Official Title of Study:

A Phase 3, Multicenter, Randomized, Double-blind, Placebo Controlled Study of Oral Ozanimod as Maintenance Therapy for Moderately to Severely Active Crohn's disease

NCT Number: NCT03464097

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A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ORAL OZANIMOD AS MAINTENANCE THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

INVESTIGATIONAL PRODUCT:	Ozanimod
PROTOCOL NUMBER:	RPC01-3203
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SPONSOR NAME/ADDRESS:	Celgene International II Sàrl Route de Perreux 1 2017 Boudry Switzerland Tel: [redacted]

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 7.0:

The overall rationale for this protocol amendment is to adjust the order of secondary [redacted] endpoints [redacted], and to accommodate a greater number of subjects entering the Maintenance Study from the Induction Studies.

The Protocol Summary was updated with all relevant changes.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 7.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2.2.2: Key Secondary Endpoints [redacted]	Moved the following endpoint [redacted] to Key Secondary: "Proportion of subjects with SES-CD ≤ 4 points and SES-CD decrease from baseline ≥ 2 points with no SES-CD subscore > 1 point at Week 52."	[redacted]
	Added a note that "Final ranking of key secondary endpoints may vary by region and will be defined in the SAP."	To allow for differences in regulatory requirements between regions.
Section 2.2.2: Key Secondary Endpoints Section 2.2.3: Additional Secondary Endpoints	Moved the following endpoints from Key Secondary to Additional Secondary: • "Proportion of subjects with CDAI score < 150 at Week 52 and at ≥ 80% of visits between Week 8 and Week 52, inclusive, in subjects with CDAI score < 150 at Maintenance Day 1" • "Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD decrease from baseline ≥ 50% at Week 52"	To consolidate the list of Key Secondary Endpoints which will be subject to hierarchical testing/ multiplicity adjustment.
[redacted]		
Section 3.1: Study Design Section 4.1: Number of Subjects	Added language to allow for additional subjects to be enrolled based on eligibility from the Induction Study.	Sample size has been revised to allow for flexibility based on the number of eligible subjects from Induction Study.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 7.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1: Overview Section 9.3.2: Power Calculations		
Section 3.3: End of Study	Added following sentence: "If the Sponsor discontinues the Maintenance Study prior to the planned end of study, active subjects will be considered completers of the study and may be eligible to enroll in the Open-Label Extension Study (RPC01-3204)."	To allow for flexibility within the study program, and to provide access to the Open-Label Extension Study for all subjects in the Maintenance Study.
Section 6.4.1.2: Simple Endoscopic Score for Crohn's Disease	Aligned scoring of SES-CD for endoscopic remission with endpoint.	To be aligned with regulatory interaction and updated scientific examination of measures of endoscopic remission.
Section 9.2: Study Population Definitions	Removed the per protocol (PP) population definition.	To align with International Council for Harmonisation (ICH) guideline E9 (R1) Section A.5.3.
Section 9.8: Treatment Failure Rules	Changed the discontinuation of investigational product (IP) from "for lack of therapeutic effect" to "due to any reason."	To align with ICH E9 (R1) Section A.3.1.
All	Minor formatting and typographical corrections/edits.	Minor, therefore have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Maintenance Therapy for Moderately to Severely Active Crohn's Disease

Indication

Crohn's disease (CD) is an immune-mediated inflammatory disease of the gastrointestinal (GI) tract. Annual incidence varies geographically, with estimates ranging from 3.1 to 14.6 per 100,000 people in the United States and from 0.1 to 16 per 100,000 worldwide (Lakatos, 2006). Subjects with CD suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever. CD is characterized by a lifelong chronic course of remissions and exacerbations. The pathology of this disease is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. The transmural inflammatory process of CD predisposes subjects to the formation of fistulas and it has been estimated that approximately 35% of subjects will have at least 1 fistula during the course of their disease (Schwartz, 2002). In a recent study, within 10 years of diagnosis, 50% of adults with CD had undergone bowel surgery (Peyrin-Biroulet, 2010).

The current standard of medical care for patients with moderately to severely active CD consists of anti-inflammatory approaches, such as corticosteroids, azathioprine (AZA)/6-mercaptopurine (6-MP), methotrexate (MTX), and biologics such as anti-tumor necrosis factor (TNF)α, anti-interleukin (IL)-12/IL-23, or anti-integrins.

Immunomodulators aid in corticosteroid withdrawal and in preventing relapse, but also are associated with considerable side effects. Infliximab, an anti-TNFα-therapy, is able to reduce signs and symptoms and induce and maintain remission in the majority of subjects for which it is indicated. However, in a large Phase 3 maintenance trial of infliximab for CD (ACCENT I), only 45% of subjects were considered in remission at Week 30 in the highest dose group (where remission was defined as the ability to achieve a Crohn's Disease Activity Index [CDAI] of < 150 points) (Hanauer, 2002). Similarly, the primary response rates in trials of adalimumab (Colombel, 2007) and certolizumab (Sandborn, 2007) were approximately 47% and 37%, respectively. Thus, a sizable proportion of the patient population is unresponsive to both conventional therapy and TNF antagonists. Vedolizumab, a gut-specific anti-integrin therapy, is also indicated for achieving clinical response and clinical remission in this population. However, in a large clinical trial of vedolizumab, only 32% of subjects had a clinical response at Week 6, and only 39% receiving vedolizumab every 8 weeks were in remission at Week 52 (Sandborn, 2013). Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, was approved for the treatment of patients who failed or were intolerant to treatment with immunomodulators, corticosteroids, or 1 or more TNF antagonists. However, in the induction trials of ustekinumab, only 32% of subjects were responders at 6 weeks (Feagan, 2016), and about 40% were in remission at Week 52 of the maintenance trial.

Therefore, there remains a considerable unmet medical need for safe and effective oral treatments for patients with CD.

Objectives

Primary Objective:

- Demonstrate the efficacy of ozanimod compared to placebo on the maintenance of clinical remission and endoscopic response

Secondary Objectives:

- Demonstrate the efficacy of ozanimod compared to placebo on maintenance of clinical response
- Demonstrate the efficacy of ozanimod compared to placebo on maintenance of endoscopic remission and mucosal healing
- Demonstrate the efficacy of ozanimod, compared to placebo, in achieving corticosteroid-free clinical remission
- Demonstrate the efficacy of ozanimod, compared to placebo, on healthcare resource utilization (HRU), subject-reported outcomes, and quality of life
- Demonstrate the safety and tolerability of ozanimod as maintenance therapy

Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to demonstrate the effect of oral ozanimod as maintenance therapy in adult subjects with moderately to severely active CD, defined as CDAI score ≥ 220 to ≤ 450. Subjects who complete the initial 12 weeks of treatment (Induction Studies RPC01-3201 or RPC01-3202) and are in clinical response (CDAI reduction from baseline ≥ 100 points or CDAI score < 150), clinical remission (CDAI score < 150), and/or have an average daily stool frequency score ≤ 3 and an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline will be eligible to participate in the Maintenance Study.

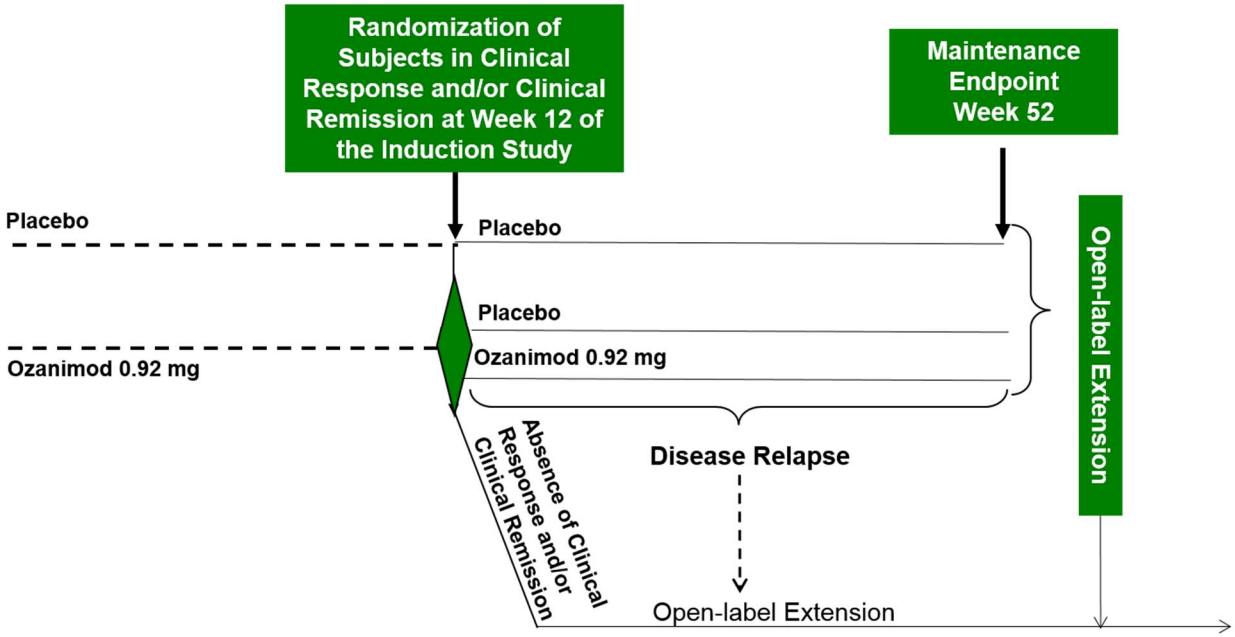
The total number of subjects enrolled (estimated at 550) will be determined based on how many subjects are eligible from the Induction Studies and choose to continue to the Maintenance Study. Approximately 410 subjects allocated to receive ozanimod in either RPC01-3201 or RPC01-3202 are expected to meet the clinical criteria described above by Week 12 and are expected to enroll in this study. Subjects will be stratified by clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no). Subjects who received ozanimod in the Induction Studies and met the clinical criteria to enter the Maintenance Study will be randomly assigned to receive ozanimod 0.92 mg or placebo in a 1:1 ratio.

Subjects who meet the clinical criteria described above after treatment with placebo in RPC01-3201 or RPC01-3202 will continue to receive placebo in a double-blinded manner.

Subjects will be assessed for disease activity through Week 52 of the RPC01-3203 study. Subjects who experience disease relapse in the RPC01-3203 study (see Section 14.2) and all subjects who complete the RPC01-3203 study will be eligible to enter the Open-Label Extension (OLE) Study RPC01-3204.

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

Overall Study Design



Note: Subjects in clinical response and/or clinical remission at Week 12 of the Induction Study who were randomized to placebo will continue to receive placebo in the Maintenance Study in a double-blind manner. Only subjects in clinical response and/or clinical remission assigned to ozanimod in the Induction Study will be randomized to either ozanimod or placebo when entering the Maintenance Study.

Study Population

Subjects who complete the initial 12 weeks of treatment (Induction Study, RPC01-3201 or RPC01-3202) and are in clinical response, clinical remission, and/or have an average daily stool frequency score ≤ 3 and an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline will be eligible to participate in the Maintenance Study.

Length of Study

The duration of this study is 52 weeks. Subjects who complete the Maintenance Study are anticipated to receive 64 weeks of treatment (12-week Induction Study + 52-week Maintenance Study). Subjects not entering the OLE Study will have [redacted]

The end of study (Maintenance Study RPC01-3203) is defined as either the date of the last visit of the last subject to complete the [redacted], or the date of receipt of the last data point from the last subject that is required for primary or secondary analysis, as pre-specified in the protocol, whichever is the later date. If the Sponsor discontinues the Maintenance Study

prior to the planned end of study, active subjects will be considered completers of the study and may be eligible to enroll in the Open-Label Extension Study (RPC01-3204).

Study Treatments

Subjects who meet the criteria to enter the Maintenance Study (RPC01-3203) and were assigned to ozanimod in the Induction Study (RPC01-3201 or RPC01-3202) will be randomly assigned to receive ozanimod 0.92 mg or placebo in a 1:1 ratio.

Subjects who were assigned to placebo in the Induction Study and met the clinical criteria for entry into the Maintenance Study will continue on placebo in a double-blind manner.

The possible treatments are as follows:

- ozanimod: taken by mouth as a single 0.92 mg capsule (equivalent to ozanimod hydrochloride [HCl] 1 mg) once daily x 52 weeks, or
- placebo: taken by mouth as a single capsule once daily x 52 weeks

Overview of Key Efficacy Assessments

Note: All endpoints will evaluate subjects on ozanimod 0.92 mg and placebo at Week 52 unless otherwise specified. Baseline is defined as Day 1 in the Induction Study.

Primary Endpoints:

- Proportion of subjects with CDAI score < 150 at Week 52
- Proportion of subjects with Simple Endoscopic Score for Crohn's Disease (SES-CD) decrease from baseline ≥ 50% at Week 52

Key Secondary Endpoints:

- Proportion of subjects with CDAI reduction from baseline ≥ 100 points or CDAI score < 150 at Week 52
- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than baseline at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52, while remaining corticosteroid free in the 12 weeks prior to Week 52, among all subjects at Maintenance Day 1
- Proportion of subjects with CDAI score < 150 at Week 52 in subjects with CDAI score < 150 at Maintenance Day 1
- Proportion of subjects with SES-CD ≤ 4 points and SES-CD decrease from baseline ≥ 2 points with no SES-CD subscore > 1 point at Week 52

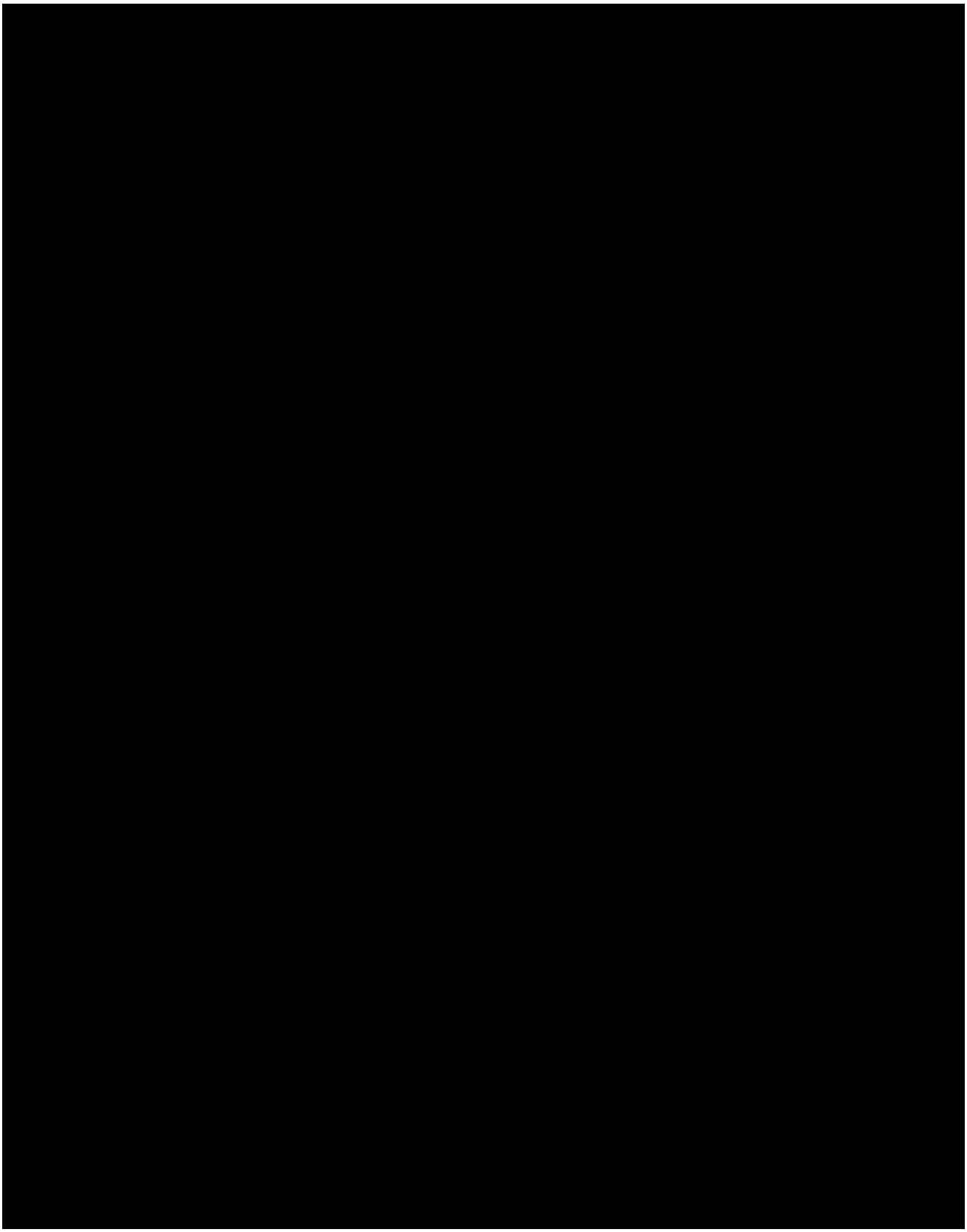
Note: Final ranking of key secondary endpoints may vary by region and will be defined in the SAP.

