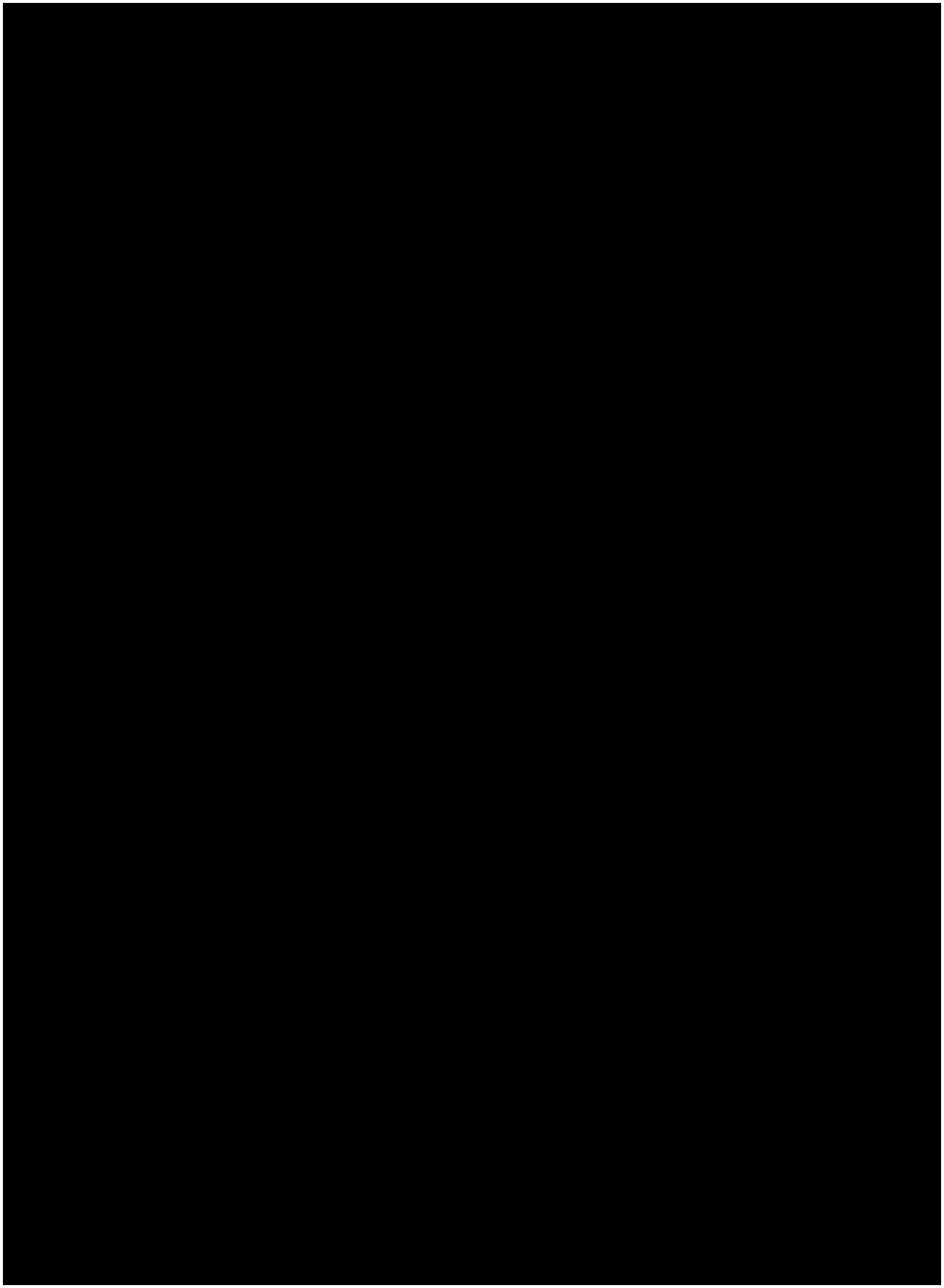
6.6 Pharmacokinetics

6.6.1 Serum CC-93538 Assessments

Serum samples to assess CC-93538 concentrations will be obtained pre-dose (except for the ET Visit and 2 Safety Follow-up Visits, if applicable) at the time points described in the Table of Events (Table 4, Table 5, and Table 6). 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 [redacted]

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





7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Product(s)

The active ingredient of CC-93538 is a recombinant humanized Immunoglobulin G1 (IgG1) monoclonal antibody directed against human IL-13. Investigational products (CC-93538 and placebo solutions for injection) are to be stored at 2°C to 8°C. The IP should not be frozen. The labeling will be in accordance with GCP and any other local regulatory requirements. During the study, IP will be dispensed in pre-filled syringes (PFS) or an [redacted] presentation provided by the Sponsor.

The 360 mg dose of CC-93538 (or placebo) will be administered by 2 injections of 1.2 mL each at a concentration of 150 mg/mL CC-93538 (PFS) during the Induction Phase and the Maintenance Phase.

During the OLE Phase, the 360 mg dose of CC-93538 will be administered by 2 injections of 1.2 mL each at a concentration of 150 mg/mL CC-93538 (PFS) or by 1 injection of 2.0 mL at a concentration of 180 mg/mL CC-93538 (PFS or [redacted]

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

Investigational Product in Pre-filled Syringes

A PFS presentation containing drug product at a concentration of 150 mg/mL CC-93538 (or placebo) in a 1.2 mL or at a concentration of 180 mg/mL CC-93538 in a 2.0 mL fill will be utilized in the study. CC-93538 solution for injection (or placebo) will be provided as a sterile liquid in PFS at a concentration of 150 mg/mL (or placebo) packaged in cartons (2 PFS per carton) or at a concentration of 180 mg/mL packaged in cartons (1 PFS per carton). CC-93538 and placebo solutions differ slightly in physical appearance and when presented in vials, the slight color difference in IP cannot be fully blinded. Therefore, for the PFS, a label cover on the active and placebo syringes (to be applied during packaging/labeling) will be used to maintain the blind. As the PFS packaging will sufficiently blind the syringe contents, an unblinded pharmacist will not be required to dispense IP in the PFS. At home self-administration (as outlined in Section 7.2 and Section 7.2.6) or administration of IP through a home health nurse (as outlined in Section 7.2 and Section 7.2.6) will be available IP administration options with the PFS.

Investigational Product in [redacted]

An [redacted] presentation containing CC-93538 drug product at a concentration of 180 mg/mL in a 2 mL fill (for a total of 360 mg/2 mL) will be also utilized in the OLE Phase. The CC-93538 360 mg in an [redacted] 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 [redacted] device. No additional drug preparation is required prior to administration. CC-93538 solution for injection will be provided as a sterile liquid in an [redacted] at a concentration of 180 mg/mL packaged in cartons (1 [redacted] per carton). At home self-administration (as outlined in Section 7.2.6) or administration of IP through a home health nurse (as outlined in Section 7.2) will be available IP administration options with the [redacted]

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

Note: The terms "investigational product" in this protocol will automatically be replaced with "post-marketing clinical study drug" on and after the date of marketing approval in Japan.

7.2 Treatment Administration and Schedule

7.2.1 Induction Phase

Subjects will be randomized 2:1 to the following treatment arms:

- CC-93538 360 mg SC once weekly for 16 weeks
- Matching placebo SC once weekly for 16 weeks

For the Induction Phase, subjects assigned to the CC-93538 360 mg SC arm will be administered two 1.2 mL CC-93538 SC injections once weekly for 16 weeks (1.2 mL x 2 = 2.4 mL at 150 mg/mL CC-93538 = 360 mg CC-93538/week). Subjects assigned to the placebo arm will receive matching placebo SC doses.

7.2.2 Maintenance Phase

Subjects who are randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized 1:1 to the following treatment arms:

- CC-93538 360 mg SC once weekly for 32 weeks
- CC-93538 360 mg SC once every other week for 32 weeks. During the Maintenance Phase, matching placebo will be administered once every other week on alternate weeks to maintain the blind.

Subjects who are randomized to receive matching placebo in the Induction Phase will continue the following treatment arm:

- Matching placebo SC once weekly for 32 weeks

For the Maintenance Phase, subjects assigned to one of the CC-93538 360 mg arms will be administered two 1.2 mL CC-93538 SC injections once weekly for 32 weeks or once every other week for 32 weeks. Subjects assigned to the CC-93538 360 mg SC once every other week arm will receive a matching placebo SC dose every other week to maintain blinding. Subjects assigned to the placebo arm will receive matching placebo SC doses.

7.2.3 OLE Phase

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

For the OLE Phase, all subjects will receive CC-93538 360 mg SC once weekly during the OLE Phase. The dosing regimen for the OLE may be revised, via an amendment to the protocol, after results from the core Induction Phase and Maintenance Phase are available and the most effective and safest dosing regimen is confirmed.

IP in PFS administration

On OLE Day 1, eligible subjects will be administered CC-93538 (360 mg) as two 1.2 mL CC-93538 SC injections (150 mg/mL). Alternatively, eligible subjects may receive CC-93538 (360 mg) as one 2 mL CC-93538 SC injection (180mg/mL).

IP in [redacted] administration

All subjects currently in the study and any new subjects entering the study will start receiving a single injection of the 360 mg/2 mL [redacted] once the fifth amendment to the protocol (Protocol Amendment 5) 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 [redacted] presentation, a switch to the new [redacted] presentation will occur at the next regularly scheduled study visit. [redacted]

In the event the IP ([redacted] is not available on-site at the time of Protocol Amendment 5 site approval, subjects should continue receiving the single 2.0 mL injection (180 mg/mL) using PFS presentation until the IP ([redacted] is available.

7.2.4 Post Injection Observation

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

As the OLE will include subjects previously treated with placebo, to ensure safety, and to preserve the maintenance of the blind from the Induction Phase and the Maintenance Phase, the first 3 weekly SC doses will be required to be administered in the clinic for all subjects entering the OLE Phase. 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.

Once the new 360 mg/2.0 mL PFS presentation is introduced into the OLE Phase via the fourth amendment to the protocol (Protocol Amendment 4), to ensure accurate dose administration and compliance with 2 mL weekly SC injection using the 360 mg/2 mL PFS presentation, for subjects who did not begin the study with the 360 mg/2.0 mL PFS presentation at one of the first 3 weekly SC doses in the OLE Phase (ie, OLE Day 1, Week 1, or Week 2), one additional in-clinic weekly dose with at least a 30-minute observation is required for the first administration; the first dose with the new presentation will be administrated during an in-clinic visit.