Additional Secondary Endpoints:

- Proportion of subjects with CDAI score < 150 and SES-CD decrease from baseline ≥ 50% at Week 52

- Proportion of subjects with average daily abdominal pain score ≤ 1 point, and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD ≤ 4 points and SES-CD decrease ≥ 2 points with no SES-CD subscore > 1 point at Week 52
- Proportion of subjects with CDAI reduction from baseline ≥ 100 points or CDAI score < 150 and SES-CD decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI score < 150 at Maintenance Day 1 and SES-CD decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI reduction from baseline ≥ 70 points at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52, while remaining corticosteroid free in the 12 weeks prior to Week 52 among subjects using corticosteroids at Maintenance Day 1
- Proportion of subjects with mucosal healing (SES-CD ≤ 4 points and SES-CD decrease ≥ 2 points with no SES-CD subscore > 1 point) and histologic improvement based on Robarts Histologic Index (RHI) at Week 52
- Time to relapse (an increase in CDAI score from Maintenance Day 1 ≥ 100 points and CDAI score > 220, SES-CD ≥ 6 [or ≥ 4 if isolated ileal disease]), and exclusion of other causes of an increase in disease activity unrelated to underlying CD (eg, infections, change in medication)
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52 and at ≥ 80% of visits between Week 8 and Week 52, inclusive, in subjects with CDAI score < 150 at Maintenance Day 1
- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD decrease from baseline ≥ 50% at Week 52

[redacted]



Overview of Safety Assessments

The incidence, severity, relationship, and type of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation of IP, and AEs of special interest (AESIs) will be summarized, as well as clinically meaningful changes from baseline for clinical laboratory measures, vital signs, and electrocardiograms (ECGs).

Statistical Methods

Analysis Populations

This is a Phase 3, randomized, blinded, placebo-controlled study to demonstrate the effect of oral ozanimod as maintenance therapy in subjects with moderately to severely active CD. The following analysis populations will be used in the statistical analysis:

- Intent-to-Treat (ITT): The ITT analysis population will consist of all randomized subjects from the Screened analysis population that receive at least 1 dose of IP. Subjects in the ITT analysis population will be analyzed according to the randomized treatment, regardless of the treatment actually given. The primary analysis population for all efficacy endpoints will be the ITT analysis population.
- Safety: The safety analysis population is defined as all subjects who are randomized and receive at least one dose of study treatment, analyzed by actual treatment received.

Determination of Enrolled Sample Size

It is estimated that approximately 550 adult subjects from RPC01-3201 and RPC01-3202 will be enrolled in the study, with approximately 410 subjects having received ozanimod in the Induction Studies. The subjects who had received ozanimod during the Induction Studies will be randomly assigned to receive ozanimod 0.92 mg or placebo in a 1:1 ratio. Subjects in response after receiving placebo in either RPC01-3201 or RPC01-3202 will continue to receive placebo in a blinded fashion. Section 9.3 presents a detailed discussion of the needed sample size to properly power the randomized component of this study, and a comparison to the approximately 410 subjects available for randomization is made.

Efficacy Analysis

For the primary analysis of responder/remitter endpoints, subjects who have insufficient data for response/remission determination for the time point under consideration will be considered non-responders/non-remitters for that time point. Sensitivity analyses, missing data imputation, and continuous endpoint efficacy analysis are discussed in the statistical analysis plan (SAP).

The primary analysis of the primary and key secondary endpoints with binary measure (eg, yes/no) such as clinical remission and clinical response at Week 52 will be carried out using the Cochran-Mantel-Haenszel (CMH) method. The stratifying factors of clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no) will be accounted for in the CMH analyses. Details regarding risk differences, odds ratios, confidence limits, and considerations for sensitivity analyses will be provided in the separate SAP.

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1 INTRODUCTION

1.1 Disease Background

Crohn's disease (CD) is an immune-mediated inflammatory disease of the gastrointestinal (GI) tract. Annual incidence varies geographically, with estimates ranging from 3.1 to 14.6 per 100,000 people in the United States and from 0.1 to 16 per 100,000 worldwide (Lakatos, 2006). Subjects with CD suffer from diarrhea, rectal bleeding, weight loss, abdominal pain, and fever. CD is characterized by a lifelong chronic course of remissions and exacerbations. The pathology of this disease is characterized by transmural infiltration of lymphocytes and macrophages, granulomas, fissuring ulceration, and submucosal fibrosis. The transmural inflammatory process of CD predisposes subjects to the formation of fistulas and it has been estimated that approximately 35% of subjects will have at least 1 fistula during the course of their disease (Schwartz, 2002). In a recent study, within 10 years of diagnosis, 50% of adults with CD had undergone bowel surgery (Peyrin-Biroulet, 2010).

The current standard of medical care for patients with moderately to severely active CD consists of anti-inflammatory approaches, such as corticosteroids, azathioprine (AZA)/6-mercaptopurine (6-MP), methotrexate (MTX), and biologics such as anti-tumor necrosis factor (TNF)α, anti-interleukin (IL)-12/IL-23, or anti-integrins.

Immunomodulators aid in corticosteroid withdrawal and in preventing relapse, but also are associated with considerable side effects. Infliximab, an anti-TNFα-therapy, is able to reduce signs and symptoms and induce and maintain remission in the majority of subjects for which it is indicated. However, in a large Phase 3 maintenance trial of infliximab for CD (ACCENT I), only 45% of subjects were considered in remission at Week 30 in the highest dose group (where remission was defined as the ability to achieve a Crohn's Disease Activity Index [CDAI] of < 150 points) (Hanauer, 2002). Similarly, the primary response rates in trials of adalimumab (Colombel, 2007) and certolizumab (Sandborn, 2007) were approximately 47% and 37%, respectively. Thus, a sizable proportion of the patient population is unresponsive to both conventional therapy and TNF antagonists. Vedolizumab, a gut-specific anti-integrin therapy, is also indicated for achieving clinical response and clinical remission in this population. However, in a large clinical trial of vedolizumab, only 32% of subjects had a clinical response at Week 6, and only 39% receiving vedolizumab every 8 weeks were in remission at Week 52 (Sandborn, 2013). Ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, was approved for the treatment of patients who failed or were intolerant to treatment with immunomodulators, corticosteroids, or 1 or more TNF antagonists. However, in the induction trials of ustekinumab, only 32% of subjects were responders at 6 weeks (Feagan, 2016), and about 40% were in remission at Week 52 of the maintenance trial.

Therefore, there remains a considerable unmet medical need for safe and effective oral treatments for patients with CD.

1.2 Compound Background

Ozanimod is a small molecule compound which selectively binds with high affinity to sphingosine 1-phosphate receptors 1 and 5 ($S1P_1$ and $S1P_5$). In vitro, ozanimod has little activity on the other

sphingosine-1-phosphate (S1P) receptors, showing half maximal effective concentration (EC_{50}) greater than 10,000 nM for $S1P_2$, > 5000 nM for $S1P_3$, and > 2000 nM for $S1P_4$. Ozanimod is extensively metabolized in humans with up to 13 metabolites identified in plasma, urine, and feces, including 2 active selective major metabolites and 1 inactive major metabolite found in human plasma at steady state. The 2 active metabolites (CC112273 and CC1084037) have similar structures to ozanimod and similar selectivity across the S1P receptor family.

Many cell types express $S1P_1$, including vascular endothelial cells, brain cells, and lymphocytes. Stimulation (agonism) of this receptor results in biological activities that includes lymphocyte retention in peripheral lymphoid organs (eg, lymph nodes and GI Peyer's patches), resulting in reversible systemic reduction in circulating lymphocytes (Mandala, 2002). Given the immune-mediated inflammation in CD, prevention of circulation of disease-exacerbating, self-reactive lymphocytes to the gut is likely to have salutary immunomodulatory effects with a consequent dampening of disease processes.

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

1.2.1 Summary of Nonclinical Studies

The nonclinical safety assessment for ozanimod included repeated dose toxicity (rodent and non-rodent), genotoxicity, carcinogenicity, reproductive and developmental toxicity, phototoxicity, and immunotoxicology studies.

The majority of the findings in the chronic toxicology studies, the carcinogenicity studies, and the reproductive toxicology studies are considered target mediated effects of $S1P_1$ and $S1P_5$ agonists. These include peripheral blood lymphopenia, lymphoid depletion in the splenic periarteriolar lymphoid sheaths and decreased thymic cortical lymphocytes. The activity of ozanimod and the characterized metabolites was evaluated in in vitro and in vivo pharmacology assays. Two mouse models of IBD, naïve T-cell adoptive transfer and 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, demonstrated significant reduction in disease severity scores as evidenced by colon weight and length measurements, and histopathology. Improvement in disease parameters correlated with lymphocyte count reduction with statistically significant effects observed when lymphocyte counts were decreased by [redacted] or more.

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.2.2 Summary of Clinical Studies in Inflammatory Bowel Disease

1.2.2.1 Ulcerative Colitis

Ozanimod has been studied in subjects with active ulcerative colitis (UC) in a Phase 2 study (RPC01-202) and a Phase 3 global study (RPC01-3101). It is being studied in a Phase 2/3 study in Japan (RPC01-3103) and the global Phase 3 open-label extension (OLE) (RPC01-3102).

At the conclusion of the Induction Phase of RPC01-202, the proportion of patients achieving clinical response and clinical remission with ozanimod 0.92 mg was greater than placebo and the

difference was both clinically meaningful and statistically significant. In addition, all secondary endpoints at the conclusion of the Induction Phase, including clinical response, the change in Mayo score, and mucosal improvement on endoscopy, were also positive and statistically significant for the ozanimod 0.92 mg dose. The overall AE profile in the induction and maintenance periods appeared comparable between the ozanimod dose groups and placebo, with no concerning safety signals observed.

RPC01-202 also had a maintenance period and an OLE period. Treatment with ozanimod 0.92 mg in the OLE period demonstrated efficacy in the endpoints of clinical remission, clinical response, histological remission, and mucosal healing in a substantial proportion of subjects. Decreases in partial Mayo scores and complete Mayo scores during the induction and maintenance periods were maintained throughout the OLE period. Correspondingly, individual Mayo subscores of stool frequency, rectal bleeding, physician's global assessment score, and endoscopy showed improvement with ozanimod 0.92 mg treatment throughout the OLE period. The safety and tolerability results from the UC RPC01-202 Phase 2 study suggest that ozanimod at doses of 0.46 and 0.92 mg daily for 32 weeks are well tolerated and have an acceptable safety profile in subjects with moderately to severely active UC (Sandborn, 2016).

RPC01-3101, a Phase 3 study in adult subjects with moderate to severe UC met both primary endpoints, demonstrating highly statistically significant (p-value < 0.0001) results for clinical remission in induction at Week 10 and in maintenance at Week 52 (Sandborn, 2021). All 3 key secondary endpoints in the Induction Period (clinical response, endoscopic improvement, and mucosal healing), and all 6 key secondary endpoints in the Maintenance Period (clinical response, endoscopic improvement, maintenance of remission, corticosteroid-free remission, mucosal healing, and durable clinical remission) were achieved by a statistically significantly greater proportion of subjects in the ozanimod 0.92 mg treatment group compared with placebo. The treatment effects for the primary and key secondary endpoints consistently supported a favorable treatment effect for ozanimod in multiple demographics, prior and concomitant medication, disease characteristics, and geographic subgroups.

1.2.2.2 Crohn's Disease

RPC01-2201, a Phase 2 study was conducted in CD to examine endoscopic and clinical outcomes following treatment with ozanimod 0.92 mg daily for 12 weeks. Simple Endoscopic Score for Crohn's Disease (SES-CD) reductions of ≥ 50% from baseline were seen in 28.6% of subjects (observed cases) as measured by paired segments, with greater endoscopic response in subjects with baseline SES-CD score ≤ 12 and a shorter disease duration. At Week 52, the proportion of subjects achieving reductions of ≥ 50% was maintained at 26.7%. Clinical response was seen in 68.5% and 93.8% of subjects (observed cases) at Week 12 and Week 52, respectively. Clinical remission was seen in 46.3% and 65.6% of subjects (observed cases) at Week 12 and Week 52, respectively. [redacted]

The safety and tolerability results from the 12-week Induction Period of RPC01-2201 suggest that ozanimod 0.92 mg daily is well tolerated and has an acceptable safety profile in subjects with

moderately to severely active CD. In the open-label period (OLP), ozanimod 0.92 mg was well tolerated and there were no new safety concerns. The AEs reported in the study were generally consistent with those seen in subjects with moderately to severely active UC. [redacted]

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.2.3 Rationale for Dose Selection

Results from Phase 1 single-ascending dose and multiple ascending dose studies were utilized to select appropriate doses for Phase 2 studies. The Phase 2 trial of ozanimod in UC was conducted comparing 0.92 mg and 0.46 mg of ozanimod with placebo. Safety was comparable across both ozanimod arms, and the 0.92 mg/day dose arm demonstrated better efficacy as compared to the 0.46 mg/day dose arm across various clinical and endoscopic endpoints (Sandborn, 2016). Results suggested a dose dependent efficacy response, making 0.92 mg more favorable for future investigation.

The favorable clinical results and the available safety data from the Phase 2 and Phase 3 UC studies as described above, as well as supportive clinical and safety data from the completed relapsing multiple sclerosis (RMS) program, provide additional data to support use of the 0.92 mg dose of ozanimod. Data from 52 weeks of treatment (RPC01-2201) demonstrated that subjects with active CD treated with ozanimod 0.92 mg experienced efficacious clinical, endoscopic, histologic [redacted] treatment responses with a comparable safety profile to subjects previously evaluated with ozanimod. The overall data supported evaluating the 0.92 mg dose in the ozanimod Crohn's disease program.

A dose-escalation regimen over the first 7 days is being utilized to mitigate the magnitude of heart rate reduction as a result of supportive data from the Phase 1 study (RPCS 001) and preliminary results from the Phase 2 UC study (RPC01-202). Preliminary evidence from these studies suggests a lower likelihood of profound decrease in heart rate or blood pressure in subjects who increase their dose progressively over the first week. A dose escalation starting with 0.23 mg of ozanimod for the first 4 days of dosing followed by 0.46 mg on Days 5 through 7 before progressing to the 0.92 mg/day dose will be used.

Please refer to the IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.3 Study Rationale

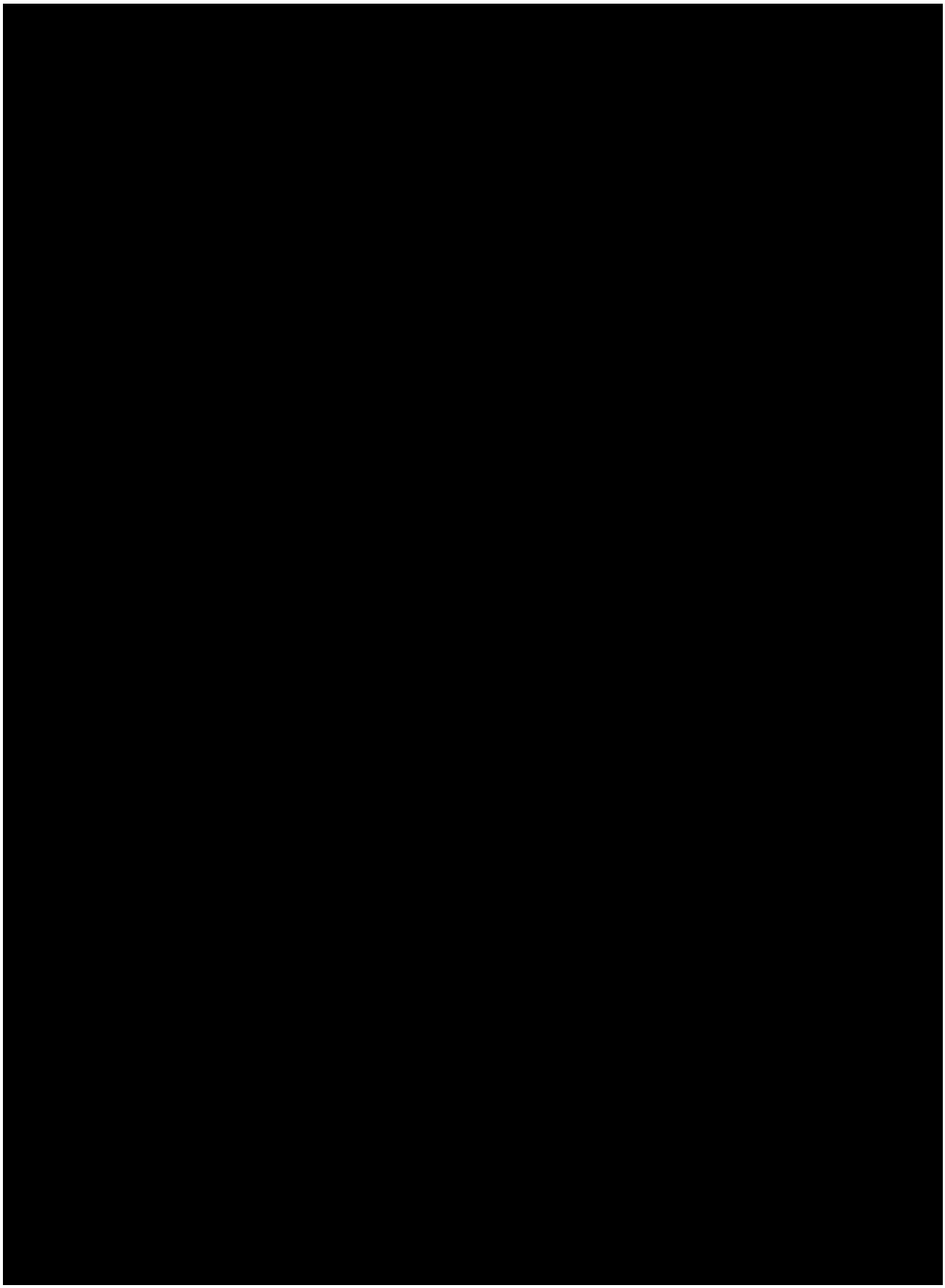
Given the mechanism of action of ozanimod, data from the preclinical animal model, the positive results from the Phase 2 UC study, RPC01-202, and preliminary results from the Induction Period of the Phase 2 study in CD, RPC01-2201, a Phase 3 program with ozanimod in CD was initiated.

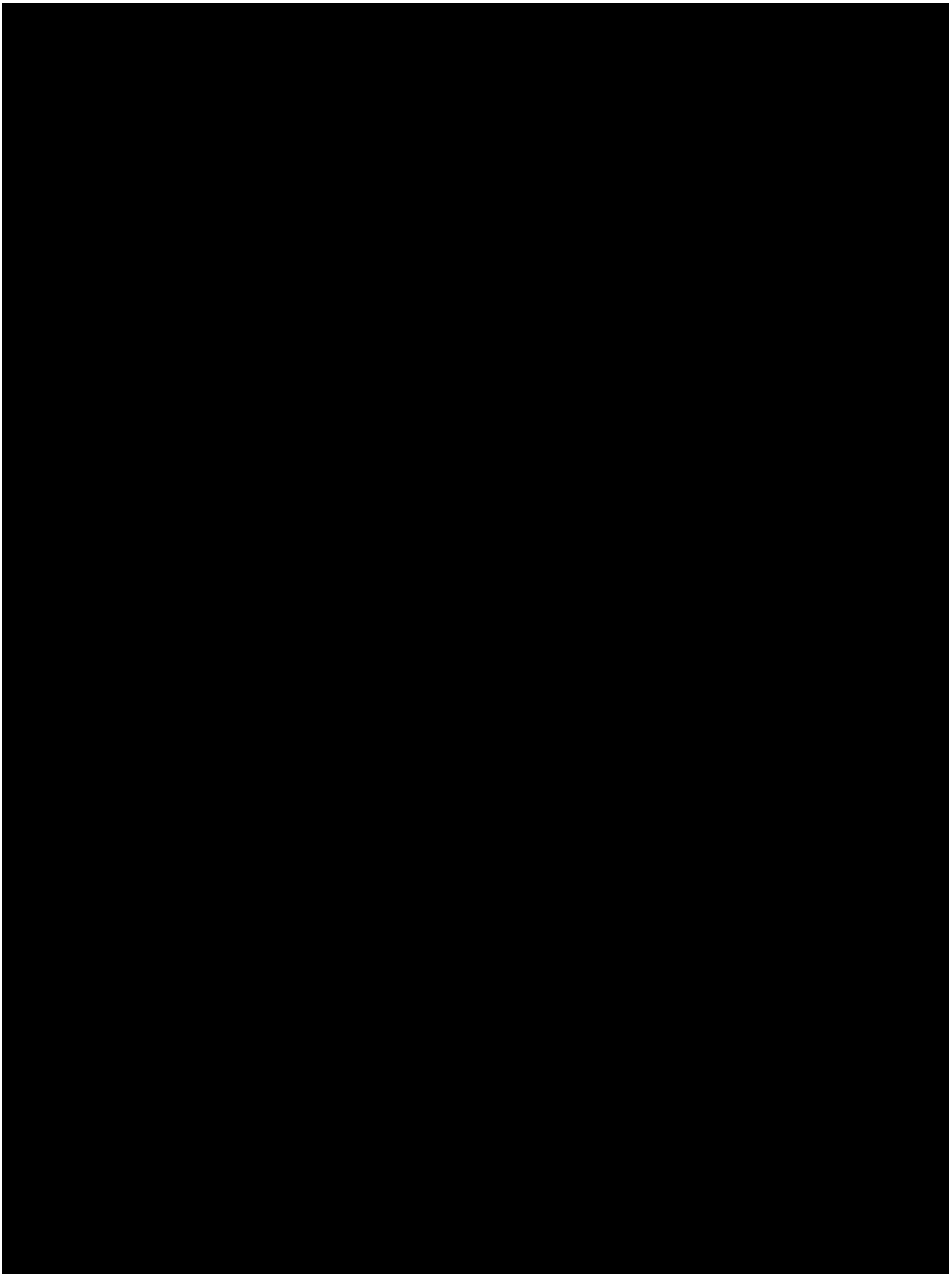
The current study, designed as a randomized, double-blind, placebo-controlled study, will assess whether ongoing treatment with ozanimod is required and effective in maintaining clinical remission (CDAI score < 150) and clinical response (CDAI reduction from baseline ≥ 100 points or CDAI score < 150) in subjects who have previously responded to ozanimod. All subjects who lose response will be offered treatment with ozanimod in an OLE Study. Primary efficacy assessment of ozanimod 0.92 mg per day for maintenance will be assessed at Week 52 in subjects who achieve clinical response after 12 weeks of treatment in the Induction Studies. Week 52 is selected based on the efficacy results seen in the RPC01-2201 after 12 weeks of treatment with ozanimod 0.92 mg daily and the time needed to evaluate maintenance of clinical remission. Safety of treatment with ozanimod for 64 weeks will be examined in subjects who complete both the Induction and Maintenance Studies.

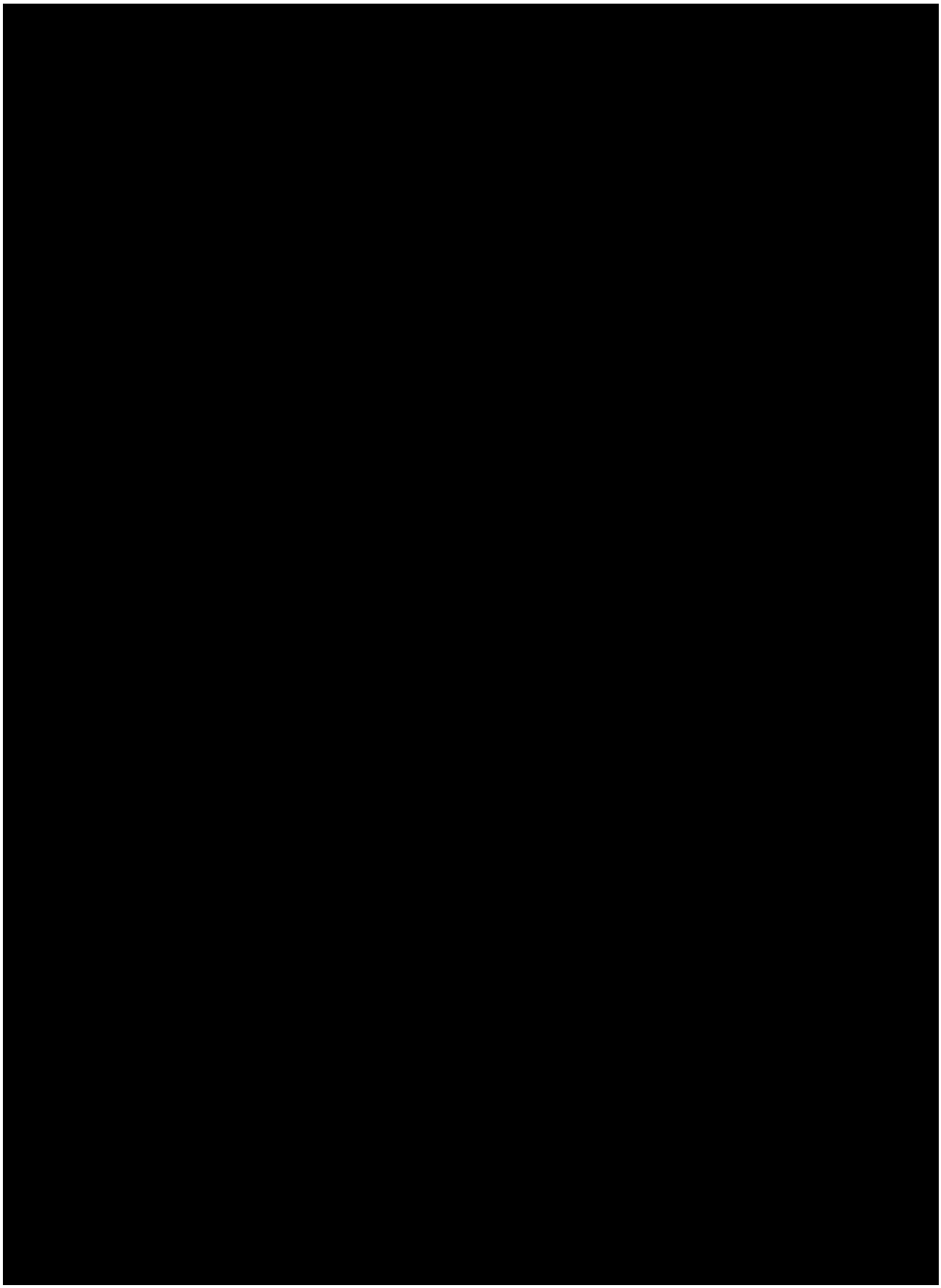
1.4 Risk/Benefit Assessment

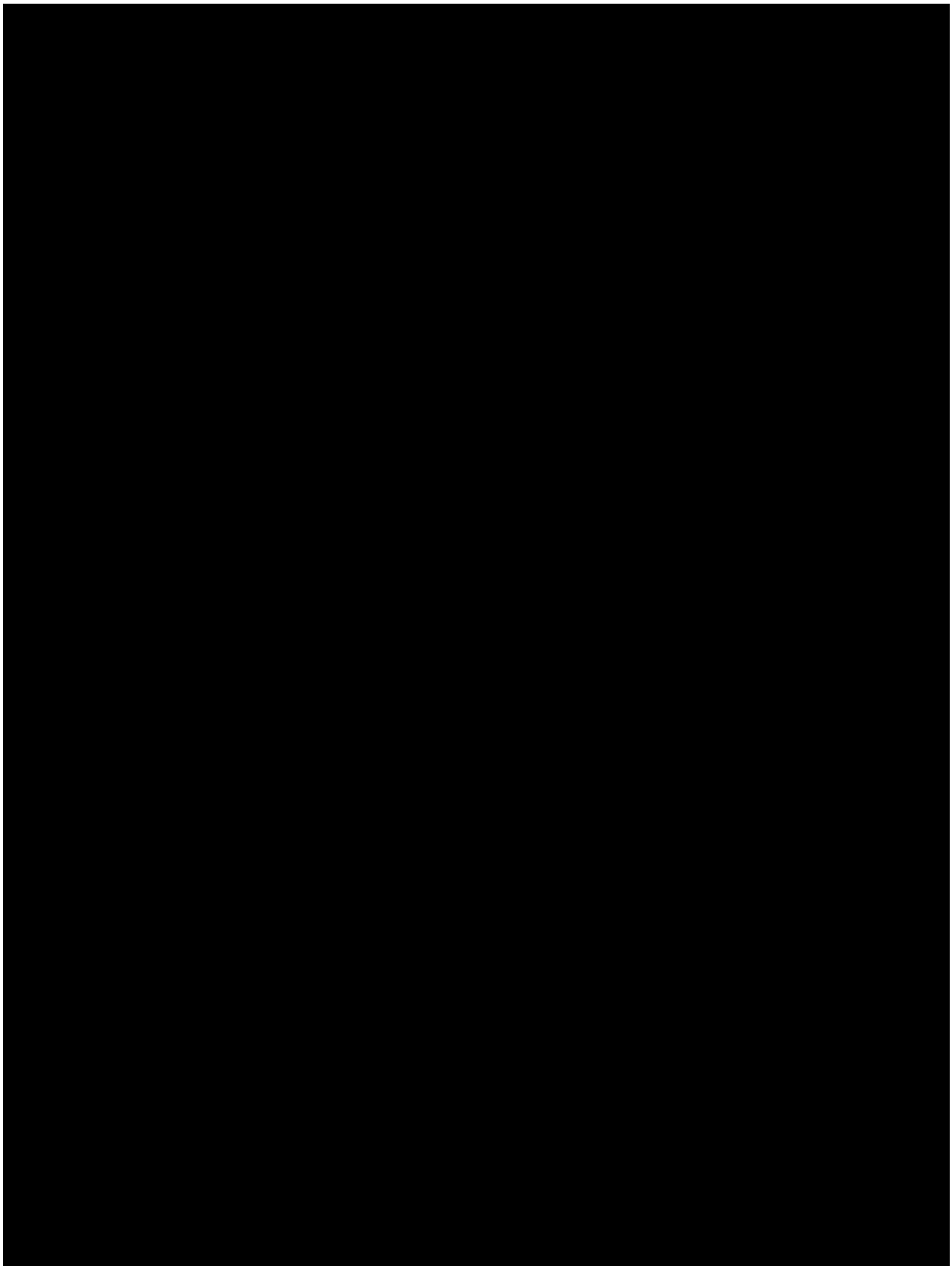
The assessment of potential risks for identified safety findings, as well as the risk mitigations, are summarized in the table below. More detailed information about the known and expected benefits and risks and reasonably anticipated adverse events (AEs) of ozanimod may be found in the IB.

Individual risk/benefit considerations remain the responsibility of the investigator. Investigators should apply clinical judgment and these risks should be considered when managing a subject and when deciding if continuation of treatment with ozanimod is warranted.









1.4.2 Benefit Assessment

The benefit in UC is established. See Section 1.2.2.1 for details. Preliminary results from a non-controlled Phase 2 trial in CD indicated that subjects derived clinical and endoscopic benefit from treatment with ozanimod. See Section 1.2.2.2 for details.