Once the new 360 mg/2 mL [redacted] presentation is introduced into the OLE Phase via the fifth amendment to the protocol (Protocol Amendment 5), to ensure accurate dose administration and compliance with the new single 2 mL weekly SC injection using the 360 mg/2 mL [redacted] 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 [redacted] Administration Visit as described in Table 6. [redacted]

7.2.5 Instructions for IP Administration

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 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).

7.2.6 Self-Administration

Self-administration (defined as either by subject or by a caregiver, applicable per local regulations) will be an option for dose administration of IP by the PFS/[redacted] presentation. Subjects will be provided with an Instructions for Use document outlining steps for proper dose administration.

Self-administration will be dependent on the subject's (or caregiver's) ability to perform it and is independent of the subject's age. 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 2-injection regimen no matter how well the subject may feel during the study. Subjects who plan to self-administer IP will be required to perform at least the first 3 weekly injections using the PFS presentation 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 additional 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 monthly scheduled study visits. To help promote consistency within the data, it is preferred that subjects do not switch their injection method during the study, unless there is a reasonable rationale for doing so (eg, change in injection proficiency, treatment compliance issue, etc) 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 health nurse (where locally feasible) to administer the IP to the subject.

Note: Self-administration should be performed by the subject him/herself in principle. Only if it is difficult for self-administration by the subject him/herself or by healthcare professionals at visits, self-administration by the subject's family is allowed.

7.2.7 Missed Dose(s)

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

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

See Section 7.2.9 for temporary interruption of dosing, and Section 7.2.10 for criteria for discontinuation of dosing.

7.2.8 Dose Adjustments

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

7.2.9 Guidelines for Temporary Interruption of Dosing

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

- Severe laboratory abnormalities in which a causal relationship to IP is not suspected of being related (ie, a causal relationship is unlikely or remote, or another medication, therapeutic intervention or underlying condition provides a sufficient explanation)
- An infection requiring parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal medications; for an infection requiring oral treatment with these medications for longer than 2 weeks, the investigator should determine if an interruption of dosing is in the best interest of the subject
- Any AE, intercurrent medical condition, or major surgery that could present an unreasonable risk to the subject due to continued study participation, as determined by the investigator
- For subjects who develop suspected or confirmed symptomatic COVID-19 infection, or it is discovered that subjects have asymptomatic COVID-19 infection during the Treatment Period (Induction Phase, the Maintenance Phase, and the OLE Phase). Investigational product should be temporary interrupted until the following conditions are met:
  - For symptomatic subjects:
    - At least 10 days (20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
    - At least 24 hours have passed since last fever without the use of fever-reducing medications, and
    - Symptoms (eg, cough and shortness of breath) have resolved and

- In the opinion of the investigator, there are no COVID-19 sequelae that may place the subject at a higher risk of receiving investigational treatment, and,
- Negative follow-up molecular test for COVID-19 based on most current institutional, local, or regional COVID-19 guidelines and/or requirements.

– For asymptomatic subjects:

- At least 7 days have passed since positive test result (based on date of collection, not date of test result availability), and,
- Negative follow-up molecular test for COVID-19 based on most current institutional, local, or regional COVID-19 guidelines and/or requirements.

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

7.2.10 Criteria for Discontinuation of Dosing

Dosing will be permanently discontinued (treatment discontinuation) for a subject if the subject experiences any of the events listed in Section 11.1 following initiation of IP. These subjects will be encouraged to remain in the study and complete all required study assessments in the phase of the study that permanent discontinuation of IP occurs with the exception of IP dosing, and will not be allowed to participate in the OLE Phase, if the subject participates in the Induction Phase and the Maintenance Phase. In order to prevent missing data, the site staff will ensure attempts are made to reach subjects by telephone or email that do not maintain contact with the investigator. Any subject discontinuing the study prematurely will be asked to complete the ET visit or the OLE-ET/EoT Visit and the Interim and the Final Safety Follow-up Visits.

7.2.11 Rescue Therapy

Subjects with a worsening of EGE symptoms requiring rescue therapy (defined as a severe EGE flare; refer to Section 6.4.2.10) during the Induction Phase may continue to participate in the phase of the study in which the EGE flare occurs. If the results of the gastric/duodenal eos count were required to determine rescue therapy during the Induction Phase, the subject will be withdrawn from the study. Subjects with a worsening of EGE symptoms requiring rescue therapy during the Maintenance Phase may enter the OLE Phase. Rescue therapy includes EGE standard of care pharmacotherapy (eg, including but not limited to concomitant corticosteroid therapy over the baseline dose) and/or dietary modification (eg, food elimination diet).

Concomitant use of systemic corticosteroid therapy with or under the baseline dose of concomitant corticosteroid treatment is not considered as rescue therapy.

7.3 Method of Treatment Assignment

7.3.1 The Induction Phase and the Maintenance Phase

Subjects enrolled in the Induction Phase will be centrally randomized on Day 1 after all screening and baseline assessments have been completed and the investigator has verified that the subject is eligible per the inclusion (Section 4.2) and exclusion criteria (Section 4.3). Subjects will be randomized 2:1 to receive active CC-93538 treatment (360 mg SC weekly for 16 weeks) or matching placebo for 16 weeks. Treatment assignment at baseline will be stratified by (with/without) concomitant use of corticosteroid treatment at baseline (up to 10 mg/day as the equivalent of prednisone) to ensure an equal balance in the treatment arms. Randomization will be performed through the Interactive Web Response System (IWRS) system.

Subjects enrolled in the Maintenance Phase will be centrally re-randomized on Week 16 (the completion of Induction Phase). Subjects who randomized to receive CC-93538 360 mg SC once weekly in the Induction Phase will be re-randomized 1:1 to receive active CC-93538 treatment (360 mg SC once weekly or 360 mg SC once every other week), and subjects who randomized to receive matching placebo in the Induction Phase will continue placebo. Re-randomization will also be performed through the IWRS system.

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

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

7.3.2 The OLE Phase

After all OLE baseline assessments have been completed, 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 Phase.

7.4 Packaging and Labeling

7.4.1 The Induction Phase and the Maintenance Phase

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

7.4.2 The OLE Phase

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

The investigator will provide IP only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, the Study Monitor will ensure that all unused IP and all medication containers, as applicable, can be destroyed on-site as long as proper documentation is supplied. If destruction on-site is not possible then any unused medication and containers, as applicable, will be returned to the Sponsor or designee. The Study Monitor will perform final accountability, package, seal and prepare for shipment. The contract research organization 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

There are specific requirements for cessation of medication use prior to enrollment, as stated in the exclusion criteria (Section 4.3). All treatments (including prescription and over the counter medications, herbal and dietary supplements, dietary modifications, vaccines, and procedures) used by subjects within the 4 weeks (28 days) prior to the first Screening Visit or at any time during the study in addition to the IP are regarded as prior or concomitant treatments and must be documented on the appropriate section of the eCRF. In addition, a history of previous treatments for EGE will be documented. The investigator must document all treatments received at the time of the EGD (for any indication) through Day 1.

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

8.1 Permitted Concomitant Medications and Procedures

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

- Subjects must have maintained a stable diet for at least 4 weeks prior to the first Screening Visit and must agree to maintain a stable diet throughout the Induction Phase and the Maintenance Phase. Subjects on a food elimination diet for the treatment of food allergy or EGE should maintain it without making any changes through the end of the study and should have maintained this diet for at least 4 weeks prior to the first Screening Visit. Subjects must agree to not introduce any changes in their diet while participating in the Induction Phase and the Maintenance Phase. However, following IP administration, subjects experiencing a severe EGE flare requiring a dietary modification for rescue therapy may be eligible to continue in the study according to protocol requirements. See Section 6.4.2.10.
- Subjects may use systemic corticosteroids up to 10 mg/day of prednisone for EGE as a concomitant corticosteroid treatment. Stable doses/regimens must have been maintained for at least 4 weeks prior to the first Screening Visit and regimens will remain stable until Week 16 (completion of the Induction Phase). If the reduction of EGE-related symptoms is observed after Week 16 (in the Maintenance Phase and the OLE Phase), the investigator should begin tapering dosage regimen of concomitant corticosteroid treatment after Week 16. The dose reduction should be 2.5 mg/week (as the equivalent of prednisone).
- Subjects may use inhaled corticosteroids, proton pump inhibitors (PPIs), leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) for indications other than EGE if on stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens will remain stable throughout the Induction Phase and the Maintenance Phase. If one of these medications was recently discontinued, it must have been discontinued at least 4 weeks prior to the first Screening Visit.
- Subjects may use medium potency topical corticosteroids (eg, mometasone furoate cream or lotion) for dermatologic conditions if on stable doses/regimens for at least 4 weeks prior to the first Screening Visit and regimens will remain stable throughout the Induction Phase and the Maintenance Phase. If the medication was recently discontinued, it must have been discontinued at least 4 weeks prior to the first Screening Visit.

- Subjects may use intranasal corticosteroids, antihistamines, or other medications for seasonal allergies or other conditions as needed.
- Subjects may use low potency topical corticosteroids for dermatological conditions as needed.
- Subjects receiving PPIs, leukotriene receptor antagonists (eg, montelukast), or mast cell stabilizers (eg, cromolyn sodium) medication for the indication of EGE at the first Screening Visit may participate if these medications has been maintained at a stable dose from at least 4 weeks prior to the first Screening Visit through the Induction Phase and the Maintenance Phase. Subjects who discontinued these medications must not have received these medications for at least 4 weeks before the First Screening Visit and must agree not to restart these medications during the study. However, following IP administration, subjects experiencing a severe EGE flare requiring the addition of these medications or modification to these medication regimens for rescue therapy may be eligible to continue in the study according to protocol requirements. See Section 6.4.2.10.
- Subjects receiving SC immunotherapy must have been on stable doses for at least 3 months prior to the first Screening Visit and for the Induction Phase and the Maintenance Phase.
- 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 when feasible, and when a delay in enrollment would not put the study participant at risk. Ideally, adverse events attributable to a vaccine should have resolved prior to enrollment.

Refer to Table 7 for a summary of the timing for stable dosing regimen requirements for certain medications and requirement for a stable diet.

8.1.1 Rescue Therapy

During the study, subjects with a worsening of EGE symptoms requiring rescue therapy (defined as a severe EGE flare; refer to Section 6.4.2.10) may be eligible to continue to participate in the study according to protocol requirements. Rescue therapy includes EGE standard of care pharmacotherapy (including but not limited to systemic corticosteroid therapy over the baseline dose) and/or dietary modification (eg, food elimination diet). Note that as part of study eligibility criteria and as described below in Section 8.2, in general, use of these treatment modalities is prohibited unless documented as required therapy for an EGE flare following IP administration.

Concomitant used of systemic corticosteroid therapy with or under the baseline dose (up to 10 mg/day of prednisone) is not considered as rescue therapy.

8.2 Prohibited Concomitant Medications and Procedures

Concomitant medications and procedures that are prohibited for a specific time period prior to the first Screening Visit and throughout the duration of the study include the following (the timeframe before the first Screening Visit is specified below); however, exceptions will occur in the event of a severe EGE flare requiring rescue therapy and in such cases, subjects may continue participation with concomitant rescue therapy (eg, systemic corticosteroids over 10 mg/day as prednisone). In such cases, a subject may be eligible to participate in the OLE Phase (Section 3.1.6):

- Subjects may not use systemic immunosuppressive or immunomodulating drugs (including but not limited to, [redacted] α4β7 integrin inhibitor antibodies, or any other monoclonal antibodies, methotrexate, cyclosporine, azathioprine, mercaptopurine, IFNα, TNFα inhibitors, etc) for at least 5 drug half-lives prior to the first Screening Visit and during the study (including the OLE Phase). Use of any of the aforementioned medications during study participation will result in the subject's permanent discontinuation from IP; exceptions are if corticosteroids are used as rescue therapy for an EGE flare (see Section 8.1.1) or if required for treatment of an AE upon discussion with the Medical Monitor.
- Subjects may not use systemic corticosteroid medication exceeding the baseline dose as background treatment (up to 10 mg/day of prednisone) from the first Screening Visit through the Induction Phase and the Maintenance Phase. Subjects who have received corticosteroid therapy for EGE or another indication must have decreased the dose under 10 mg/day of prednisone and kept the systemic corticosteroid dose at that level within 4 weeks of the first Screening Visit. However, if a subject experiences a severe EGE flare during study participation following IP administration, the subject may continue participating in the Induction Phase and the Maintenance Phase with concomitant corticosteroid rescue therapy according to protocol pre-specified criteria (see Section 6.4.2.10).
- Subjects may not use high potency topical corticosteroids (eg, augmented betamethasone dipropionate, clobetasol propionate, etc) for dermatologic conditions within 8 weeks prior to the first Screening Visit through the Induction Phase and the Maintenance Phase.
- If subjects have not received PPIs, leukotriene receptor antagonists (eg, montelukast) or mast cell stabilizers (eg, cromolyn sodium) for the indication of EGE prior to the first Screening Visit, the subjects may not initiate these medications for the indication of EGE after 4 weeks prior to the first Screening Visit through the Induction Phase and the Maintenance Phase.
- Subjects may not receive oral or sublingual immunotherapy (treatment to desensitize to an allergen) within 6 months prior to the first Screening Visit through the end of the study (including the OLE Phase).
- Subjects may not receive live (including attenuated) vaccines within 1 month prior to the first Screening Visit through the end of the study (including the OLE Phase).
- 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 and through the end of the OLE study. For subjects who received an investigational COVID-19 vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the investigator and the Clinical Trial Physician.

Refer to Table 7 for a summary of the timing of restrictions on medication use as well as for certain procedures or dietary modifications required prior to study enrollment.

Table 7: Medications, Diets, or Procedures Requiring Stable Dosing Regimens or Restricted Use Prior to Study Enrollment

Medication, Diet or Procedure	**Restriction Timeframe**		
Medication (or procedure)	**Subjects must not have received the following medication within the timeframe below before the first Screening Visit**	**Induction/Maintenance Phase**	**Open-label Long-term Extension (OLE) Phase**
Systemic immunosuppressive or immunomodulating drugs	5 half-lives	Prohibited	Prohibited
Systemic corticosteroids exceeding the baseline dose (up to 10 mg/day of prednisone)	4 weeks	Prohibited	No restriction
High potency topical corticosteroids	8 weeks	Prohibited	No restriction
Initiation of proton pump inhibitors (PPIs), leukotriene receptor antagonists or mast cell stabilizers (for the indication of eosinophilic gastroenteritis [EGE])	4 weeks	Prohibited	No restriction
Oral or sublingual immunotherapy	6 months	Prohibited	Prohibited
Live (including attenuated) vaccines	1 month	Prohibited	Prohibited
Any other investigational product [a]	5 half-lives	Prohibited	Prohibited
Medication (or diet)	**Subjects must be on stable dosing regimens within the timeframe below before the first Screening Visit**	**Induction/Maintenance Phase**	**OLE Phase**
Diet (eg, food elimination diet)	4 weeks	Stable	No restriction
Systemic corticosteroid therapy with or under the baseline dose (up to 10 mg/day of prednisone)	4 weeks	Stable/Induction Phase Can be tapered or increased to the baseline dose /Maintenance Phase	No restriction, tapering is recommended
Inhaled corticosteroids, proton pump inhibitors (PPIs), leukotriene receptor antagonists, or mast cell stabilizers (for indications other than EGE)	4 weeks	Stable	No restriction
PPIs, leukotriene receptor antagonists, or mast cell stabilizers (for indications of EGE)	4 weeks	Stable	No restriction

Table 7: Medications, Diets, or Procedures Requiring Stable Dosing Regimens or Restricted Use Prior to Study Enrollment

Medication, Diet or Procedure	Restriction Timeframe		
Medication (or procedure)	**Subjects must not have received the following medication within the timeframe below before the first Screening Visit**	**Induction/Maintenance Phase**	**Open-label Long-term Extension (OLE) Phase**
Medium potency topical corticosteroids for dermatologic conditions	4 weeks	Stable	No restriction
Subcutaneous immunotherapy	3 months	Stable	No restriction

[a] For subjects who received an investigational Coronavirus disease 2019 (COVID-19) vaccine as part of a clinical trial prior to the first Screening Visit, enrollment must be delayed until the biologic impact of the vaccine is stabilized, as determined by discussion between the investigator and the Clinical Trial Physician.

8.3 Required Concomitant Medications and Procedures

See inclusion criteria and exclusion criteria (Section 4.2 and Section 4.3) for a description of corticosteroid treatment requirements and PPIs, leukotriene receptor antagonists, or mast cell stabilizer medication requirements and for study eligibility. See Section 6.1 for Screening EGD requirements.

9 STATISTICAL CONSIDERATIONS

9.1 Overview

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled induction and maintenance study to assess the efficacy and safety of CC-93538 in adult and adolescent subjects with EGE. The study will incorporate a 16-week Induction Phase followed by a 32-week Maintenance Phase and an OLE Phase. Subjects will be randomized according to the following stratification factor: concomitant steroid use (yes or no). An independent DMC will be used to review the safety data regularly during the course of the study.

A primary database lock will be performed when all randomized subjects in this study have completed Week 48 of the Maintenance Phase or discontinued the study, including all Safety Follow-up Period data available to date. Analyses in the primary clinical study report (CSR) will be based on this database.

Analysis details not explained in the statistical section of the protocol will be provided in the Statistical Analysis Plan (SAP).

9.2 Study Population Definitions

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

Intent-to-treat (ITT) Population

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

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

Safety Population

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

9.3 Sample Size and Power Considerations

The sample size is based on two-sample t-test for the primary endpoint, changes in mean number of peak eos per hpf in GI biopsies from baseline to Week 16. The null hypothesis and the alternative hypothesis for the primary endpoint are as follows;

- Changes in mean number of peak eos from baseline at Week 16

  Null hypothesis H_0: $\mu_{CC\text{-}93538} = \mu_{Placebo}$

  Alternative hypothesis H_a: $\mu_{CC\text{-}93538} \neq \mu_{Placebo,}$

where $\mu_{CC\text{-}93538}$ represents the true mean change value relative to CC-93538 and $\mu_{Placebo}$ represents true mean change value relative to placebo.

Using this hypothesis, if the expected mean change in eos count in the active treatment group was -70, the expected mean change in eos count in the placebo group was 0, and the standard deviation (SD) was 70, the sample size necessary to achieve at least 80% power in a t-test at a significance level of 0.05 was calculated. Using a 2:1 ratio of active to placebo, 39 subjects are required. Assuming a Week 16 drop-out rate of approximately 10%, the goal is to enroll a total of 45 subjects.

The expected change from baseline in eos count in the active treatment group is based on the Phase 2 EoE study (Study RPC02-201); mean value at baseline for the CC-93538 360 mg treatment group of 139.4, and mean value at Week 16 of 31.3, with a percent change of approximately 80%. The baseline value in patients with EGE was assumed to be approximately 90 based on the results of studies of other drugs in patients with EGE (Dellon, 2020). Therefore, the expected change from baseline in eos in the active treatment group is assumed to be approximately 70. Change from baseline in eos count in the placebo group was assumed to be 0 based on the results of studies of other drugs (Dellon, 2020). With reference to the baseline GI eos count results of other drug studies of 52 (Dellon, 2020), the results of Study RPC02-201 in the CC-93538 360 mg group of 90, and the results of Study RPC02-201 in the CC-93538 180 mg group of 71, SD was assumed to be 70, which is approximately the mean of those values.

9.4 Background and Demographic Characteristics

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

9.5 Subject Disposition

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

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

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

9.6 Efficacy Analysis

9.6.1 Efficacy Analysis of the Primary Endpoint

9.6.1.1 Intercurrent Event and Analysis Strategies

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

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

For intercurrent event (ICE) number 1, all observed data will be included in the primary analysis regardless of the occurrence of the ICE according to the respective endpoint definition. For ICE numbers 2 and 3, all observed data will be included in the primary analysis.

9.6.1.2 Changes in Mean Number of Peak eos Count from Baseline to Week 16 (Induction Phase)

The primary analysis will be conducted on the ITT population based on an analysis of covariance (ANCOVA) model with treatment group, concomitant steroid use (yes or no), and baseline eos count included in the model. The comparison between CC-93538 360 mg SC once weekly and placebo for change in number of peak eos count from baseline at Week 16 will be made using the difference in least squares mean (LSM) at a 5% 2-sided significance level. Point estimates for the mean difference between the two treatment groups using the LS mean changes and corresponding 95% Wald CI will be reported. In addition, LSMs (standard error [SE]), arithmetic means (SD), and arithmetic mean changes (SD) will be summarized by treatment group.

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

Sensitivity analyses will be performed to support the primary analysis and provide additional insights to understand the treatment effect. For the primary estimand analysis, robustness due to missing data MI under MAR assumption will be explored using tipping point analysis (Yan, 2009; Campbell, 2011; Yuan, 2014). In considering the ICEs of study interest (ie, ICE number 2, use of rescue therapy/prohibited medication, and ICE number 3, treatment discontinuation followed by use of rescue therapy/prohibited medication), an analysis using the hypothetical estimand strategy for change in eos count at Week 16 will be conducted.

9.6.2 Subgroup Analyses

To assess whether the treatment effect is consistent across various groups, subgroup analyses will be performed for the primary endpoint at Week 16. Treatment differences and 2-sided 95% CIs

will be provided for each subgroup listed below. Forest plots for the treatment differences by subgroup will also be provided.