1.4.3 Overall Risk/Benefit Conclusion

Despite recent progress in CD treatment, there remains an unmet need for agents that are safe and convenient oral treatments and can provide effective induction and long-term maintenance of clinical remission. The risk/benefit profile for ozanimod has been evaluated for the indication of CD. Results from subjects with moderate to severe disease who previously failed prior therapy and were treated with ozanimod 0.92 mg daily for at least 12 weeks suggested clinical and endoscopic benefit. In addition, the safety results suggest that ozanimod is well tolerated in patients with CD and is consistent with that observed in other patient populations (UC and RMS). The overall data to date suggest that this ozanimod Maintenance Study (RPC01-3203) has a potential favorable risk/benefit profile for patients with active CD who have achieved clinical response after 12 weeks of treatment.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective:

- Demonstrate the efficacy of ozanimod compared to placebo on the maintenance of clinical remission and endoscopic response

2.1.2 Secondary Objectives:

- Demonstrate the efficacy of ozanimod compared to placebo on maintenance of clinical response
- Demonstrate the efficacy of ozanimod compared to placebo on maintenance of endoscopic remission and mucosal healing
- Demonstrate the efficacy of ozanimod, compared to placebo, in achieving corticosteroid-free clinical remission
- Demonstrate the efficacy of ozanimod, compared to placebo, on healthcare resource utilization (HRU), subject-reported outcomes, and quality of life
- Demonstrate the safety and tolerability of ozanimod as maintenance therapy

2.2 Study Endpoints

Note: All endpoints will evaluate subjects on ozanimod 0.92 mg and placebo at Week 52 unless otherwise specified. Baseline is defined as Day 1 in the Induction Study.

2.2.1 Primary Endpoints:

- Proportion of subjects with CDAI score < 150 at Week 52
- Proportion of subjects with SES-CD decrease from baseline ≥ 50% at Week 52

2.2.2 Key Secondary Endpoints:

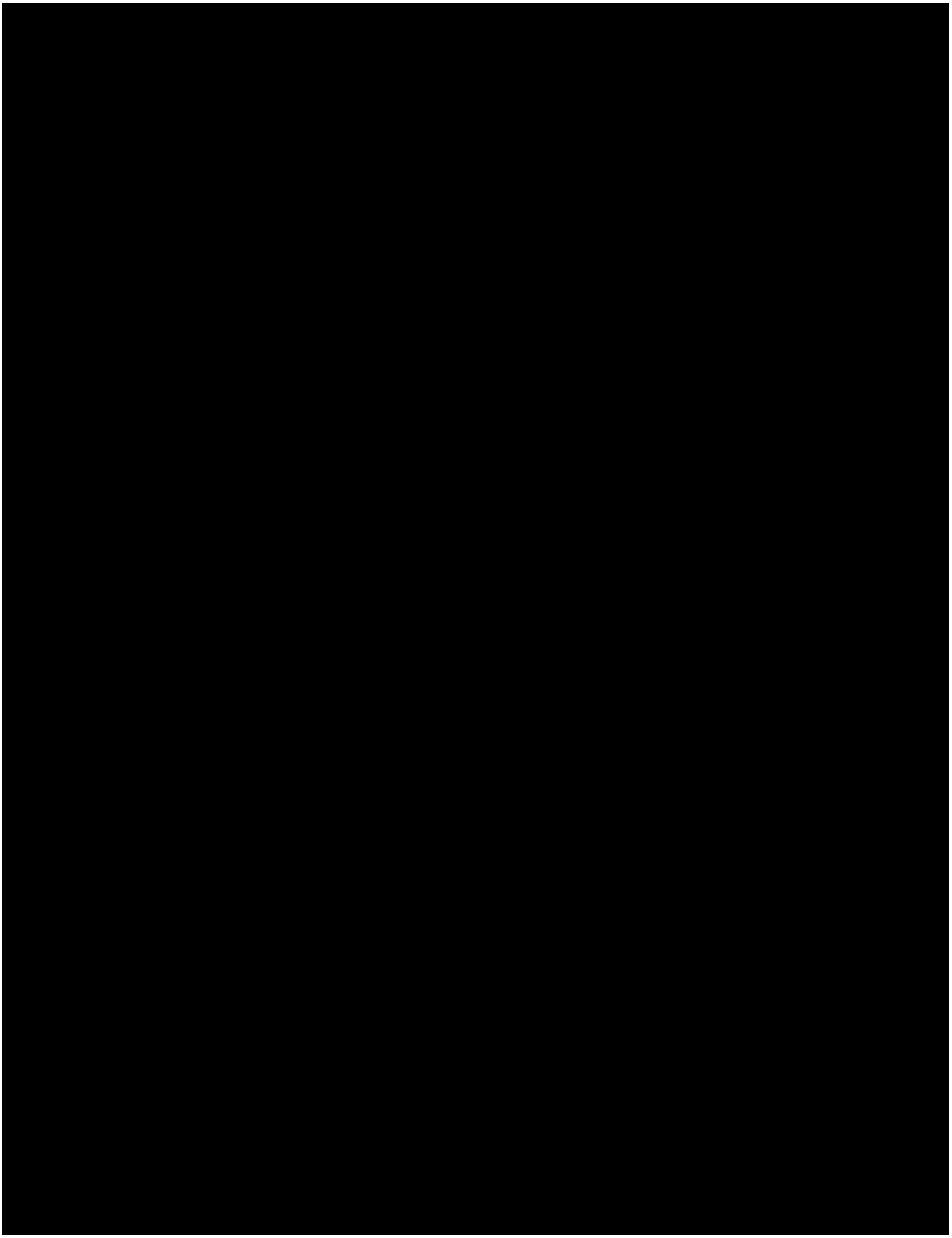
- Proportion of subjects with CDAI reduction from baseline ≥ 100 points or CDAI score < 150 at Week 52
- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than baseline at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52, while remaining corticosteroid free in the 12 weeks prior to Week 52 among all subjects at Maintenance Day 1
- Proportion of subjects with CDAI score < 150 at Week 52 in subjects with CDAI score < 150 at Maintenance Day 1
- Proportion of subjects with SES-CD ≤ 4 points and SES-CD decrease from baseline ≥ 2 points with no SES-CD subscore > 1 point at Week 52

Note: Final ranking of key secondary endpoints may vary by region and will be defined in the SAP.

2.2.3 Additional Secondary Endpoints:

- Proportion of subjects with CDAI score < 150 and SES-CD decrease from baseline ≥ 50% at Week 52

- Proportion of subjects with average daily abdominal pain score ≤ 1 point, and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD ≤ 4 points and SES-CD decrease ≥ 2 points with no SES-CD subscore > 1 point at Week 52
- Proportion of subjects with CDAI reduction from baseline ≥ 100 points or CDAI score < 150 and SES-CD decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI score < 150 at Maintenance Day 1 and SES-CD decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI reduction from baseline ≥ 70 points at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52, while remaining corticosteroid free in the 12 weeks prior to Week 52 among subjects using corticosteroids at Maintenance Day 1
- Proportion of subjects with mucosal healing (SES-CD ≤ 4 points and SES-CD decrease ≥ 2 points with no SES-CD subscore > 1 point) and histologic improvement based on Robarts Histologic Index (RHI) at Week 52
- Time to relapse (an increase in CDAI score from Maintenance Day 1 ≥ 100 points and CDAI score > 220, SES-CD ≥ 6 [or ≥ 4 if isolated ileal disease]), and exclusion of other causes of an increase in disease activity unrelated to underlying CD (eg, infections, change in medication)
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline ≥ 50% at Week 52
- Proportion of subjects with CDAI score < 150 at Week 52 and at ≥ 80% of visits between Week 8 and Week 52, inclusive, in subjects with CDAI score < 150 at Maintenance Day 1
- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD decrease from baseline ≥ 50% at Week 52



2.2.7 Overview of Safety Assessments

The incidence, severity, relationship, and type of treatment-emergent adverse events (TEAEs), serious adverse event (SAEs), AEs leading to discontinuation of IP (see Section 14), and AESIs will be summarized, as well as clinically meaningful changes from baseline for clinical laboratory measures, vital signs, and electrocardiograms (ECGs).

3 OVERALL STUDY DESIGN

3.1 Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to demonstrate the effect of oral ozanimod as maintenance therapy in subjects with moderately to severely active CD. Subjects who complete the initial 12 weeks of treatment (Induction Studies RPC01-3201 or RPC01-3202) and are in clinical response (CDAI reduction from baseline ≥ 100 points or CDAI score < 150), and/or clinical remission (CDAI score < 150 points), and/or have an average daily stool frequency score ≤ 3 and an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline will be eligible to participate in the Maintenance Study.

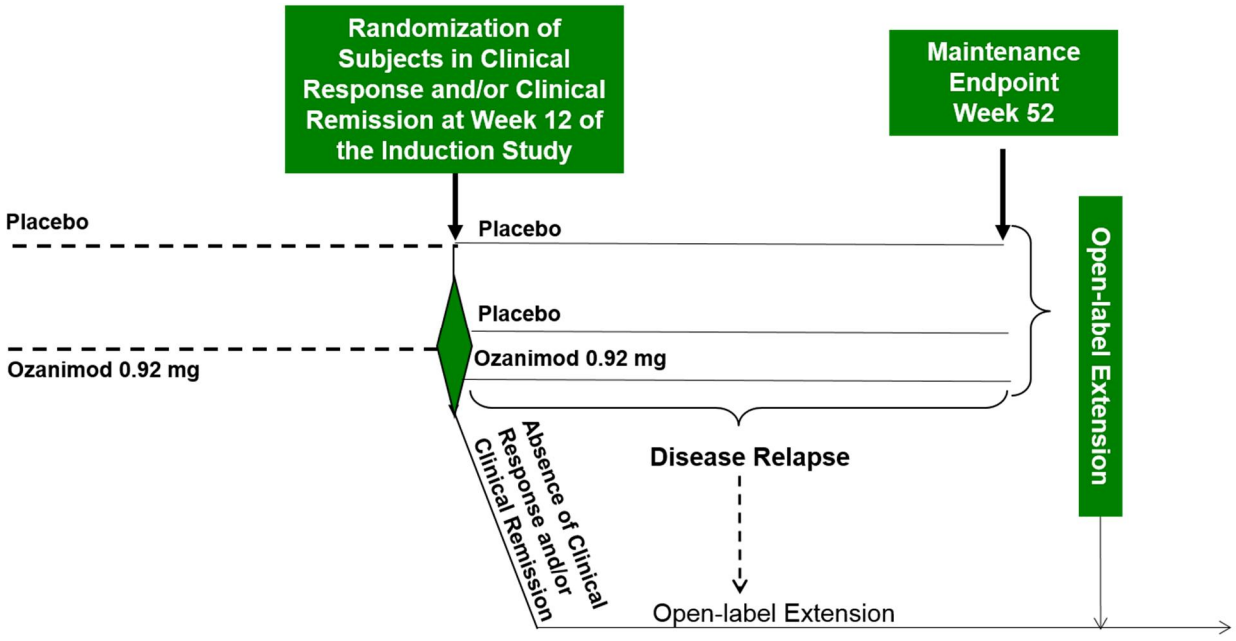
The total number of subjects enrolled (estimated at 550) will be determined based on how many subjects are eligible from the Induction Studies and choose to continue to the Maintenance Study. Approximately 410 subjects who received ozanimod in either RPC01-3201 or RPC01-3202 (Induction Studies) and are in clinical remission, clinical response, and/or have an average daily stool frequency score ≤ 3 with an average abdominal pain score ≤ 1 and abdominal pain and stool frequency no worse than baseline by Week 12, are expected to enroll in this study. For additional details see Section 4.1. Subjects who received ozanimod in the Induction Studies will be randomly assigned to receive ozanimod or placebo in a 1:1 ratio. Subjects will be stratified by clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no).

In addition, subjects who meet the criteria for the Maintenance Study (RPC01-3203) after receiving placebo in either RPC01-3201 or RPC01-3202 will continue to receive placebo in a blinded fashion.

Subjects will be assessed for disease activity through Week 52 of the RPC01-3203 study. Subjects who experience disease relapse in the RPC01-3203 study (see Section 14.2) and all subjects who complete the RPC01-3203 study will be eligible to enter the OLE Study (RPC01-3204).

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

Figure 1: Overall Study Design



Note: Subjects who meet the criteria for the Maintenance Study (RPC01-3203) at Week 12 of the Induction Study who were randomized to placebo will continue to receive placebo in the Maintenance Study in a double-blind manner. Only subjects assigned to ozanimod in the Induction Study will be randomized into ozanimod or placebo when entering the Maintenance Study. Refer to Section 3.1.

3.2 Study Duration for Subjects

Subjects who complete the Maintenance Study are anticipated to receive 64 weeks of treatment (12-week Induction Study + 52-week Maintenance Study). Subjects not entering the OLE Study will have [redacted].

3.3 End of Study

The end of study (Maintenance Study RPC01-3203) is defined as either the date of the last visit of the last subject to complete the [redacted], or the date of receipt of the last data point from the last subject that is required for primary or secondary analysis, as pre-specified in the protocol, whichever is the later date. If the Sponsor discontinues the Maintenance Study prior to the planned end of study, active subjects will be considered completers of the study and may be eligible to enroll in the Open-Label Extension Study (RPC01-3204).

4 STUDY POPULATION

4.1 Number of Subjects

The total number of subjects enrolled (estimated at 550) will be determined based on how many subjects are eligible from the Induction Studies and choose to continue to the Maintenance Study. Approximately 410 subjects who were allocated to receive ozanimod in either RPC01-3201 or RPC01-3202 and are in clinical remission, clinical response, and/or have an average daily stool frequency score ≤ 3 with an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline by Week 12 are estimated to be randomized to receive ozanimod or placebo in a 1:1 ratio. Subjects in clinical remission and/or clinical response after receiving placebo in either RPC01-3201 or RPC01-3202 will continue to receive placebo in a blinded fashion.

4.2 Inclusion Criteria

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

1. Subject fulfilled the inclusion criteria at time of entry into the Induction Study (RPC01-3201 or RPC01-3202) and has completed the Week 12 efficacy assessments of the Induction Study.
2. Subject should not have any constraints under local regulations, must provide written informed consent prior to any study-related procedures, and must have the ability to comply [redacted].
3. Subject is in clinical response (a reduction from baseline in CDAI ≥ 100 points or CDAI score < 150 points) and/or clinical remission (CDAI score < 150 points) and/or has an average daily stool frequency score ≤ 3 and an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline at Week 12 of the Induction Study.
4. Female subjects of childbearing potential (FCBP):

   Note: For the purposes of this study, a female subject is considered to be of childbearing potential if she 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

   Must agree to practice a highly effective method of contraception throughout the study until completion of the [redacted]. 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. Examples of acceptable methods of birth control in the study are the following:

   - combined hormonal (containing oestrogen and progestogen) contraception, which may be oral, intravaginal, or transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
   - placement of an intrauterine device (IUD)
   - placement of an intrauterine hormone-releasing system (IUS)

- bilateral tubal occlusion
- vasectomized partner
- complete sexual abstinence

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for FCBP. [redacted]

4.3 Exclusion Criteria

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

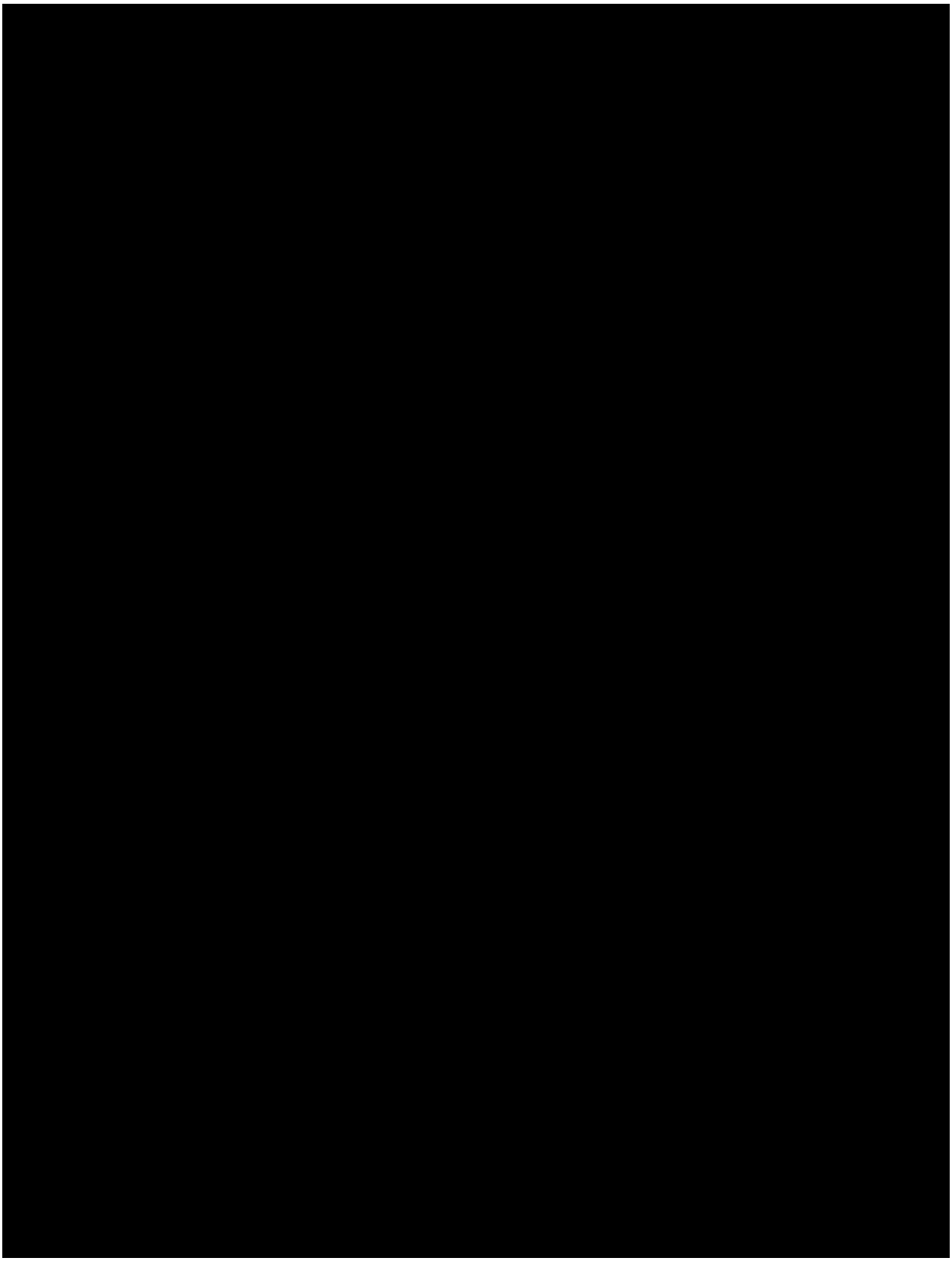
4.3.1 Exclusions Related to General Health:

1. Subject has any clinically relevant cardiovascular, hepatic, neurological, pulmonary (severe respiratory disease [pulmonary fibrosis or chronic obstructive pulmonary disease]), ophthalmological, endocrine, psychiatric, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study. In France, hypotension is exclusionary if it makes the implementation of the protocol or interpretation of the study difficult or would put the subject at risk by participating in the study.
2. Subject is pregnant, lactating, or has a positive urine beta human chorionic gonadotropin (β-hCG) test measured prior to randomization.
3. Subject has suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated.
4. Subject has undergone a colectomy (partial or total), small bowel resection, or an ostomy (ie, temporary colostomy, permanent colostomy, ileostomy, or other enterostomy) since Day 1 of the Induction Studies or has developed symptomatic fistula (enterocutaneous or entero-enteral).
5. Subject has had cancer within 5 years including solid tumors and hematological malignancies (except basal cell and in situ squamous cell carcinomas of the skin or cervical dysplasia/cancer that have been excised and resolved); or colonic dysplasia that has not been completely removed.

4.3.2 Exclusions Related to Medications:

6. Hypersensitivity to active ingredients or excipients of ozanimod or placebo

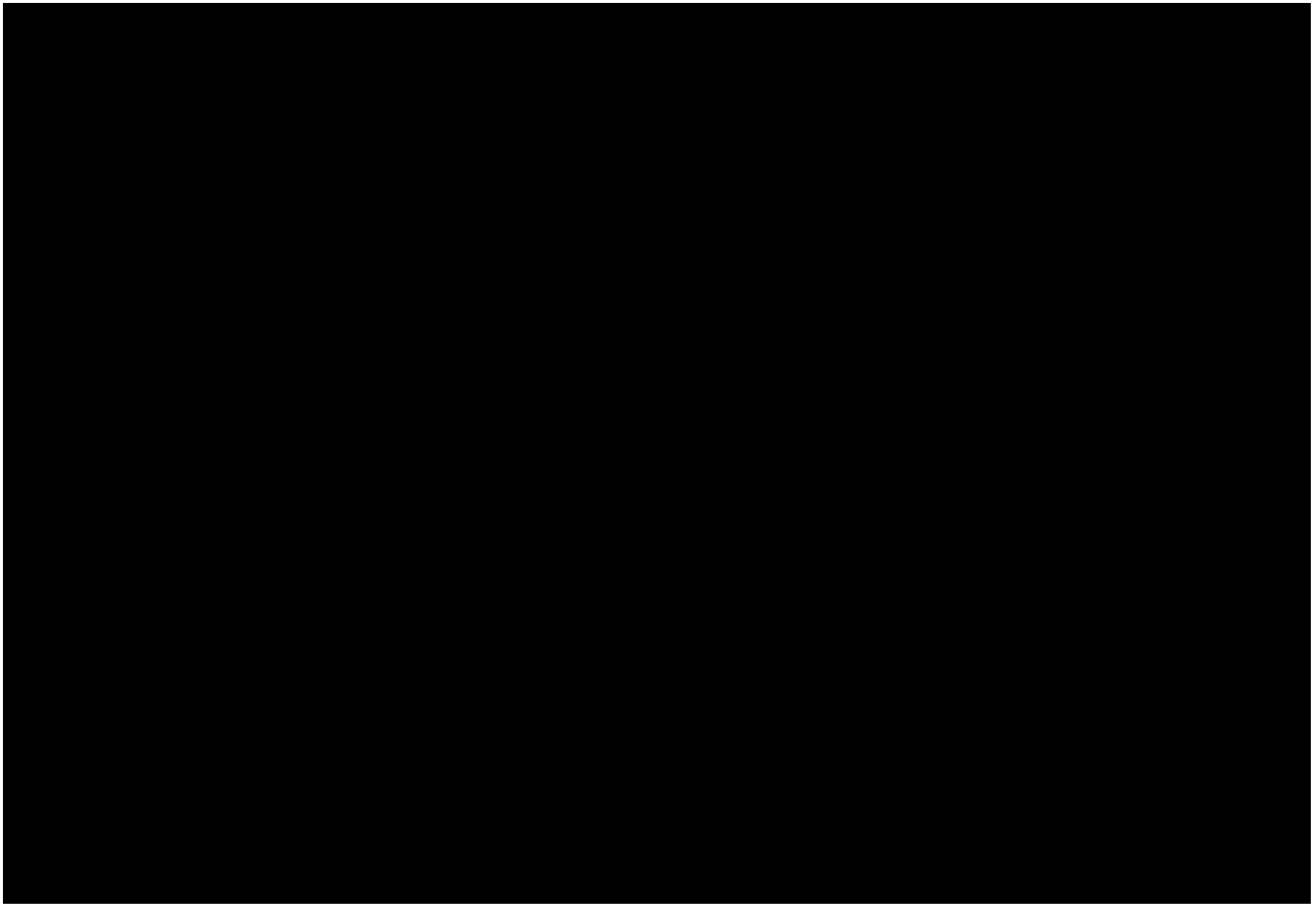
[redacted]

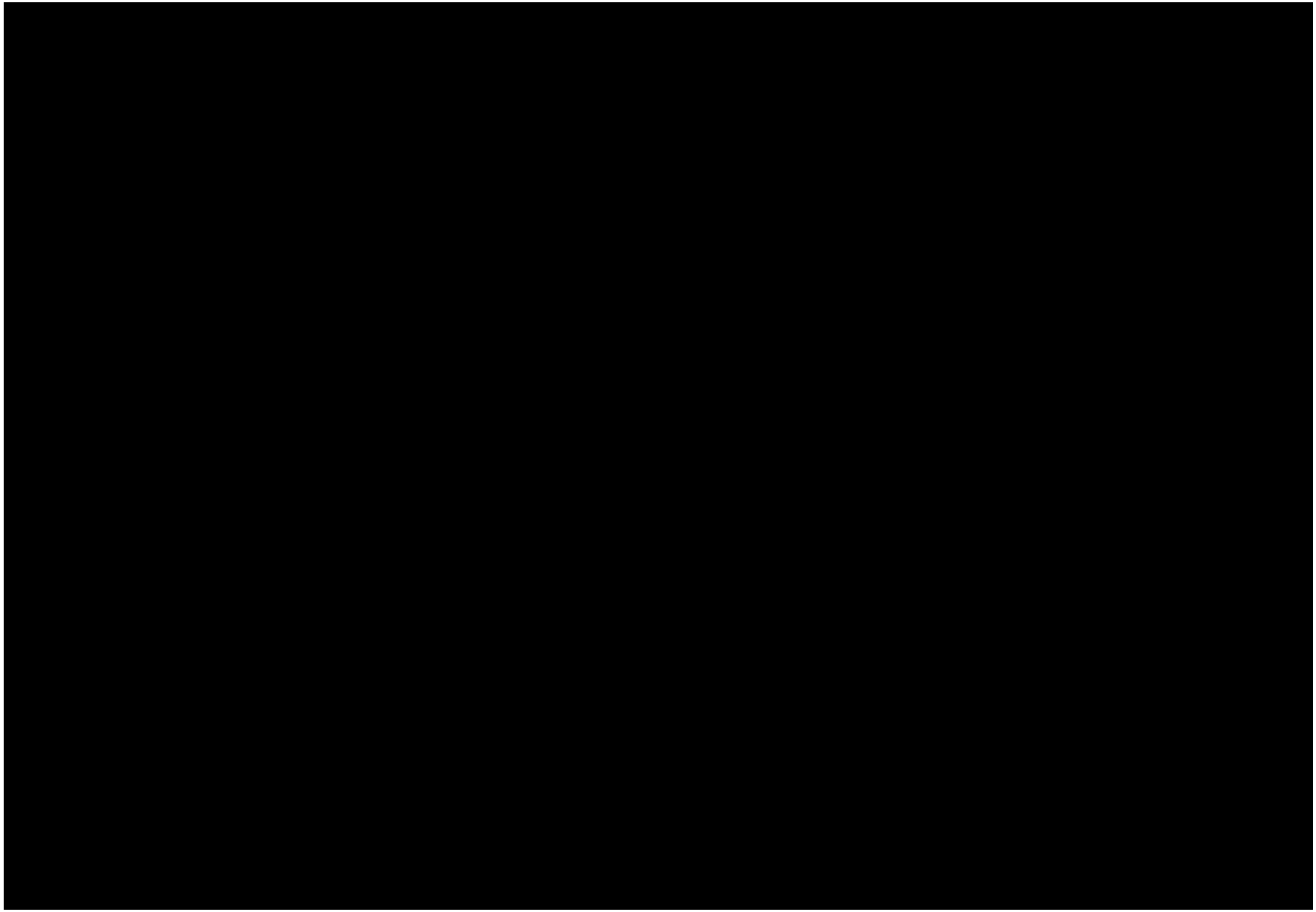


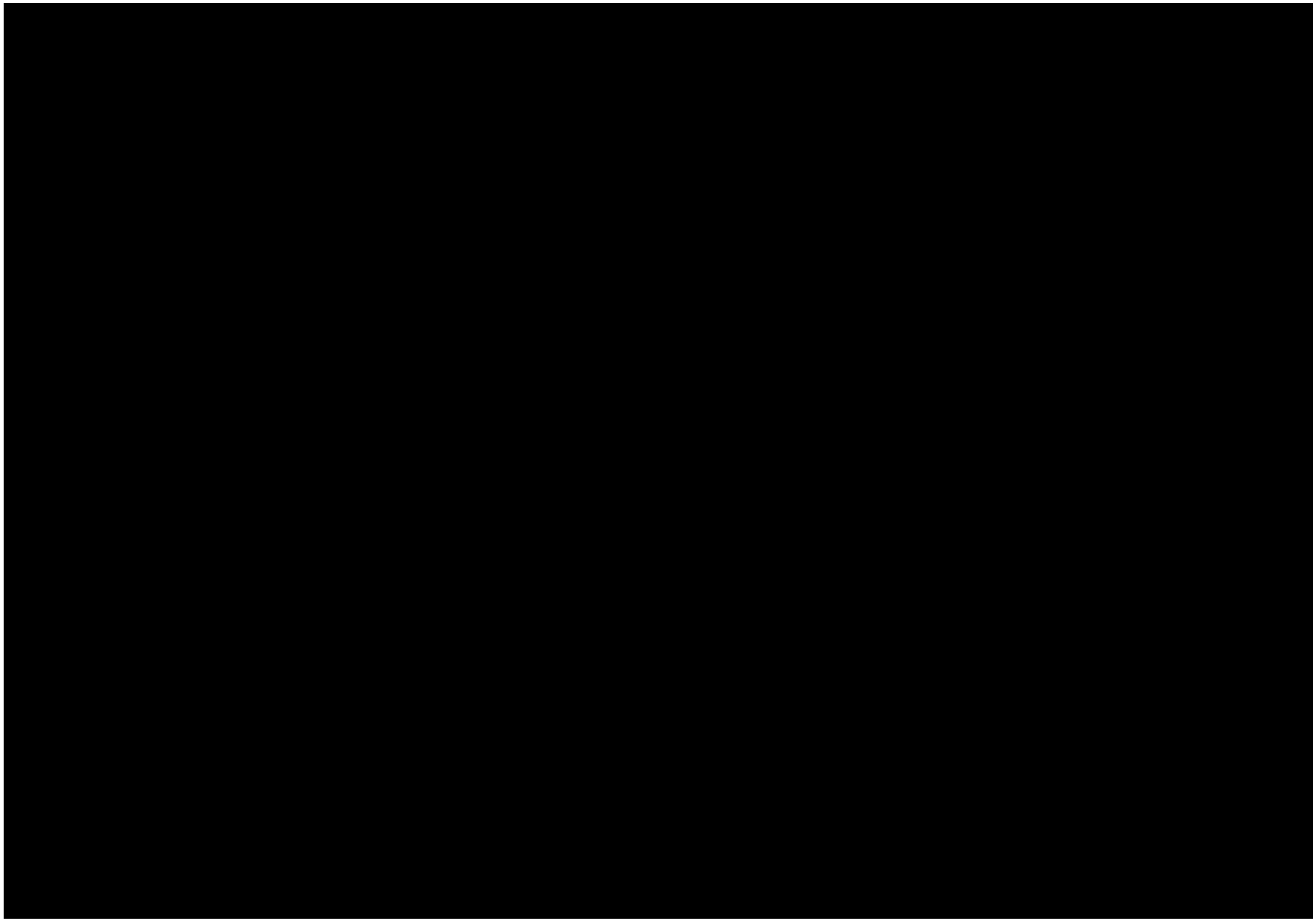
19. Subjects who have met the discontinuation criteria in the Induction Period.

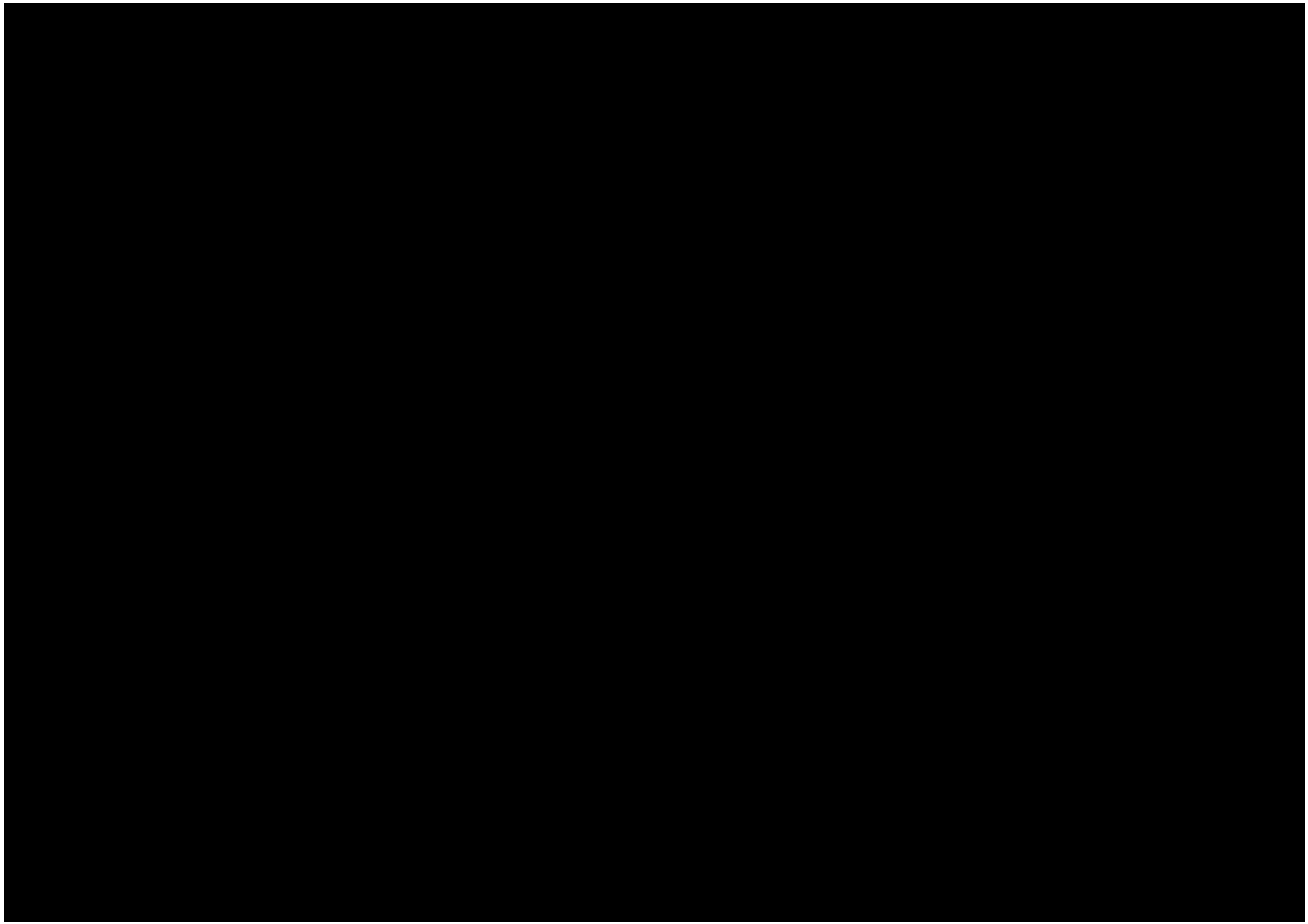
4.3.3 Exclusions Related to Laboratory Results and Other Assessments:

20. Subject has any clinically significant abnormal results (eg, labs or ECG) which, in the opinion of the investigator, may put the subject at risk.









[redacted]

6 [redacted]

[redacted]

6.1 Pre-Randomization Procedures

Written, signed, and dated informed consent from the subject prior to the performance of any study-related procedures must be obtained by the investigator or designee (refer to Section 16.3 for further details regarding obtaining subject's informed consent). A copy of the signed Informed Consent Form (ICF) must be given to the subject for his/her records.

Assessments and procedures as per [redacted] are to be performed by the investigator or a qualified designee.

[redacted]

[redacted] See APPENDIX C for further SARS-CoV-2 guidance.

6.2 Treatment Period

Eligible subjects will be randomized to treatment on Day 1. [redacted] Guidelines for dose escalation and instructions for missed doses are in Section 7.2.

[redacted]

6.2.2 Relapse Assessment Visit

If during the Maintenance Period, the investigator becomes aware of potential relapse outside the normal visit schedule, subjects should be evaluated for relapse as outlined in the [redacted] ([redacted]; see Section 14.2).

6.2.3 Study Stopping Rules

The sponsor has the right to terminate the study for safety reasons. In addition, the sponsor may terminate the study for administrative reasons. In all cases, all necessary measures must be taken to guarantee appropriate [redacted] of all subjects already included in the study.

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the Regulatory Authorities will be informed in writing about any termination of the study.

[redacted]

6.4 Efficacy Assessment

See Section 2 for a description of study endpoints.

6.4.1 Primary Efficacy Assessments

The CDAI and SES-CD will be used to evaluate the primary efficacy endpoints.

6.4.1.1 Crohn's Disease Activity Index

The CDAI is a composite score that is used to measure the clinical activity of CD. The CDAI uses a questionnaire with responses scored numerically and weighted. Scores range from 0 to approximately 600, with higher scores indicating greater disease activity. The 8 components used to assess the CDAI and their weighting factors are noted in Table 2. The definitions of mild, moderate, and severe CD are provided in Table 3.

Clinical remission based on CDAI score is defined as CDAI score < 150. Clinical response is defined as CDAI reduction from baseline ≥ 100 points or CDAI score < 150. Clinical remission based on abdominal pain and stool frequency is defined an average daily stool frequency score ≤ 3 and an average abdominal pain score ≤ 1 with abdominal pain and stool frequency no worse than baseline.

Subject-reported components of the CDAI (stool frequency and abdominal pain components and general well-being) will be collected in an electronic diary. Subjects will complete their electronic diary starting at Randomization visit and will continue throughout the study.

Subjects will be instructed on the use and completion of questions on the electronic diary.

The diary entries will be reviewed by site personnel during Randomization and throughout the study.

Table 2: Crohn's Disease Activity Index Assessment

Clinical or Laboratory Variable	Weighting Factor, ×
Number of liquid or soft stools each day for 7 days	2
Abdominal pain (graded from 0-3 on severity) each day for 7 days	5
General well-being, assessed from 0 (well) to 4 (terrible) daily for 7 days	7
Presence of complications	20
Taking diphenoxylate/atropine, loperamide, or opiates for diarrhea	30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	10
Hematocrit 47-HCT in men and 42-HCT in women	6
Percentage deviation from standard weight	1
Total Score[b]	

Abbreviations: HCT = hematocrit.

[redacted]

[b] One point each is added for each set of complications: arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum, aphthous stomatitis; anal fissure, fistula or perirectal abscess; other bowel-related fistula; febrile (fever) episode over 100 degrees during the past week.

Table 3: Crohn's Disease Severity Definitions

Severity	CDAI Score
Mild	150-219
Moderate	220-450
Severe	> 450

Abbreviations: CDAI = Crohn's Disease Activity Index.

6.4.1.2 Simple Endoscopic Score for Crohn's Disease

The SES-CD assesses the degree of inflammation. The SES-CD assesses the following 4 components: size of ulcers, ulcerated surface, affected surface, and presence of narrowing. Each of these components are scored on a scale of 0 to 3 as outlined in Table 4.

In the SES-CD, each of these 4 components are assessed in the 5 segments of the ileum and colon: Ileum, right, transverse, left (descending and sigmoid), and rectum. The SES-CD is the sum of the individual scores of each of the components across the 5 segments.

Endoscopic response has not yet been validated and may be defined as a 25% to 50% or greater decrease in SES-CD from baseline. Endoscopic remission may be defined as SES-CD ≤ 4 points and SES-CD decrease from baseline ≥ 2 points with no SES-CD subscore > 1 point.

To ensure quality data and standardization, the same endoscopist and the same diameter colonoscope as used in screening should be used throughout the study wherever possible. During the colonoscopy, each subject will have 2 biopsies taken from the most affected areas of each accessible segment (maximum of 10 biopsies), or a minimum of 1 biopsy from each segment if restricted by national or local regulations. Details regarding the biopsies are provided in the biopsy manual and Histology Image Charter. Colonoscopies will be read at a centralized reading facility in a process outlined in the Endoscopy Image Charter. Centralized reading will be the primary assessment for endoscopy; local endoscopy scores will also be collected.

Table 4: Definitions of Simple Endoscopic Score for Crohn's Disease

	Simple Endoscopic Score for Crohn's Disease Values			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (0.1 to 0.5 cm)	Large ulcers (0.5 to 2 cm)	Very large ulcers (> 2 cm)
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected segment	< 50%	50%-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

6.4.2 Other Efficacy Measures

6.4.2.1 Abdominal Pain and Stool Frequency

The abdominal pain and stool frequency scores are based on 2 components of the CDAI (Khanna, 2015). See Section 6.4.1.1 above for more details.

Stool frequency and abdominal pain, as described in Section 6.4.1.1, will be obtained and calculated without a weighting factor for use as part of the inclusion criteria. These unweighted subject-reported assessments will also be used as efficacy endpoints (Section 2).

The [redacted] is an additional tool for the visual evaluation of diarrhea, and will be collected from all subjects in the electronic diary.

[redacted]

6.4.2.2 Histology

A central reader will evaluate biopsies taken during colonoscopy and determine the [redacted] RHI (Table 6). Biopsies will be taken from the explored ileal and colonic segments. The [redacted] RHI scores provided from the central reader will be used for histopathology endpoints.

[redacted]

[redacted]

Table 6: Robarts Histological Index Grading System

RHI Descriptors and Levels	
Chronic inflammatory infiltrate	0: No increase 1: Mild but unequivocal increase 2: Moderate increase 3: Marked increase
Lamina propria neutrophils	0: None 1: Mild but unequivocal increase 2: Moderate increase 3: Marked increase
Neutrophils in epithelium	0: None 1: < 5% crypts involved 2: < 50% crypts involved 3: > 50% crypts involved
Erosion or ulceration	0: No erosion, ulceration, or granulation tissue 1: Recovering epithelium + adjacent inflammation or probable erosion-focally stripped 2: Unequivocal erosion 3: Ulcer or granulation tissue

6.5 Other Assessments

6.5.1 Physical Examination

A complete physical examination will be performed to evaluate the heart, lungs, head and neck, abdomen, skin and extremities, and weight as well as to check for visual symptoms (ie, blurred vision [redacted] as reported by the subject). A full examination of the skin should be repeated every 6 months. An interim physical examination will include weight, a check for visual symptoms, and an evaluation of body systems with previously noted abnormalities and/or

those body systems associated with any new complaints from the subject. [redacted]

6.5.2 Vital Signs

Systolic and diastolic blood pressure and pulse will be assessed in a supine and standing position. 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.

6.5.3 Electrocardiogram

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the trial. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the trial-specific manual and provided to the site before the start of the trial. Paper versions of ECG tracings will be printed and photocopied to preserve the ink if necessary, and kept at the site as source documentation. An ECG will be performed while resting. Only clinically significant abnormalities should be reported in the medical history/current medical conditions or the AE electronic case report form (eCRF).

6.5.4 Pulmonary Function Test

The pulmonary function test (PFT) refers to "pulmonary function test – no bronchodilator" (eg, spirometry which includes total and timed vital capacity, and expiratory flow rate measurement). [redacted]

Pulmonary function tests may be performed at a qualified pulmonary function laboratory, respiratory department, or at the clinical trial site. If being performed at the clinical trial site, the Principal Investigator may delegate the performance of this test to any staff member that is qualified to perform the pulmonary function test. If the pulmonary function test results are not within normal range and are considered clinically significant, the results must be verified by a pulmonologist, and potential confounding factors identified. Please refer to the American Thoracic Society / European Respiratory Society guidelines for standardization of spirometry and single breath determination of carbon monoxide uptake in the lung (MacIntyre, 2005; Miller, 2005a; Miller, 2005b).

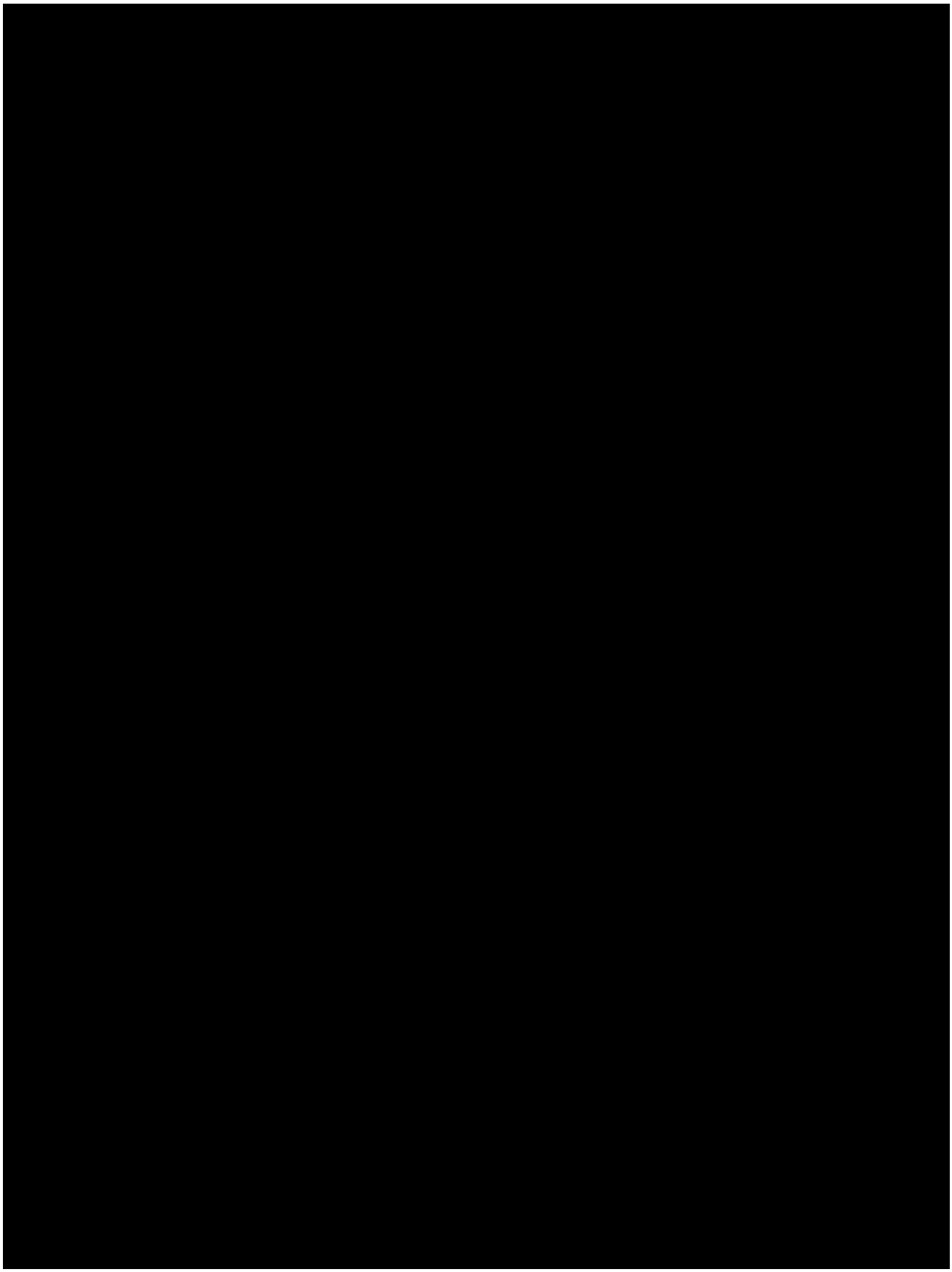
[redacted]

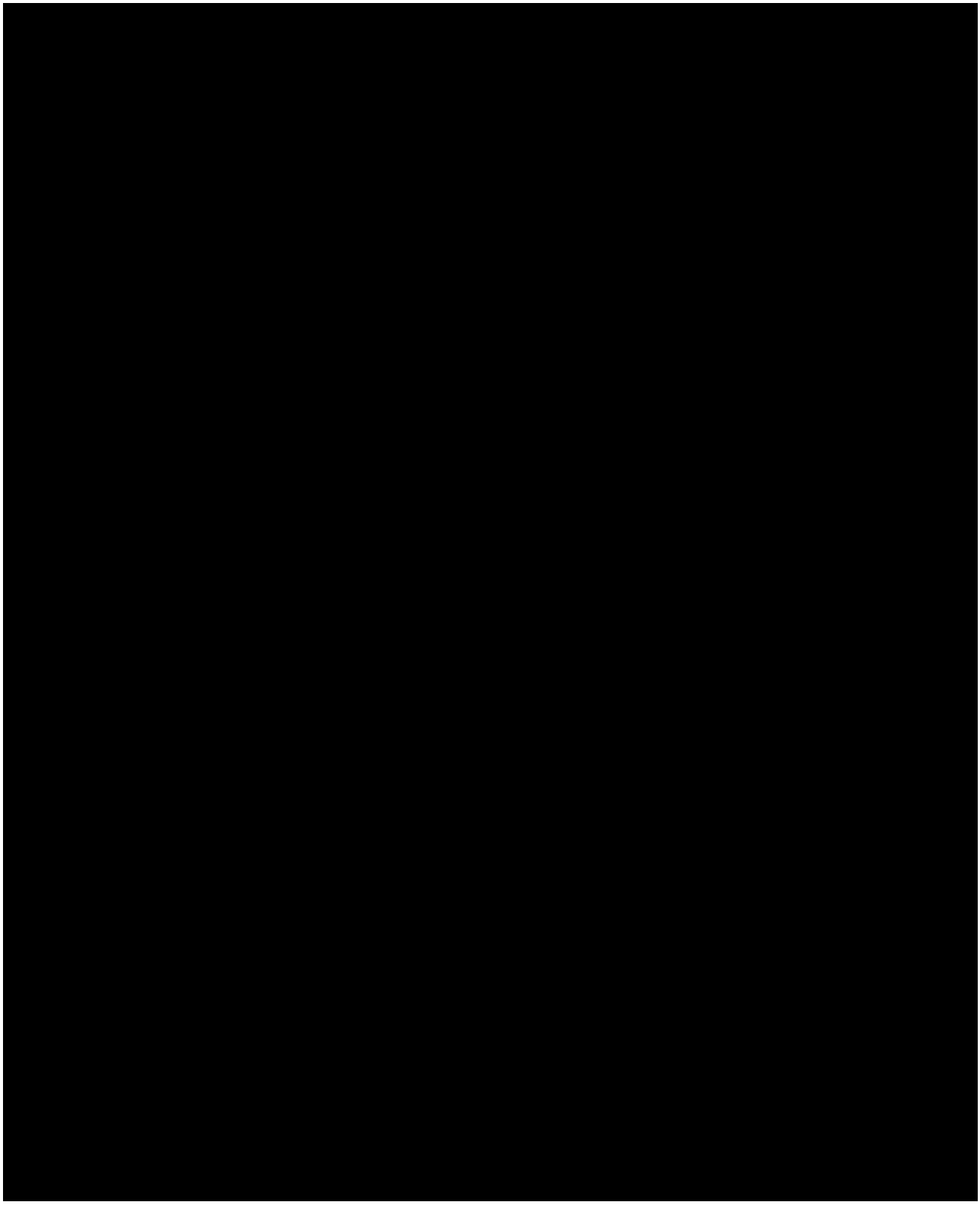
[redacted]

[redacted]

6.7 Health-related Quality of Life and Health Economics Assessments

The health-related quality of life questionnaires will be provided to each subject via electronic device and completed by the subjects at those visits as described in [redacted].