1. Concomitant steroid use (yes versus no)
2. Prior history of corticosteroid use for the treatment of EGE (yes versus no)
3. Age group (adolescents [12 to 17 years] versus adults [≥ 18 years], non-elderly adults [< 65 years] versus elderly adults [≥ 65 years]).
   For EGID Severity Score, adolescents is set as 12 to 19 years
4. Sex (female versus male)

If there are not enough subjects within a subgroup enabling a valid statistical inference, the corresponding subgroup analyses will not be performed, and summary statistics will be provided instead.

9.6.3 Analysis of Secondary Efficacy Endpoints

9.6.3.1 Analyses Methods

Continuous variables:

- Changes in mean number of peak eos count per hpf from baseline to Week 48
- Changes from baseline in each of 5 domain scores of the Izumo Scale (Weeks 14, 16, 32, and 48)
- Changes from baseline in total score of EGID Severity Score (Weeks 16, 32, and 48)
- Percent changes in mean number of peak eos per hpf in GI biopsies from baseline (Weeks 16 and 48)
- The time until concomitant corticosteroid treatment to zero (and continued by Week 48) (from Week 16 through Week 48)

The analysis for continuous variables of the secondary endpoints will be conducted on the ITT population using the ANCOVA model with treatment group (CC-93538 360 mg SC once weekly, CC-93538 360 mg SC once every other week, and placebo), prior steroid use (yes or no), and baseline values included in the model. Point estimates for the mean difference between the treatment groups using the LS mean changes and corresponding 95% Wald CI will be reported. The transition from the Maintenance Phase to the OLE Phase will be treated as ICE. Missing data and ICEs will be handled via the same strategy as for the primary analysis.

Dichotomous variables:

- The proportion of responders defined as subjects who achieve both clinical and histologic response (Weeks 16 and 48):
  - Clinical response is defined as the proportion of subjects achieve < 4/15 in all Symptoms of Interest (Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain) of the Izumo Scale
  - Histologic response is defined as a > 75% reduction of peak gastric and/or duodenal eos count from baseline

- The proportion of subjects achieving eosinophilic histologic response defined as a > 75% reduction of peak gastric and/or duodenal eos count from baseline (Weeks 16 and 48)
- The proportion of subjects who achieve < 4/15 in all Symptoms of Interest (Gastric Pain Symptoms domain, Stomach Heaviness Symptoms domain, and Diarrhea Symptoms domain) of the Izumo Scale (Weeks 14 to 16, 30 to 32, and 46 to 48)
- The proportion of subjects for whom the dose of concomitant steroids is reduced to zero (Weeks 24, 32, 40, and 48)

The analysis of the response endpoint will be conducted on the ITT population using the Cochran-Mantel-Haenszel (CMH) test stratified by concomitant corticosteroid treatment at baseline (yes or no). In case the Mantel-Fleiss criterion is not met, the Fisher's exact test will be performed instead of the CMH test. For treatment comparison between a CC-93538 dose and placebo, the 2-sided 95% stratified Newcombe CI (Yan, 2010) for the difference in proportions using the CMH weights will be provided. Missing data and any observed data after rescue therapy/prohibited medication which may impact the efficacy assessment will be set as non-responders.

Time to event data:

- The time to event of EGE flare (Through Week 48)
- The time to event of use of rescue therapy (Through Week 48)
- The time until concomitant corticosteroid use to zero (From Week 16 through Week 48)

For the time-to-event endpoints, the numbers of subjects who have an event will be summarized. The Kaplan-Meier (KM) estimates of the 25th, median, and 75th percentile of the time to the first event and the 2-sided 95% CIs will be provided. The cumulative number of events, the number of subjects at risk, and the KM estimate of the event rate (i.e., failure probability instead of survival probability) and SE will be provided by time point. The KM plot of failure curves (instead of survival curves) with the number of subjects at risk at each time point will be presented. To test the KM curve in the treatment group is different from that in the placebo group in at least one stratum, a stratified log-rank test will be conducted.

Multiplicity Adjustment

Only one formal statistical test will be performed for the primary endpoint. For any other comparisons, nominal p-value (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than a formal statistical test. Therefore, the multiplicity adjustment is not applicable in this study.

9.7 Safety Analysis

Safety analysis will be performed for the Induction Phase and by treatment and in total CC-93538 for the Maintenance Phase. The assessment of safety will include AEs, SAEs, AEs leading to discontinuation of study treatment, changes from baseline in laboratory values and vital signs, and incidence and type of laboratory, vital signs, and physical examination abnormalities. Safety data

will be summarized by treatment group using descriptive statistics. Individual data listings will also be provided.

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

Laboratory assessments will be performed by a central laboratory. All summaries will be based on the standard International System of Units (SI) provided by the central laboratory. Each subject's hematology, blood chemistry, and urinalysis values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory.

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

Overall safety and tolerability will be summarized for each drug presentation (the 360 mg dose of CC-93538 administered by two injections of 1.2 mL each at a concentration of 150 mg/mL CC-93538 or by one injection of 2.0 mL at a concentration of 180 mg/mL CC-93538 administered with the PFS device constituent part or by one injection of 2 mL at a concentration of 180 mg/mL CC-93538 administered with the [redacted] device constituent part) utilizing descriptive statistics.

9.8 Interim Analysis

No formal interim analysis will be conducted for the study.

9.9 Other Topics

9.9.1 Pharmacokinetics, [redacted]

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

[redacted]

9.9.3 Internal Safety Management Team

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

9.9.4 External Data Monitoring Committee

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

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 EGE flare requiring an EGE Flare Assessment, as referenced in Section 6.4.2.10. However, any EGE flare that meets the criteria for seriousness as detailed in Section 10.2.1, should be documented as an SAE in addition to an EGE flare. A diagnosis or syndrome should be recorded on the AE page of the case report form (CRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP 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 CRF. (See Section 7.2 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP which meets the definition of an adverse event, should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. 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, [redacted]/PFS device 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 specialized eCRF pages, 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 until 16 weeks after the last dose of IP or the final 16-week Safety Follow-up Visit, whichever is longer, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAE to Drug Safety.

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 AE, 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 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 each AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6 Outcome

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

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

10.3 Abnormal Laboratory Values

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

- results in discontinuation from the study;

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

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

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

10.4 Pregnancy

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

10.4.1 Females of Childbearing Potential

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

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

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

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as 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 to Celgene Drug Safety by

facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.5 Reporting of Serious Adverse Events

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

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

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

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

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

10.5.1 Safety Queries

Queries pertaining to SAEs will be communicated through EDC.

10.6 Adverse Events of Special Interest

Investigators should identify AEs that meet the following criteria for adverse events of special interest (AESIs). 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 [redacted]. These include:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions

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

10.7 Expedited Reporting of Adverse Events

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

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

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

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

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

Celgene Drug Safety Contact Information:

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

11 DISCONTINUATIONS

11.1 Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the IP(s):

- 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 IP:

- Pregnancy
- An SAE which is suspected of being related to IP
- Anaphylactic reaction or other severe systemic reaction (eg, hypersensitivity, allergic, or autoimmune) suspected of being related to IP
- Malignancy diagnosis, excluding carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin if it can be successfully treated by local resection
- Presence of an opportunistic infection suggestive of immunocompromisation
- The following severe laboratory abnormalities suspected of being related to IP (laboratory indices should be repeated for confirmation prior to permanent IP discontinuation, within 48 to 72 hours after the abnormality was first observed):
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values > 3 × ULN with total bilirubin > 2 × ULN or INR > 1.5, excluding confirmed Gilbert Syndrome or therapeutic anticoagulation
  - ALT and/or AST > 5 × ULN for greater than 2 weeks duration
- 3 or more consecutive missed doses, unless in consultation with the Medical Monitor it is determined that despite 3 or more consecutive missed doses it is in the best interest of the subject to continue participation with the possibility of re-starting CC-93538 at an appropriate time in the future
- Disclosure of the results of the gastric/duodenal eos count (in Induction Phase only)
- Use of systemic immunosuppressive or immunomodulating drugs prohibited per protocol (see Section 8.2)

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

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

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

In the OLE Phase, Subjects who demonstrate a persistent lack of improvement or worsening of EGE 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.

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

In the Induction Phase, subjects who discontinue from the study for any reason prior to completing Week 16, or who complete Week 16 and do not enter the Maintenance Phase will complete an ET Visit conducted as close as possible to the time of study discontinuation. If study discontinuation occurs at the regularly scheduled visit (eg, Induction Phase Week 16) the ET Visit/procedures should be performed. These subjects, with the exception of those continuing in the OLE Phase, will also have 2 Safety Follow-up Visits (at 8 and 16 weeks) after final IP administration for the assessment of safety and clinical status after exiting the study. For subjects who are permanently discontinued from IP during the Induction Phase and remain in the study to complete safety and efficacy assessments, the Interim and Final Safety Follow-up Visits will be conducted at 8 and 16 weeks, respectively, after their last study visit in the Induction Phase. Assessments should be performed in accordance to the schedule of events (Table 4).

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

In the OLE Phase, subjects who discontinue the study will have an OLE-ET/EoT Visit within 2 weeks after final CC-93538 administration and an Interim and Final 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 schedule of events (Table 6).

11.3 Emergency Contact

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

In the unlikely event that the Clinical Research Physician (also referred to as Clinical Trial Physician)/Medical Monitor or designee cannot be reached, please contact the global Emergency

Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

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

11.4 Emergency Identification of Investigational Products

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

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

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

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

12 REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Council on 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 themselves to acknowledge their willingness to continue in the study.

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 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, 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/IEC approval but will be submitted to the IRB/IEC 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.

Investigational product 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 noncompliance;

- 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 IP 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/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. The 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 details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the 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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APPENDIX A TABLE OF ABBREVIATIONS

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADL	Activity of daily life
AE	Adverse event
AESI	Adverse event of special interest
[redacted]	
ALT	Alanine aminotransferase (SGPT)
[redacted]	
ANCOVA	Analysis of covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
[redacted]	
CI	Confidence interval
C_{max}	Observed maximum serum concentration
CMH	Cochran-Mantel-Haenszel
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
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSD	Dysphagia Symptom Diary
EC	Ethics Committee
ECG	Electrocardiogram
ECP	Eosinophil cationic protein
eCRF	Electronic case report form
EDC	Electronic data capture system

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
[redacted]	
EG	Eosinophilic gastritis
EGD	Esophagogastroduodenoscopy
EGE	Eosinophilic gastroenteritis
EGID	Eosinophilic gastrointestinal disorder
EGPA	Eosinophilic granulomatosis with polyangiitis
[redacted]	
EoE	Eosinophilic esophagitis
eos	Eosinophils
EoT	End of Treatment
ePRO	Electronic patient-reported outcome
[redacted]	
ET	Early Termination
FCBP	Female of childbearing potential
Fc	Fragment, crystallizable
FDA	Food and Drug Administration
FGID	Functional gastrointestinal disorders
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
[redacted]	
H&E	Hematoxylin and eosin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hct	Hematocrit
HCV	Hepatitis C virus
HES	Hypereosinophilic syndrome
hgb	Hemoglobin
HFI	Hereditary fructose intolerance
HIV	Human immunodeficiency virus

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
hpf	High-power field
[redacted]	
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IE	Intercurrent event
IFNα	Interferon alpha
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
IgG1κ	Immunoglobulin G1 kappa
IGRA	Interferon gamma release assay
IL	Interleukin
IL-13Rα1	Interleukin-13 receptor alpha 1
IL-13Rα2	Interleukin-13 receptor alpha 2
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
JAK	Janus kinase
IWRS	Interactive Web Response System
JIDC	Japan Intractable Diseases Center
KM	Kaplan-Meier
LSM	Least squares mean
mAb	Monoclonal antibody
MAR	Missing at random
MCH	Mean corpuscular hemoglobin

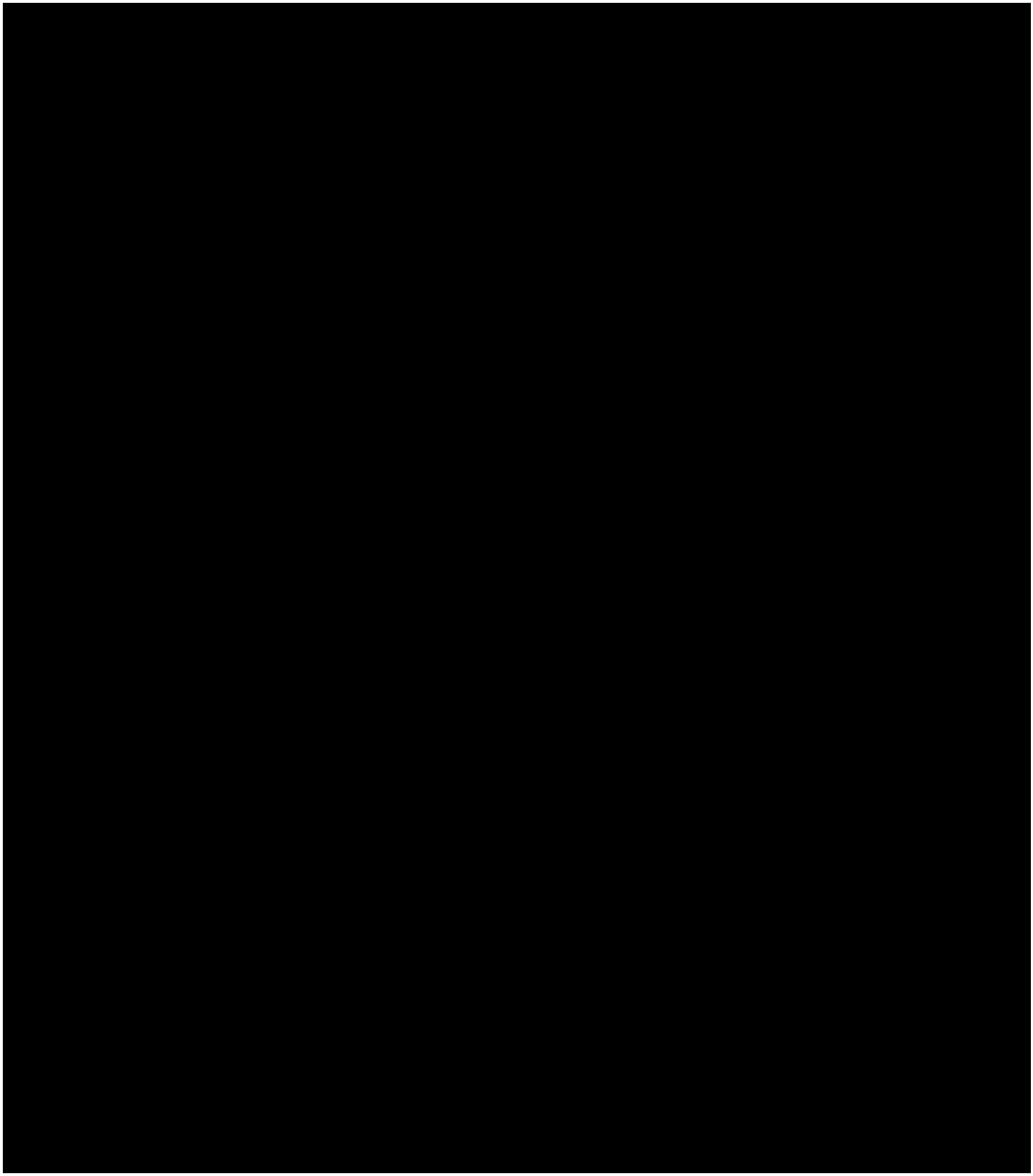
Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MHLW	Japan Ministry of Health, Labour and Welfare
MI	Multiple imputation
OLE	Open-label Long-term Extension
[redacted]	
PFS	Pre-filled syringe(s)
[redacted]	
PIN	Personal identification number
PK	Pharmacokinetic(s)
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
PT	Prothrombin time
RANTES	Regulation upon Activation Normal T-cell Expressed and Secreted
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
[redacted]	
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneously/Subcutaneous (dose/injection)
SD	Standard deviation
SE	Standard error
[redacted]	
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System of Units
SMT	Safety Management Team
[redacted]	
SOP	Standard Operating Procedure

Table 8: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
SUSARs	Suspected unexpected serious adverse reactions
$t_{½}$	Terminal elimination half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th2	T-helper type 2
t_{max}	Time to the observed maximum concentration
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
[redacted]	
WBC	White blood cell
[redacted]	

APPENDIX B IZUMO SCALE



Reference (English version)

Questionnaire on Gastrointestinal Symptoms

You will be asked about your condition during the past week. For each question, please check (☑) the one response that best applies to your condition.

For each question, please select the one response that best applies to your condition over the past week.		I was not bothered at all	I was not bothered much	I was somewhat bothered	I was bothered	I was moderately bothered	The condition was intolerable
Q1	Were you bothered by reflux of stomach acid? (Reflux of stomach acid is when you feel like a small amount of bitter water is coming up to your throat from your stomach.)	☐0	☐1	☐2	☐3	☐4	☐5
Q2	Were you bothered by feeling like your chest was burning?	☐0	☐1	☐2	☐3	☐4	☐5
Q3	Were you bothered by a feeling of discomfort in your throat? (While throat discomfort may be different for different people, this is generally a feeling like something is stuck in your throat, like your throat is stinging, or like something is pinching your throat)	☐0	☐1	☐2	☐3	☐4	☐5
Q4	Were you bothered by stomach pain? (Excluding any pain you may experience on an empty stomach)	☐0	☐1	☐2	☐3	☐4	☐5
Q5	Were you bothered by stomach pain on an empty stomach?	☐0	☐1	☐2	☐3	☐4	☐5
Q6	Were you bothered by a feeling like the area around the pit of your stomach (the area between your belly button and chest) was burning?	☐0	☐1	☐2	☐3	☐4	☐5
Q7	Were you bothered by feeling full immediately after starting to eat a meal?	☐0	☐1	☐2	☐3	☐4	☐5
Q8	Were you bothered by feeling nauseated and heavy like food is always stuck in your stomach after a meal?	☐0	☐1	☐2	☐3	☐4	☐5
Q9	Were you bothered by a feeling of distention in the stomach? (A feeling of stomach distention is the feeling like your stomach is bloated and full of gas)	☐0	☐1	☐2	☐3	☐4	☐5

For each question, please select the one response that best applies to your condition over the past week.		I was not bothered at all	I was not bothered much	I was somewhat bothered	I was bothered	I was moderately bothered	The condition was intolerable
Q10	Were you bothered by a feeling like you weren't able to completely empty your bowels (a feeling of incomplete bowel movement)?	☐0	☐1	☐2	☐3	☐4	☐5
Q11	Were you bothered by constipation or hard stool that persist for several days?	☐0	☐1	☐2	☐3	☐4	☐5
Q12	Were you bothered by constipation that occurs whenever you are highly stressed?	☐0	☐1	☐2	☐3	☐4	☐5
Q13	Were you bothered by a feeling like you want to run to the bathroom because of a sudden urge to defecate (defecation urgency)? (Defecation urgency is when you feel like you may have a bowel movement)	☐0	☐1	☐2	☐3	☐4	☐5
Q14	Were you bothered by diarrhea or soft stool?	☐0	☐1	☐2	☐3	☐4	☐5
Q15	Were you bothered by diarrhea that occurs whenever you are highly stressed?	☐0	☐1	☐2	☐3	☐4	☐5

The last question for you to answer
Of the following five items, which symptoms have presented the greatest obstacles to your daily activities during the past four weeks? Please check all that apply if you experienced the same level of obstacles with multiple items.