7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Product(s)

Ozanimod capsules will be manufactured, quality control tested, and released in accordance with Good Manufacturing Practices (GMP).

Ozanimod and matching placebo will be provided as powder-filled capsules. Ozanimod drug substance is blended with microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate in opaque hard-gelatin capsules. Two ozanimod dosage strengths have been prepared for the clinical investigations: 0.23 mg (size 4 capsule; equivalent to 0.25 mg ozanimod HCl) and 0.92 mg (size 4 capsule; equivalent to 1 mg ozanimod HCl). For matching placebo, the same size 4 opaque hard-gelatin capsules will contain the same blended excipients described above. All doses of ozanimod and placebo capsules are identical in appearance.

The capsules will be orally administered singularly, or in varying combinations, to achieve the desired dose for clinical studies. There is no provision for dose adjustments in this study. Subjects who cannot tolerate IP must be withdrawn from the study.

7.2 Treatment Administration and Schedule

Subjects will receive a single oral dose of ozanimod 0.92 mg (equivalent to ozanimod HCl 1 mg) or matching placebo administered daily starting on Day 1.

Subjects should be instructed to take IP (either ozanimod or placebo) at approximately the same time each day with or without food.

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 ozanimod. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor or other designated Drug Safety Center. The overdose should be recorded in the Overdose eCRF. Adverse Events associated with an overdose should be reported on the relevant AE/SAE sections in the eCRF.

Please refer to the IB for more information.

7.2.1 Instructions for Missed Doses

Subjects should be instructed that if they forget to take a dose, they can take the dose within 4 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the subject vomits the capsule, he/she should be instructed not to take another capsule on the same day, but to take the next dose at the regular time on the following day.

If the subject misses more than 14 consecutive doses for any reason, the Medical Monitor must be contacted to discuss procedures for resuming therapy, which may include cardiac monitoring procedures on the first day that the subject resumes dosing. If treatment is to be re-initiated after 14 days, the subject will require a 7-day dose escalation regimen as follows:

- Days 1 through 4: Ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) (or matched placebo)

- Days 5 through 7: Ozanimod 0.46 mg daily (equivalent to ozanimod HCl 0.5 mg) (administered as two 0.23-mg capsules or 2 matched placebo capsules)
- Days 8 through Week 52: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg) (or matched placebo)

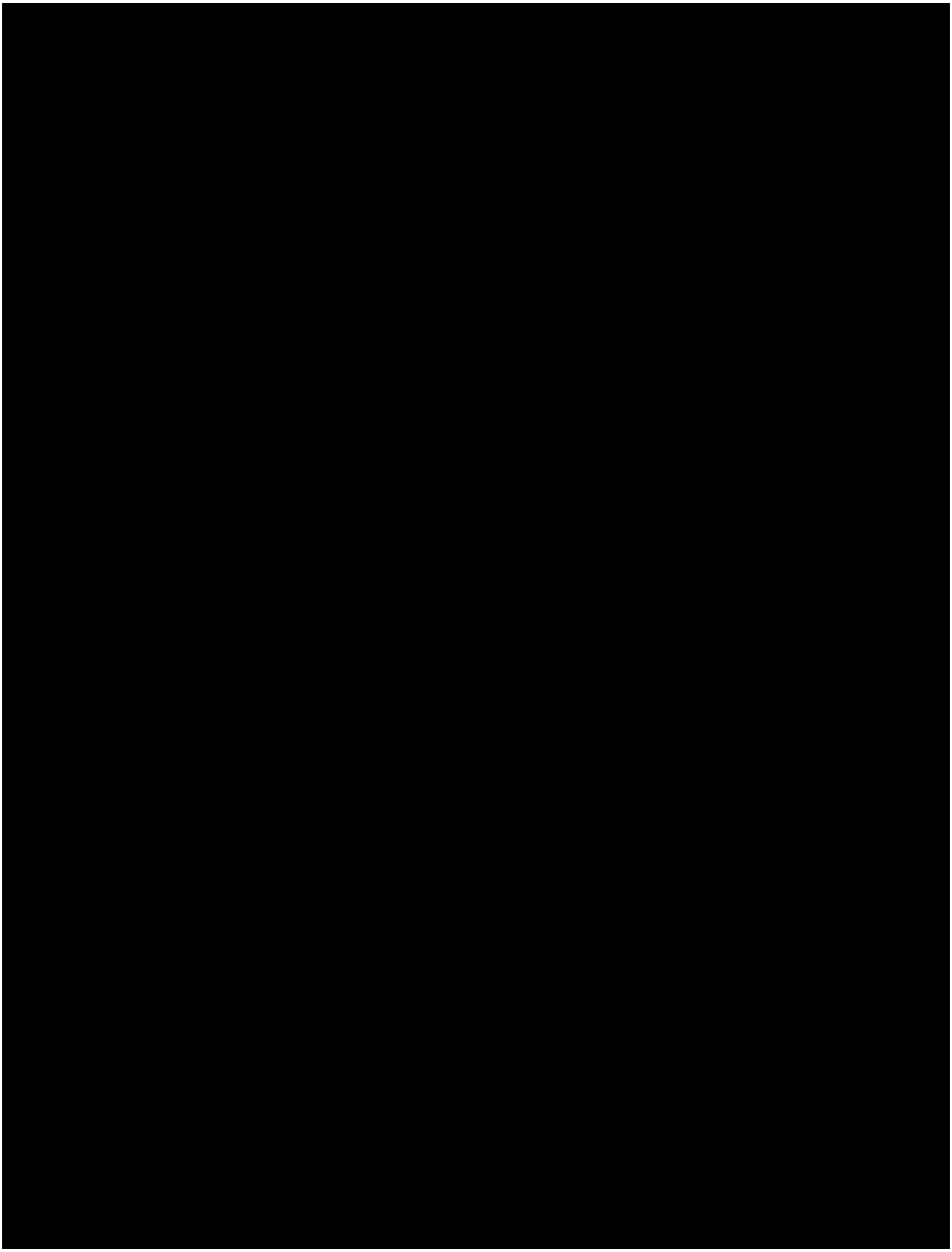
[redacted]

If IP is re-initiated and a single dose is missed during the first 14 days of treatment re-initiation (ie, the dose-escalation period and the following week), or if doses are missed for more than 7 consecutive days during the following 2 weeks (ie, 15-28 days after treatment re-initiation), the Medical Monitor should be contacted to discuss completing the dose escalation and to again reinitiate treatment [redacted]. The missed dose and extended days for dose escalation need to be documented as appropriate in the eCRF.

7.2.2 Guidelines for Monitoring Subjects at Risk for Cardiac Events During Re-Initiation of Treatment with Investigational Product

Due to the risk of transient decreases in heart rate with the initiation of ozanimod, [redacted]

[redacted]



[redacted]

Subjects should be instructed not to drive on the same day after the first dose of IP administration.

7.3 Method of Treatment Assignment

Subjects will be assigned as follows:

- ozanimod 0.92 mg capsule orally
- matching placebo capsule orally

7.4 Packaging and Labeling

Ozanimod capsules will be packaged in 30 cc white high-density polyethylene bottles (35 capsules per bottle, apart from the dose escalation kits), closed with a 28-mm child-resistant screw-cap that is induction sealed. The ozanimod 0.23 mg capsules (and matched placebo capsules) will be bottled in a 12-count bottle, intended to supply the dose-escalation period only. The ozanimod 0.92 mg capsules (and matched placebo capsules) will be bottled into a 35-count bottle, intended to supply daily treatment of the intended regimen following the dose-escalation period. To aid with visual identification of dosage strength, the cap on the 12-count dose-escalation bottles is blue, and the cap on the 35-count bottles is white.

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

Investigational product should not be used for purposes other than as defined in this protocol.

All supplies of IP will be accounted for in accordance with GCP. There will be an individual IP accountability record for each subject and the investigator should maintain accurate records of the disposition of all IP supplies received during the study. These records should include the amounts and dates that clinical drug supplies were received, dispensed to the subject, returned by the subject, and returned to the sponsor. If errors or damages in the clinical drug supply shipments occur, the investigator should contact the Clinical Monitor immediately. Each investigator will provide copies of the IP accountability records for inclusion in the Study Master File after database lock. The Clinical 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 the 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 Clinical Monitor will perform final accountability, package, seal, and prepare for shipment. Investigational product and

all medication containers will be returned to the clinical supply distribution vendor and documentation will be returned to the contract research organization (CRO). The CRO will verify that a final report of IP accountability is prepared and maintained in the investigator's Trial Center File.

The sponsor (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 sponsor (or designee).

7.6 Investigational Product Compliance

It is the investigator's responsibility to ensure that subjects are correctly instructed on how to take their IP, and that each subject is fully compliant with his/her assigned dosage regimen. Records of IP used at intervals between visits will be kept during the study. Drug accountability will be noted by the Clinical Monitor during site visits and at the completion of the study. Subjects will be asked to return all unused IP at the end of the study. The IP should be dispensed by the investigator, or by a qualified individual under the investigator's supervision.

Overall study noncompliance is defined as taking less than 80% or more than 120% of IP during the entire treatment period.

At each visit, previously dispensed IP capsules will be collected by the investigator, or by a qualified individual under the investigator's supervision, and compliance assessed. Subjects exhibiting poor compliance (ie, 2 or more missed medication days in 1 week) as assessed by medication counts and their response to a medication compliance question at each visit should be counseled on the importance of good compliance to the study dosing regimen. Subjects who are persistently noncompliant (< 80% or > 120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the study.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

All treatments, other than ozanimod, being taken by the subjects on entry into the study or at any time during the study, including through the [redacted], are regarded as concomitant medications and must be documented on the appropriate section of the eCRF. Additionally, all diagnostic, therapeutic, or surgical procedures relating to CD should be recorded.

Administration of concomitant medications must be reported along with dosage information, dates of administration, and reasons for use. For concomitant medications with a single active ingredient, generic names for concomitant medications should be used if possible. For combination products, brand names should be used. The total daily dose should be filled in whenever possible.

8.1 Permitted Concomitant Medications and Procedures

Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with IP may be continued during the study.

The decision to temporarily interrupt dosing for treatment of an intercurrent medical condition, or for major surgery that could present an unreasonable risk to the subject, remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. Prior to interruption of dosing, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion. The Investigator will report the action taken with IP. The Medical Monitor should be contacted to discuss treatment re-initiation (Section 7.2.1). See Section 14 for permanent discontinuation of IP.

8.1.1 Corticosteroids

Subjects who were taking baseline corticosteroids during the Induction Study may continue receiving these medications. However, corticosteroids should be tapered following completion of the Induction Study.

[redacted]

8.1.2 Aminosalicylates or Purified Medicinal Probiotics

Subjects who are receiving oral 5-ASA, or purified medicinal probiotics prior to randomization should, if possible, keep their prescribed dosage steady through Week 52. Oral 5-ASAs or probiotics should only be discontinued or reduced in dose if required by an investigator's

judgment. Oral 5-ASA or purified medicinal probiotics should not be started in subjects who are not receiving them. Ideally, subjects receiving 5-ASA or purified medicinal probiotics should maintain a stable dose throughout the study unless reduction or discontinuation is clinically indicated.

8.1.3 COVID-19 Vaccination

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during treatment with IP and after the last dose of IP.

Non-live COVID-19 vaccination 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 ozanimod is unknown. The individual risk/benefit assessment of a vaccine remains with the Investigator. If the assessment of the Investigator suggests the vaccine to be beneficial, it must be a non-live, replication-incompetent vaccine, and be approved or otherwise authorized (eg, Emergency Use Authorization [FDA] or equivalent) by national health authorities.

See APPENDIX C for further SARS-CoV-2 guidance.

8.2 Prohibited Concomitant Medications and Procedures

[redacted]

[redacted]

[redacted]

8.3 Required Concomitant Medications and Procedures

Not Applicable.

9 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1 Overview

This is a Phase 3, randomized, double-blind, placebo-controlled study to demonstrate the effect of oral ozanimod as maintenance therapy in adult subjects with moderately to severely active CD, defined as CDAI score ≥ 220 to ≤ 450 which will enroll an estimate of 550 subjects.

Approximately 410 subjects allocated to receive ozanimod in either RPC01-3201 or RPC01-3202 are expected to be in clinical remission or clinical response at Week 12 and are expected to enroll in this study. These subjects will be randomized to receive ozanimod 0.92 mg or placebo in a 1:1 ratio. Subjects will be stratified by clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no). To maintain the blind, subjects in response after receiving placebo in either RPC01-3201 or RPC01-3202 will continue to receive placebo in a blinded fashion.

Interactive Response Technology (IRT) will be utilized to implement a centralized randomization. See Section 9.3.3 for more details. An independent Data Monitoring Committee (DMC) will be used to monitor the study conduct.

9.2 Study Population Definitions

The following analysis populations will be used in the statistical analysis:

- Intent-to-Treat (ITT): The ITT analysis population will consist of all randomized subjects from the Screened analysis population receiving at least 1 dose of IP. Subjects in the ITT analysis population will be analyzed according to the randomized treatment, regardless of the treatment actually given. The primary analysis population for all efficacy endpoints will be the ITT analysis population.
- Safety: The safety analysis population is defined as all subjects who are randomized and receive at least one dose of study treatment, analyzed by actual treatment received.
- Additional analysis populations are defined and their use described in the SAP.

9.3 Sample Size and Power Considerations

9.3.1 Primary Endpoints

This study has 2 co-primary endpoints. The first primary endpoint is CDAI clinical remission at Week 52. Subjects will be deemed responders with respect to this endpoint if they meet the definition, CDAI score < 150 at Week 52.

The second primary endpoint is endoscopic response at Week 52. Subjects will be deemed responders with respect to this endpoint if they meet the definition, SES-CD decrease from baseline ≥ 50% at Week 52.

9.3.2 Power Calculations

It is assumed that the placebo remission rate at Week 52 (64 weeks total treatment) will be not more than 19% in a randomized withdrawal study in CD subjects. It is assumed that the ozanimod remission rate at Week 52 will be not less than 33%. This study is therefore designed to have at least 90% power to reject the first co-primary endpoint when these conditions are met. The two group chi-square test of equal proportions for 1:1 balanced treatment arms was applied and the following sample size was obtained (Table 8).

Table 8: Sample Size Calculation

Endpoint	Assumed Placebo Rate	Assumed Ozanimod Rate	Odds Ratio	Delta	Type I Error Rate	Power	Estimated Sample Size
Clinical Remission (CDAI < 150)	19%	33%	2.1	+14%	5%	90%	409

CDAI = Crohn's Disease Activity Index.