① Heartburn symptoms: ☐
② Gastric pain symptoms: ☐
③ Stomach heaviness symptoms: ☐
④ Constipation symptoms: ☐
⑤ Diarrhea symptoms: ☐

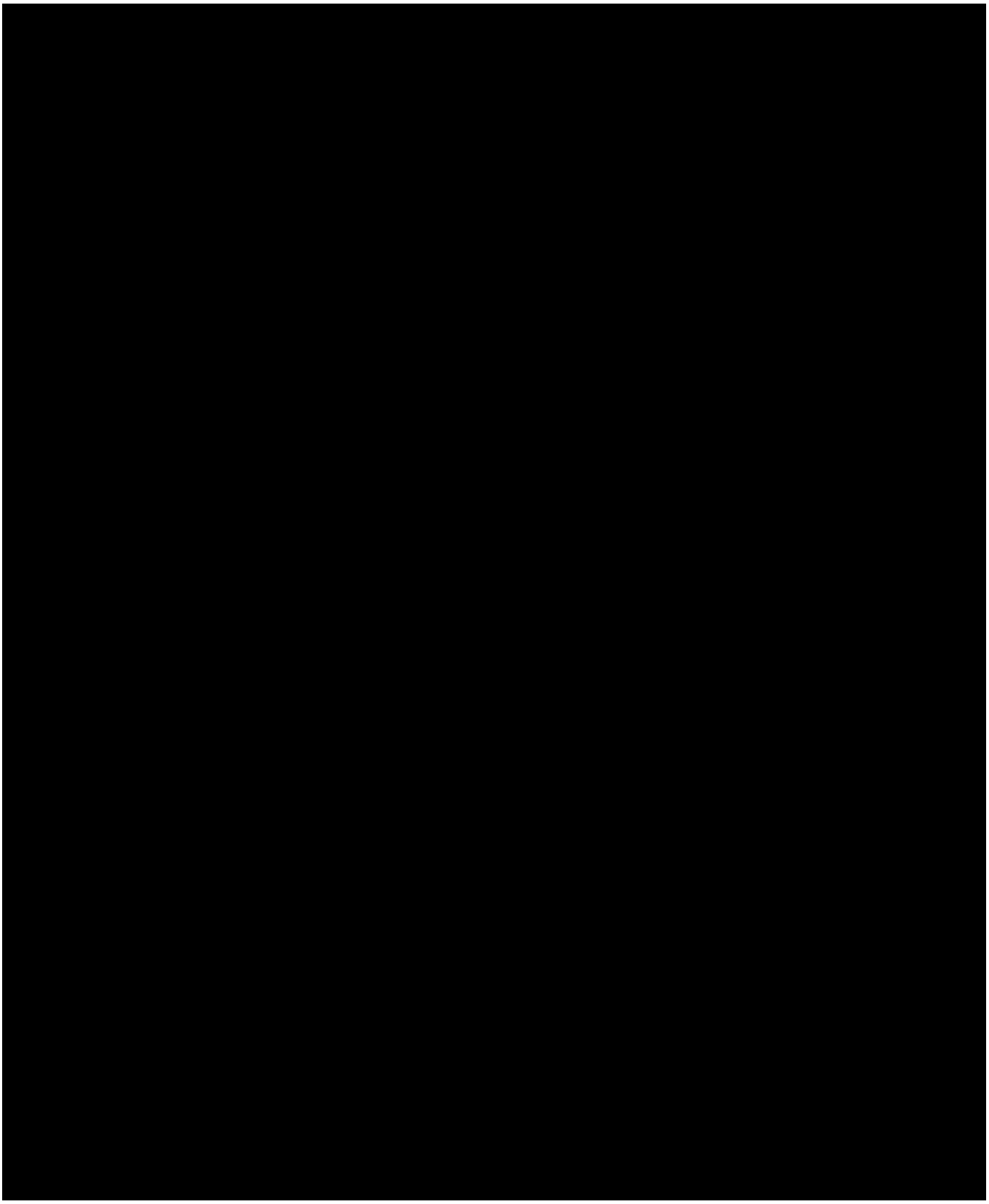
APPENDIX C EGID SEVERITY SCORE (FOR AGES ≥ 20 YEARS OLD)

[redacted]

Reference (English version)

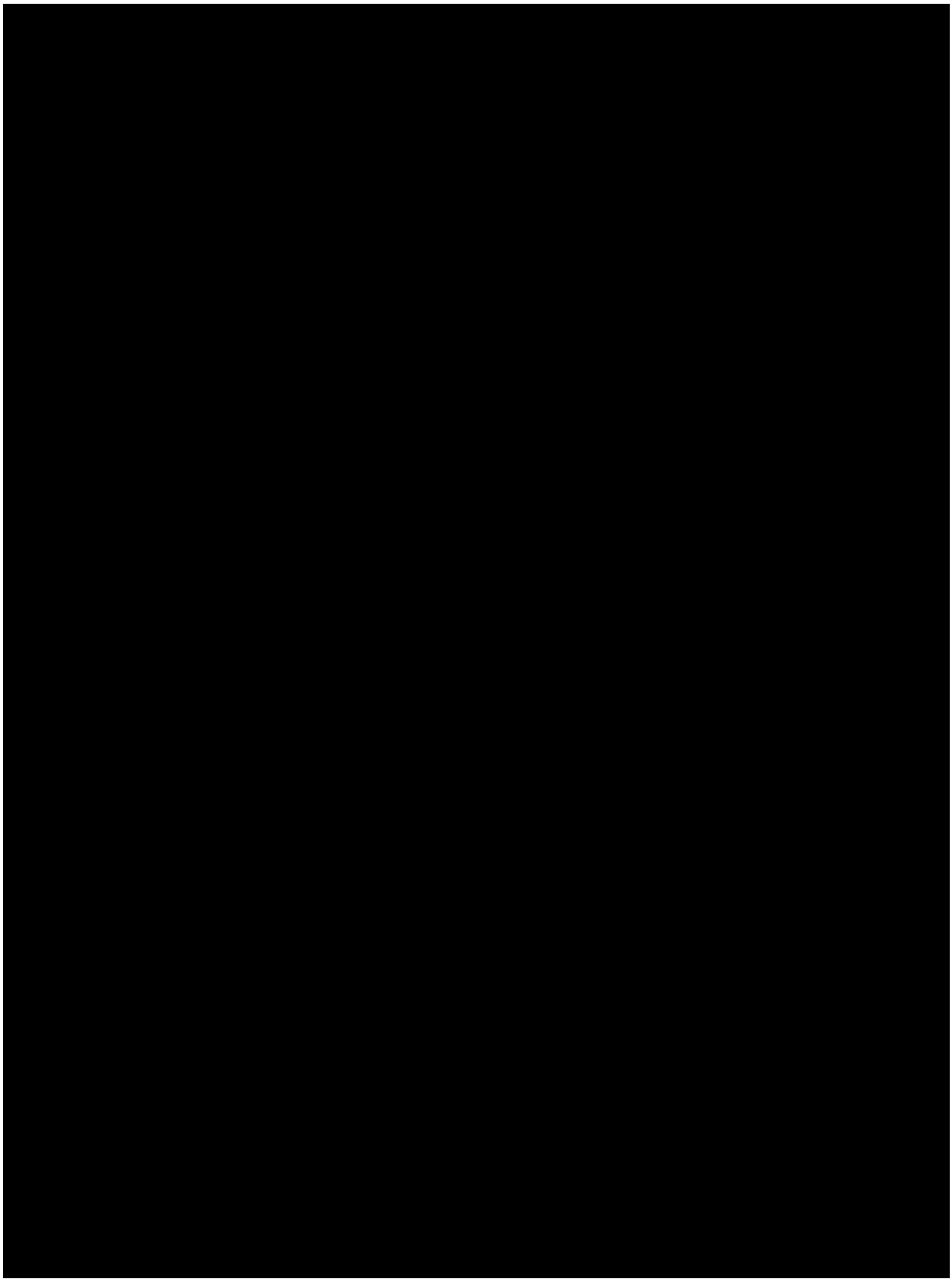
Adult symptom score scoring table
Decision in one month immediately preceding 40 points or more severe, 15-39 points moderate, 14 points or less mild
Symptoms typical of the upper gastrointestinal tract (1) Vomiting
3 points: Nausea present (no vomiting) 5 points: 1 time per day vomiting 4 days or more in a month 7 points: 2-5 times/day vomiting 4 days or more in a month 9 points: 6 times / day or more vomiting 1 day or more per month
Symptoms typical of the upper gastrointestinal tract (2) Dysphagia
6 points: Always has difficulty swallowing 9 points: Experienced food press-fitting or endoscopic removal
Symptoms typical of the upper gastrointestinal tract (3) Loss of appetite
6 points: Don't always have an appetite 9 points: Almost no appetite and requires tube feeding etc.
Abdominal pain
3 points: Mild, short time, no restrictions on activity 6 points: Moderate, long lasting every day, or occurring after sleep 9 points: Severe, always pain requiring the use of painkillers
Symptoms typical of the lower gastrointestinal tract (1) Diarrhea
3 points: 2-5 watery stools more than 4 days a month 6 points: 6 or more watery diarrhea 4 days or more in a month 9 points: Dehydration occurred.
Symptoms typical of the lower gastrointestinal tract (2) Bloody stool
3 points A small amount of blood is mixed at least once a month 6 points: Obvious bloody stool at least once a month 9 points: Large amounts of bloody stools every day
Laboratory findings (choose the minimum value)
3 points: 3.0 ≤ Alb <3.5 6 points: 2.0 ≤ Alb <3.0 9 points: Alb <2.0
Peripheral blood eosinophil ratio (choose maximum)
3 points: 5% or more and less than 10% 6 points: 10% or more and less than 20% 9 points: 20% <
So far, surgery has been performed to eliminate complications of EGlDs (perforation, stenosis, etc.)
0 points: No 5 points: Yes
Have you used steroids, immunosuppressive drugs, or other drugs of concern for side effects in the past year for the treatment of EGlDs?
0 points: Not used 5 points: Used

APPENDIX D EGID SEVERITY SCORE (FOR AGES FROM 2 TO 19 YEARS OLD)



Reference (English version)0

Symptom score scoring table for ages 2-19 years old
Decision in one month immediately preceding 40 points or more severe, 15-39 points moderate, 14 points or less mild
General condition (probable deterioration due to EGIDs)
0 points: Good condition, no action restrictions 3 points: Age-appropriate behavior is more restricted than usual 6 points: Poor condition and often restricted behavior 10 points: There is a clear delay in development
Weight
0 points: Weight gain or stability 3 points: Can't gain weight 6 points: Weight <-2SD 9 points: Weight <-3SD
Height
0 points: -1SD ≤ height 3 points: -2SD ≤ height <-1SD (Do not count if there is no problem from the height of parents) 6 points: Height <-2SD 9 points: First height <-3SD
Symptoms typical of the upper gastrointestinal tract (1) Vomiting
0 points: No nausea 3 points: Nausea present (no vomiting) 4 days or more per month 5 points: 1 time per day vomiting 4 days or more in a month 7 points: 2-5 times/day vomiting 4 days or more in a month
Symptoms typical of the upper gastrointestinal tract (2) Dysphagia
0 points: Can swallow food normally 3 points: Difficulty swallowing 4 or more times per month 6 points: Always has difficulty swallowing 9 points: Experienced food press-fitting or endoscopic removal
Symptoms typical of the upper gastrointestinal tract (3) Loss of appetite
0 points: Appetite present 3 points: 4 days or more a month with no appetite 6 points: Don't always have an appetite 9 points: Almost no appetite and requires tube feeding etc.
Abdominal pain
0 points: No abdominal pain 3 points: Mild, short time, no restrictions on activity 6 points: Moderate, long lasting every day, or occurring after sleep 9 points: Severe, always pain requiring the use of painkillers
Symptoms typical of the lower gastrointestinal tract (1) Diarrhea, number of times per day
0 points: Up to 0-1 watery stools 3 points: 2-5 watery stools more than 4 days a month 6 points: 6 or more watery stools a day or more 9 points: Dehydrated and required IV drip
Symptoms typical of the lower gastrointestinal tract (2) Bloody stools, number of times per day
0 points: No bloody stools 3 points: At least once with a small amount of blood 6 points: 1 or more obvious bloody stools 9 points: Large amounts of bloody stools every day
Laboratory findings
0 points: No abnormality in albumin (Alb) or hemoglobin (Hb) 3 points: 3.0 ≤ Alb <3.5, and / or 9.0 ≤ Hb <11.0 6 points: Alb <3.0 and/or Hb <9.0 9 points: Alb <2.0 and/or Hb <7.0
Peripheral blood eosinophil ratio
0 points: 0 to less than 5% 3 points: 5% or more and less than 10% 6 points: 10% or more and less than 20% 9 points: 20% or more



APPENDIX F PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 4.0, 07-Dec-2022:

Protocol Amendment 4.0 is created to correct inconsistencies in the document and provide administrative changes.

Summary of Changes for Protocol Amendment 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Medical Monitor/Emergency Contact Information	Change in address of Bristol-Myers Squibb K.K.	Updated contact information of Medical Monitor due to Bristol-Myers Squibb K.K. headquarters relocation
Title Page and Signature Pages	Personnel changes	Administrative changes
Title Page	Removed Investigational New Drug (IND) number	Removed IND number since this clinical trial is not actually planned to be submitted to the United States Food and Drug Administration
Title Page Protocol Summary Section Section 1.2.1: Mechanism of Action	Added Bristol-Myers Squibb (BMS) compound number (BMS-986355)	For clarification purposes
Section 1.2.2.4: Phase 1 Study, CC-93538-CP-002	New section added	A new section was added to include the results of Study CC-93538-CP-002, which provides the pharmacokinetic (PK) comparability, safety, tolerability, and immunogenicity of a single subcutaneous (SC) dose of 360 mg CC-93538 using 2 different drug concentrations, 180 mg/mL and 150 mg/mL, in healthy adult subjects
Table 6: Table of Events for the Open-label Long-term Extension (OLE)	Added language that the first dose with the 360 mg/2.0 mL pre-filled syringe (PFS) presentation will be administered during an in-	For the OLE Phase, the CC-93538 SC dose with single injection of 360 mg/2.0 mL PFS will be implemented in order to study the higher concentration

Summary of Changes for Protocol Amendment 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.2: Treatment Administration and Schedule	clinic visit in the OLE Phase to ensure accurate dose administration and compliance	and higher volume presentation for use with long-term CC-93538 treatment
Section 1.3.2.1: Benefit-Risk Assessment	Added information related to concomitant use of coronavirus disease 2019 (COVID-19) vaccines in subjects receiving CC-93538	Updates made to clarify that non-live COVID-19 vaccinations are allowed and considered as a simple concomitant medication within the study, and details such as type and date of vaccine received should be recorded on the COVID-19 Vaccination Form
Section 1.3.2.1: Benefit-Risk Assessment	Added text to clarify that the overall safety profile of CC-93538 remains consistent with the information that has been presented in the Investigator's Brochure (IB).	For clarification purposes
Protocol Summary Section 3.2: Study Duration for Subjects	Added text to clarify that "post-marketing clinical study" will be used to refer to this study following market approval in Japan	Added a sentence to clarify that this study will continue until market launch and then be converted to “post-marketing clinical study” after the marketing approval date in Japan
Section 4.2: Inclusion Criteria	In criterion 1, changed the age of the subject for whom a proxy consent is required from under 20 years old to under 18 years old	Updates made to reflect a change that the age of majority in Japan has been reduced from 20 to 18 years old due to the Civil Code amendment
Section 4.2: Inclusion Criteria Section 6: Procedures	Deleted the sentence “for subjects aged from 18 to 19 years, assent is not necessarily required if the patient is considered to have a level of understanding comparable to that of adults by the investigator”	The sentence is no longer needed since the Civil Code amendment lowered the age of majority from 20 to 18 years old
Section 4.2: Inclusion Criteria	Updated criterion 7 in that a female subject who has undergone bilateral salpingectomy is not	Updated definition of an FCBP to keep consistency across CC-93538 study protocols

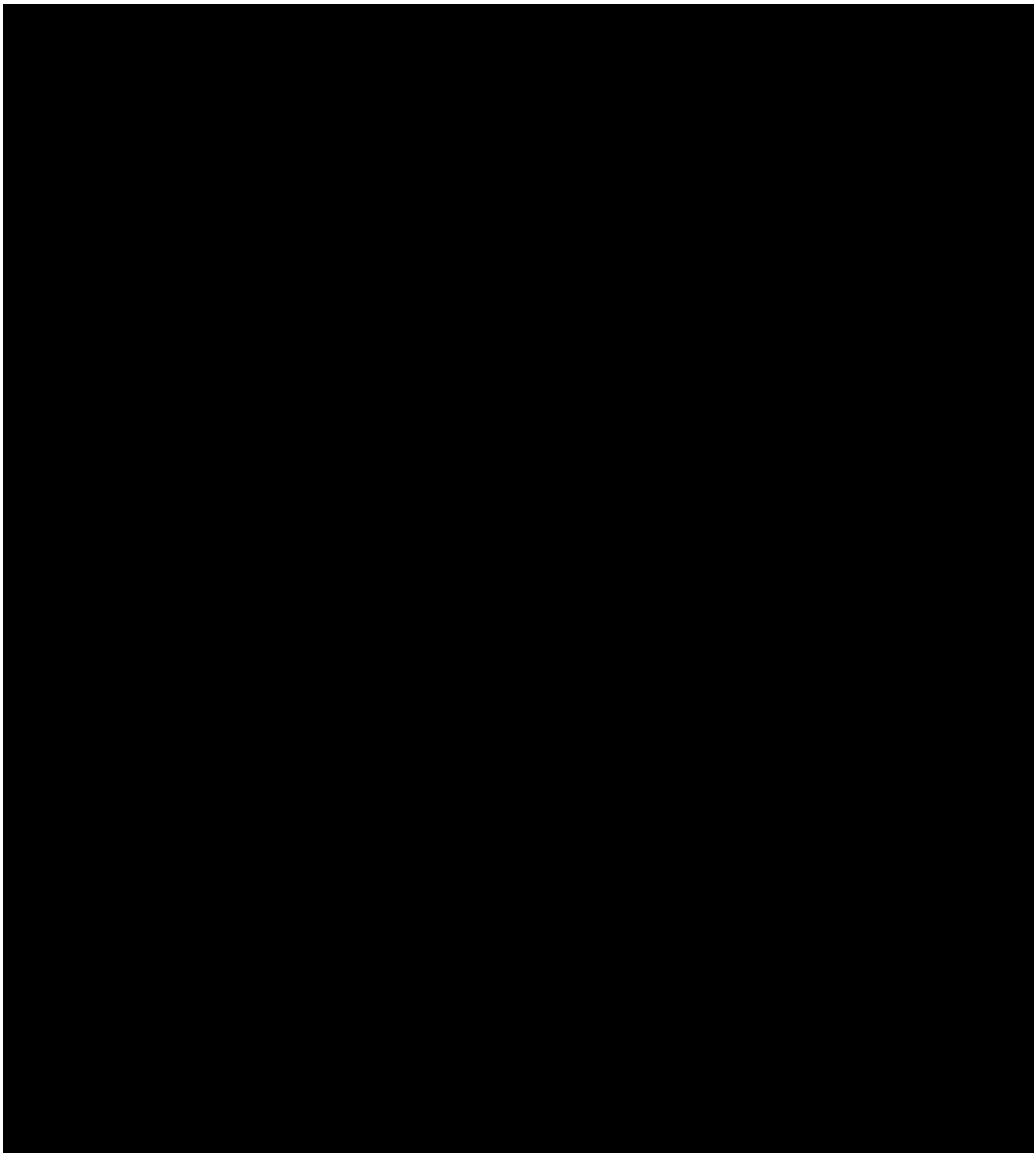
Summary of Changes for Protocol Amendment 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
	considered a female of childbearing potential (FCBP)	
Section 4.3: Exclusion Criteria	Clarified in criterion 8 that corticosteroids are allowed as background or rescue therapy	For clarification purposes Systemic corticosteroids at stable doses (up to 10 mg/day of prednisone) are allowed in this study
[redacted]		

Summary of Changes for Protocol Amendment 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 6.1: Screening Period	Removed the detailed description regarding a human immunodeficiency virus (HIV) antibody confirmation assay methodology	Revision due to methodology change for HIV antibody confirmation assay performed in a central laboratory in accordance with the recommendation of World Health Organization (WHO) guidelines for HIV testing strategy
Table 4: Table of the Events for the Induction Phase Table 5: Table of the Events for the Maintenance phase Table 6: Table of Events for the Open-label Long-term Extension (OLE)	[redacted] measured at all applicable visits after Day 1 which the EGID severity scoring is scheduled	Considering that different score scales are used for patients under 20 years of age, [redacted] to assess the EGID severity score more accurately
Section 7.1: Description of Investigational Product(s)	Added note to clarify "investigational product" in this protocol will automatically be replaced with "post-marketing clinical study drug" on and after the date of marketing approval in Japan	At the same time that this study is converted to "post-marketing clinical study" after the marketing approval date in Japan, the investigational product will be also replaced with post-marketing clinical study drug
Section 7.1: Description of Investigational Product(s) Section 7.2.1: Self-Administration	Added new text related to "Instructions of Use" document	For clarification purposes
Section 8.1: Permitted Concomitant Medications and Procedures Table 7: Medications, Diets, or Procedures Requiring Stable Dosing Regimens or Restricted	Added permitted concomitant use of PPIs for indications other than EGE	Corrections made to resolve in-document inconsistency

Summary of Changes for Protocol Amendment 4.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Use Prior to Study Enrollment		
Section 9.6.2: Subgroup Analyses	Updated language regarding subgroup analyses	Updates made to align with the Statistical Analysis Plan (SAP)
Section 9.6.3.1: Analyses Methods	Added language regarding the Fisher's exact test	Updates made to clarify and to align with the SAP
Section 9.7: Safety Analysis	Provided clarification that the overall safety and tolerability data will be summarized by presentation utilizing descriptive statistics	Text added to describe the assessment of the safety profile of CC-93538 based on PFS presentation that the subjects will receive during the study
Section 10.5: Reporting of Serious Adverse Events	Revised sentence related to SAE report to require all SAEs occurring after the time of signing the informed consent form (ICF)/assent to be reported to Celgene Drug Safety	Changes made to align with the company requirements
All	Minor formatting, typographical corrections, and revisions for clarity	Corrections made to resolve in-document inconsistency

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:



Addition of 180 mg/mL pre-filled syringe (PFS) in the Open-label Long-term Extension (OLE) Phase

A newly developed CC-93538 180 mg/mL formulation is added for use in the OLE Phase in addition to the currently used 150 mg/mL formulation.

Revised sections:

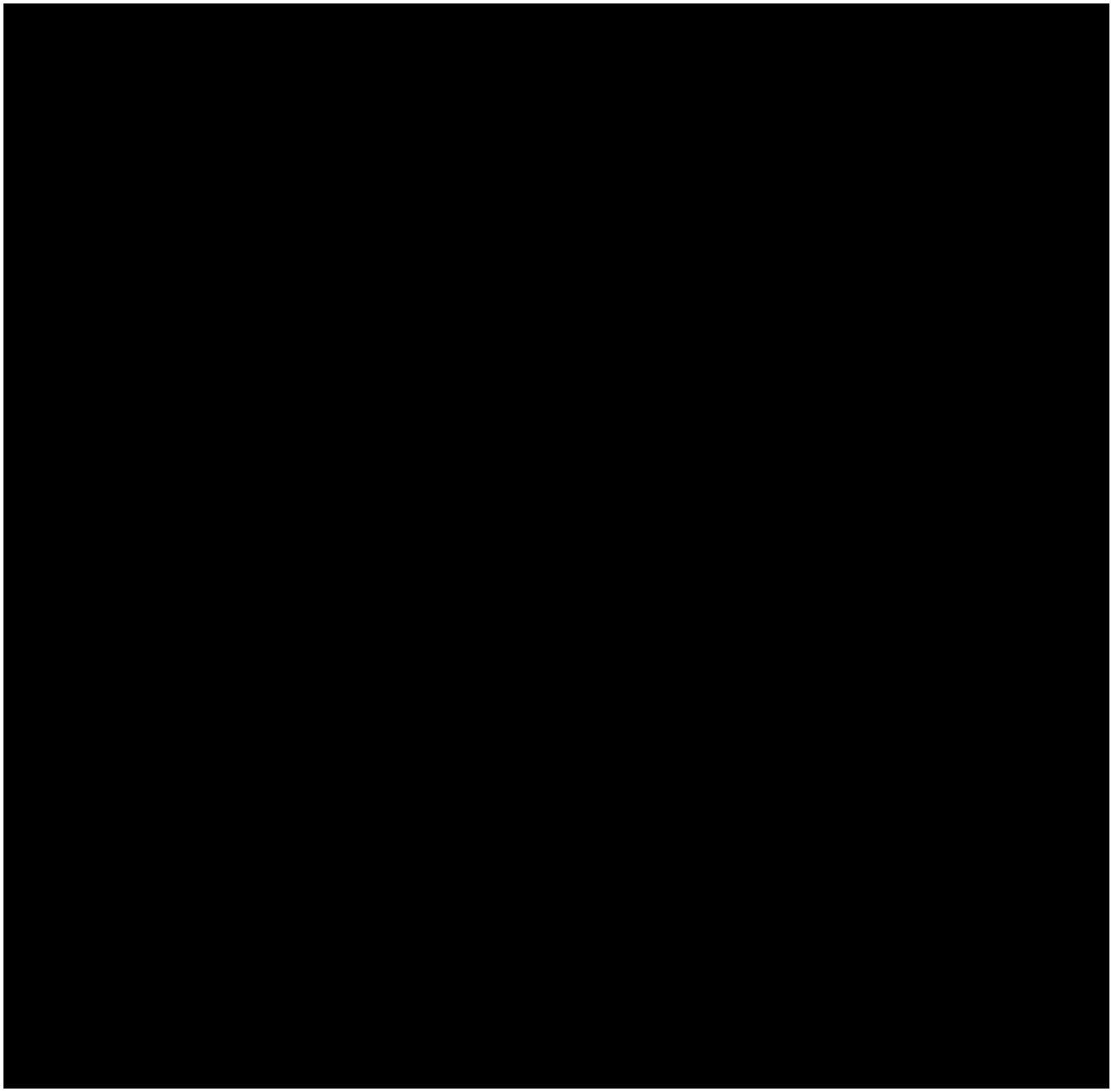
- Protocol Summary
- Section 7 Description of Study Treatments

  Section 7.1 Description of Investigational Product(s)

References:

[redacted]

1. JUSTIFICATION FOR AMENDMENT



Addition of an extra specimen for gastric/duodenal biopsies

Updated to allow an additional sample to be obtained based on the investigator's judgment in order to secure the flexibility of gastric/duodenal biopsies in the evaluation of eosinophil count.

Revised section:

- Section 6.4 Efficacy Assessment

The amendment also includes another minor change

- Replacement of Clinical Trial Physician (Medical Monitor/Emergency Contact Information)

- Change of Sponsor Address
- Correction of typographical errors

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Change of Patient-Reported Outcome (PRO) from [redacted] to Izumo Scale

The primary purpose of this protocol amendment is to change the key PRO to assess gastrointestinal (GI) symptom of Japanese patients with Eosinophilic Gastroenteritis (EGE). [redacted]

On the other hand, the Izumo scale was developed as a questionnaire [redacted] with the past 7 days gastrointestinal symptoms with Japanese language as an original. Izumo Scale was confirmed useful as a disease-specific [redacted] assessment scale for Japanese patients with gastrointestinal symptoms (Furuta, 2009). Since this study is a study conducted only in Japanese patients with EGE, weekly assessment by Izumo scale was considered more appropriate in this study than [redacted] for a key secondary endpoint. Therefore, the PRO instrument for this study has been changed from the [redacted] to the Izumo Scale.

Procedures to enhance subject adherence to questionnaire completion have also been modified to clarify alarm and surveillance were kept and telephone call reminders have been removed, since daily assessments have changed to weekly assessments.

Revised sections:

- Protocol Summary
- Section 2 Study Objectives and Endpoints (Tables 2 and 3)
- Section 3.1 Study Design (Section 3.1.1 Screening Period, Section 3.1.2 Induction Phase)
- Section 4.2 Inclusion Criterion #4
- Section 5 Tables of Events
- Section 6.1 Screening Period
- Section 6.2 Induction Phase and Maintenance Phase
- Section 6.3 Follow-up Period
- Section 6.4 Efficacy Assessment (Section 6.4.2.1 Izumo Scale Questionnaire)
- Section 9.6 Efficacy Analysis (Section 9.6.3.1 Analyses Methods)
- Appendix B

[redacted]

Recategorization of secondary endpoints

To clarify that clinical symptoms of EGE are assessed using the Izumo Scale as an axis, clinical response using Eosinophilic Gastrointestinal Disorder (EGID) Severity Score is moved from Key Secondary Endpoint to Secondary Endpoint in the Induction and Maintenance Phases.

Revised sections: Protocol Summary, Section 2 Study Objectives and Endpoints (Table 2), Section 5 Tables of Events, Section 6.1 Screening Period

Update of timeframe of endpoints

The timeframe of Weeks 30 to 32 in study endpoints is removed from the endpoints timeframes to focus on assessments at end of each phase (Week 16/Induction Phase and Week 48/Maintenance Phase).

Please note that the timeframes in the Tables of Events are not changed.

Revised section: Section 2 Study Objectives and Endpoints (Table 2)

Update of main symptoms of EGE

Vomiting as a major symptoms was replaced by nausea based on recent findings (Dellon, 2019).

Revised sections: Protocol Summary, Section 1.1 Disease Background

Update of definition of histologic evidence of EGE

The criteria for evidence of EGE (≥ 30 eosinophils [eos]/high-power field [hpf] in at least 5 hpf in the stomach and/or ≥ 30 eos/hpf in at least 3 hpf in the duodenum while on stable background therapy) was clarified in this amendment.

Revised section: Protocol Summary, Section 3.1.2,Section 4.2 Inclusion Criterion #3

Update of examples of any other disease listed in Exclusion Criterion #5

Gastritis and enterocolitis are removed from examples of 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, to clarify eligible patients.

Revised sections: Section 4.3 Exclusion Criterion #5

Addition of definition of hypereosinophilic syndrome (HES)

The definition of HES is added to clarify eligible patients.

Revised section: Section 4.3 Exclusion Criterion #5

[redacted]

Revised section: Section 5 Tables of Events

Clarification of Esophagogastroduodenoscopy (EGD) Procedure

The EGD Procedure is clarified such that biopsies for the Open-label Long-term Extension (OLE) Day 1/Baseline will be read in a blinded manner.

Revised section: Section 6.4.1 Esophagogastroduodenoscopy (EGD)

Addition of the statistical method of time-to-event data

The analyses method of time-to-event data is added to clarify the statistical approach.

Revised section: Section 9.6.3.1 Analyses Methods

The amendment also includes several other minor clarifications and corrections

- Clarification of definition of adolescent (Protocol Summary and Section 6)
- Update of coronavirus disease 2019 (COVID-19) vaccine language (Section 1 and Section 8)
- Correction of timeframe of study endpoints (Section 2, Tables 2 and 3)
- Addition of footnote to Inclusion Criterion #1 (Section 4.2)
- Addition of height timepoint for adolescent to calculate EGID Severity Score (Section 5)

[redacted]

- Update of EGID Severity Score due to the release of Japan EGID guideline (Section 6.4, Appendix C, and Appendix D)
- Clarification to the Early Termination Visits in the Maintenance Phase and in the Open-label Long-term Extension Phase.(Section 3, Section 5, Section 6, and Section 7.2)
- Change of language accompanying protocol template update (Section 10.1, Section 14.1, Section 14.3)
- Correction of administrative language (Section 10.4, Section 14.1)
- Addition and revision of references (Section 16)
- Update of Abbreviations and Specialist Terms (Appendix A)
- Correction of in-document links
- Correction of typographical errors

References:

Dellon ES, Peterson KA, Murray JA, Falk GW, Gonsalves N, Chehade M, et al. AK002 (Antolimab) in Adult Patients with Active Eosinophilic Gastritis and/or Eosinophilic Gastroenteritis: Primary Results from a Randomized, Double-Blind, Placebo- Controlled Phase 2 Trial (ENIGMA; NCT03496571). Poster presented at: ACG 2019; October 25th - 30th 2019; San Antonio, TX.

[redacted]

Furuta K, Ishihara S, Sato S, Miyake T, Ishimura N, Koshino K, et al. Shoukaki Shoujou wo yuusuru Kanja no QOL Hyouka no tame no Monshinhyou. “Izumo Scale” no Sakusei to sono Kensyou (Development and verification of the Izumo Scale, new questionnaire for quality of life assessment of patients with gastrointestinal symptoms). Nihon Shoukakibyouhgakkai Zasshi (J Japanese Society of Gastroenterol). 2009: 106; 1478-87. (published in Japanese)

[redacted]