The same effect size with a smaller placebo response rate is expected for the endoscopic response endpoint, implying that this estimated sample size of subjects receiving ozanimod will be adequate for that endpoint as well. The power for both of these co-primary endpoints is bounded below by 81%, and it is expected that these endpoints are strongly positively correlated so that the actual power to reject both null hypotheses will be greater than 81%. Therefore, a sample size of approximately 410 subjects who received ozanimod in either RPC01-3201 or RPC01-3202 and enrolled in this study is *a priori* estimated to be adequate for both co-primary endpoints.

Note: The overall type I error rate across all controlled endpoints will be maintained at 5% using methods discussed in Section 9.6.

9.3.3 Stratified Block Randomization

Subjects enrolled in this study from the ozanimod arms of the Induction Studies will be randomized using stratified block randomization in order to account for the study design. These subjects will be randomized with the following stratification factors: clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no). Each unique combination of the stratification factors will have an independent randomization list that will be used to assign subjects to either ozanimod or placebo in a 1:1 allocation ratio.

9.4 Background and Demographic Characteristics

Subject demographics and baseline characteristics from Studies RPC01-3201 and RPC01-3202 will define subject demographics and baseline characteristics for RPC01-3203. Descriptive summaries will be presented for all collected baseline and demographic information. Continuous variables will be summarized using number of subjects (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Baseline characteristics and subject demographics will include, at minimum, age at CD symptom onset, age at CD diagnosis, years since CD symptom onset, years since CD diagnosis, baseline

CDAI score, baseline SES-CD score, prior anti-TNF biologic (anti-TNF and others) use, and prior corticosteroid use.

9.5 Subject Disposition

Subject disposition will be based on the following:

- number of subjects randomized
- number of subjects receiving blinded placebo
- number of subjects dosed
- number of subjects completing the Maintenance Study
- number of subjects not completing the Maintenance Study by reason for dropout
- number of subjects entering the OLE Study

9.6 Efficacy Analysis

Because most of the primary and secondary endpoints for this study, including both co-primary endpoints and all of the key secondary endpoints, are either remission or responder endpoints (ie, proportions of subjects meeting the criteria to be classified as remitters or responders for the two treatment groups), the analysis of endpoints using a continuous measure will not be described here, but rather discussed in the SAP.

The ITT analysis population will be the primary analysis population for all efficacy endpoints. Furthermore, for the primary analysis of remission or responder endpoints and for a given time point or study visit, ITT subjects who have insufficient data for remission or response determination will be considered non-remitters/non-responders for that time point or study visit. Sensitivity analyses and missing data imputation are discussed in the SAP.

9.6.1 Analysis of Primary and Key Secondary Endpoints

The primary analysis of the primary and key secondary endpoints with binary measure (ie, yes/no) such as clinical remission and clinical response at Week 52 will be each carried out using the Cochran-Mantel-Haenszel (CMH) method. The stratifying factors of clinical remission at entry into the Maintenance Study (yes/no) and corticosteroid use at entry into the Maintenance Study (yes/no) will be accounted for in the CMH analyses. Details regarding risk differences, odds ratios, confidence limits, and considerations for sensitivity analyses will be provided in the separate SAP.

9.6.2 Control of Family-wise Type I Error Rate

The primary endpoints and key secondary endpoints will be tested using a closed, hierarchical testing procedure in order to control the overall type I error rate for multiple endpoints. The details will be provided in the SAP. Only the primary and key secondary endpoints will have type I error rates controlled at the family-wise level. All other endpoints will be tested at a nominal $\alpha = 0.05$ level.

9.7 Safety Analysis

All safety data will be listed and summarized by treatment group as appropriate. All TEAEs will be coded and tabulated by system organ class and preferred term. The incidence of AEs, SAEs,

and AEs leading to discontinuation will be summarized and presented in descending order of frequency. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline will be produced. The change from baseline for each of the vital signs and ECG parameters will be summarized. The incidence of abnormal vital signs parameters and outlier ECG results will be tabulated. Adverse events will be summarized by patient years of exposure (PYE).

9.8 Treatment Failure Rules

Treatment failure rules (TFR) will be applied to the primary analyses of all efficacy endpoints. Subjects will be considered to have failed treatment if any of the following occur:

- Surgical resection of small intestine or colon as a treatment of CD related symptoms
- Endoscopic dilation treatment for CD associated stricture(s)
- Discontinuation of IP due to any reason before the Week 52 efficacy evaluations

9.9 Other Topics

9.9.2 Data Monitoring Committee

An independent, external Data Monitoring Committee (DMC) will be charged with monitoring accumulating safety and efficacy data from the study, as well as general aspects of study conduct.

The committee will meet periodically during the study to review aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to schedule, and safety data from the study. The DMC may recommend modifying or stopping the study early due to safety concerns based on data reviews.

The blinding plan to assure that all personnel involved in the conduct of the study remain blinded to the results of interim reviews will be specified 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 11), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

CD relapse and related symptoms will be monitored as study endpoints. These occurrences will not be recorded as AEs unless they are new or worse than baseline or if they meet the criteria for seriousness.

Reductions in ALC levels for subjects in this study is an expected primary [redacted] effect. Reductions in ALC, in general, need not be reported as AEs unless there are clinical consequences. The protocol requirements in Section 11.1 should be followed for confirmed [redacted]. The decision to report decreased ALC as an AE is at the investigator's discretion.

In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS-CoV-2 should be reported from the time of consent until the final study visit.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

An adverse drug reaction (ADR) is defined as all noxious and unintended responses to a medicinal product related to any dose (ICH E2A, II.A.2).

An unexpected ADR is defined as an adverse reaction, the nature of which is not consistent with the applicable product information (ICH E2A, II.A.3).

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the IP. The action taken and the outcome must also be recorded.

Abuse, withdrawal, sensitivity or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, that are associated with an AE should be reported on the eCRF. See Section 7.2 for the definition of overdose. Any sequela of an accidental or intentional overdose of an IP should be reported as an AE on the AE eCRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE Report Form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE Report Form and eCRF but should not be reported as an SAE itself.

10.1.1 Treatment of Overdose of Investigational Product

An overdose is any dose of IP given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the CRO's Medical Monitor or other designated Drug Safety Center. Overdose should be recorded in the Overdose eCRF. Only AEs associated with an overdose should be reported on relevant AE/SAE sections in the eCRF.

10.1.2 Monitoring of Subjects with Adverse Events and Serious Adverse Events

Investigators must carefully monitor each subject for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, severity, and relationship to the administration of the IP. [redacted] Safety reporting must comply with ICH E6, 4.11.

All AEs will be recorded by the investigator from the time the subject signs informed consent until [redacted] as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. All SAEs that occur [redacted], whether or not considered related to the IP, must also be reported. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. Refer to Section 13 for instructions on how to report SAEs to Drug Safety.

10.2 Evaluation of Adverse Events

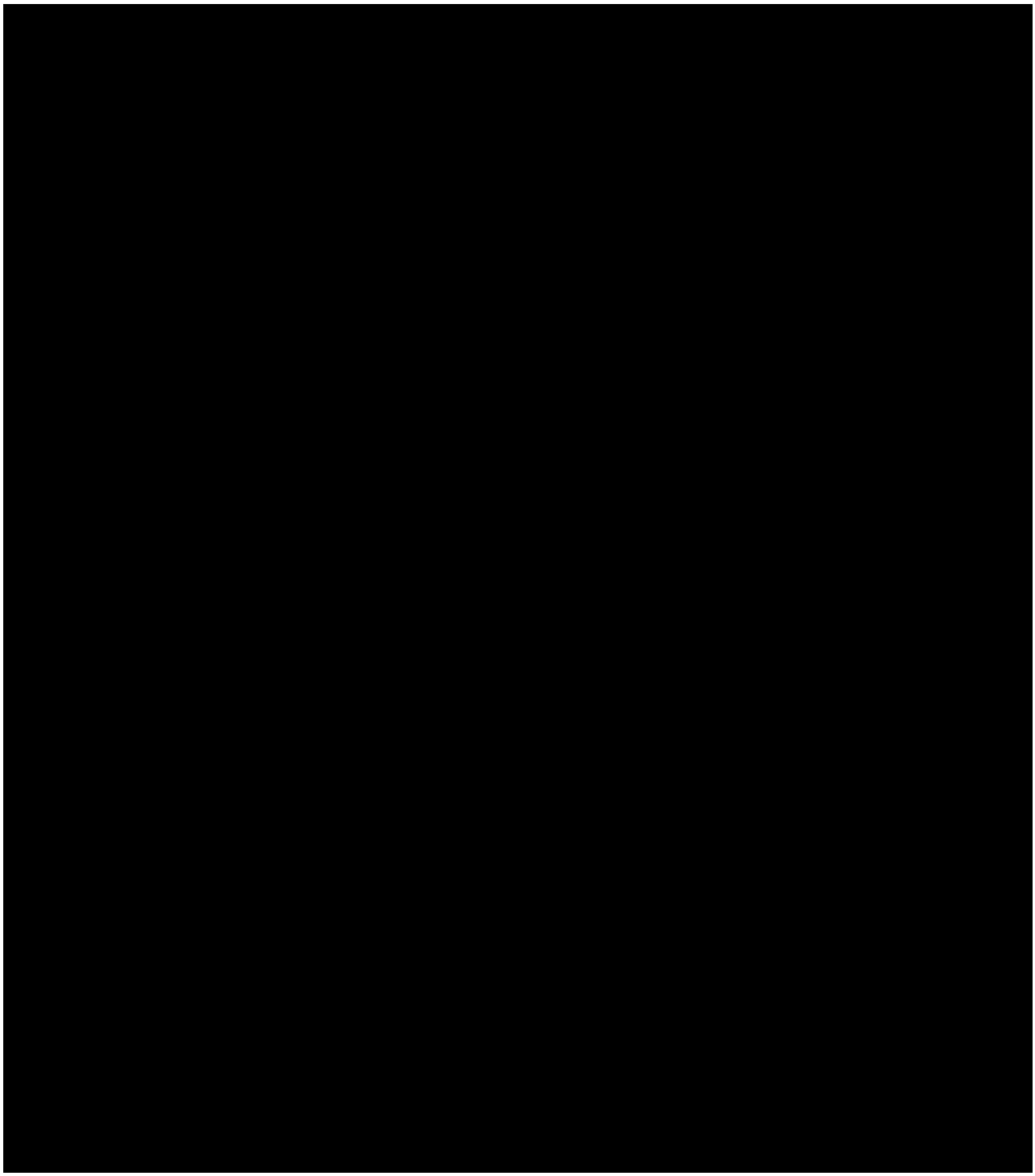
A qualified investigator will evaluate all AEs based on seriousness, severity, causality, duration, action taken, and outcome.

10.2.1 Seriousness

An SAE (experience) or reaction is any untoward medical occurrence that at any dose (ICH E2A, II.B):

- results in death
- is life-threatening

  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital abnormality/birth defect



If an AE is considered serious, the AE page/screen of the eCRF must be completed. The SAE Report Form may also need to be completed if required per the applicable reporting process.

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

10.2.2 Severity

For both AEs and SAEs, the investigator must assess the severity of the event. The severity of the AE will be characterized as “mild, moderate, or severe” according to the following definitions:

[redacted]

10.2.3 Causality

The causal relationship between the IP and the AE has to be characterized as Not Suspected or Suspected as defined below.

[redacted]

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 decision to temporarily interrupt dosing as a result of an AE or SAE remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. Prior to interruption, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

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

If dosing is interrupted, the Investigator should contact the Medical Monitor to discuss treatment reinitiation (Section 7.2.1). See Section 14 for permanent discontinuation of IP.

10.2.6 Outcome

The investigator will report the outcome of the event for both AEs and SAEs.

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).

10.2.7 Adverse Events of Special Interest

Potential AEs that may be a consequence of S1P receptor modulation, AESIs, will be monitored during the study. [redacted]. For AESIs, the Sponsor may request additional medical information concerning the AESIs that are non-serious.

[redacted]

11 CLINICAL LABORATORY EVALUATIONS

The central laboratory will analyze clinical laboratory samples. Further details of the procedures to be followed for sample collection, storage, and shipment will be documented in a laboratory manual.

Repeat testing for protocol-required laboratory tests are to be analyzed by the central laboratory. Additional testing may be performed for significant variations in protocol-required tests at the discretion of the investigator and in consultation with the Medical Monitor or designee, or at the request of the Sponsor. Approval from the Medical Monitor or designee must be obtained if retest is required to be repeated > 2 times and is not already pre-specified in the protocol.

[redacted]

11.1 Hematology

Red blood cell count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Total WBC count and all differential WBC counts will be blinded information for the treating investigator after initiation of IP. Of note, WBC, basophil, eosinophil, lymphocyte, monocyte, and neutrophil counts will not be disclosed to preserve the blind.

Reductions in ALC levels is a known [redacted] effect of ozanimod. [redacted]

[redacted]

[redacted]

11.2 Chemistry

- Full chemistry panel prior to randomization: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, [redacted], and low-density lipoprotein, [redacted]
- All other visits: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, total bilirubin, conjugated bilirubin, [redacted]. Total cholesterol, triglycerides, [redacted], and low-density lipoprotein will also be included at the Week 52 or Early Termination Visits. [redacted]
  - [redacted]
- Urinalysis: Leukocytes, specific gravity, bilirubin, blood, glucose, ketones, pH, protein, and urobilinogen
- The central laboratory will analyze routine blood samples. 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.
- 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.

- [redacted]

12 PREGNANCY

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication; however, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. In cases of live birth, with the consent of a parent, the infant may be followed for up to a year.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to Sponsor's Drug Safety or designee.

12.1 Female Subjects of Childbearing Potential

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for FCBP. [redacted]

Pregnancies and suspected pregnancies (including [redacted] in a FCBP regardless of disease state) occurring while the subject is on IP, [redacted] 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 Sponsor's Drug Safety or designee immediately using the Pregnancy Initial Report Form, or approved equivalent form.

The investigator will follow the female subject until completion of the pregnancy, and must notify Sponsor's Drug Safety or designee 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 Sponsor's Drug Safety or designee 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 [redacted] of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after [redacted] that the investigator suspects is related to the in utero exposure to the IP should also be reported to Sponsor's Drug Safety or designee within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Note: For the purposes of this study, a female subject is considered to be of childbearing potential if she 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

12.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the pregnant female partner should be advised to call her healthcare provider immediately.

13 REPORTING OF SERIOUS ADVERSE EVENTS

Reporting requirements for SAEs will be managed on behalf of the sponsor by Sponsor's Drug Safety or designee. Full details of the procedures to be adopted will be documented in a safety management plan approved by responsible parties, in brief:

The investigator will report any SAE that occurs to any subject from the time written informed consent is signed through the last visit. All SAEs that occur [redacted], whether or not considered related to the IP, must also be reported. Any SAE that is ongoing when the subject completes the study or discontinues from the study will be followed by the investigator until the event has resolved, stabilized, or returned to baseline status.

Any AE considered serious by the investigator or sub-investigator or that meets serious criteria should be reported to Sponsor's Drug Safety or designee using the designated SAE reporting forms and procedures. Data entry must be completed within 24 hours from the time the study site personnel first learned of the event.

The SAE contact information is as follows:

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

The initial report should be promptly followed by detailed, written reports, which will include copies of hospital case records, discharge summaries, autopsy reports, and other documents when requested and applicable. For unrelated cases, a full detailed case description may negate the need for additional hospital case records, discharge summaries, etc.

Investigators will be notified by the Sponsor's Drug Safety or designee of all SAEs that require prompt submission to their IRB or IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the CRO. The CRO will ensure that all SAEs are reported to the appropriate regulatory authorities as required. Reporting of SAEs must comply with ICH E6, 4.11.1.

13.1 Safety Queries

Queries pertaining to SAEs will be communicated from Sponsor's Drug Safety or designee to the site. [redacted]

13.2 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Sponsor's Drug Safety will determine the expectedness of events suspected of being related to ozanimod based on the IB.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as 'IND safety reports' and will be reported in accordance with 21 CFR 312.32. For reporting to the FDA, events that are not suspected to be causally related to ozanimod by the sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population (as per the Reference Safety Information section

in the IB), will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

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

Sponsor or its authorized representative shall notify the investigator of the following information:

- 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.

Where required by local legislation, the investigator shall notify his/her IRB/IEC promptly of these new SUSARs or significant risks to subjects.

The investigator must keep copies of all pertinent safety information on file including correspondence with the sponsor and the IRB/IEC. See Section 17.3 for record retention information.

13.3 Sponsor Drug Safety Contact Information

For Sponsor's Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

14 DISCONTINUATIONS

14.1 Treatment Discontinuation

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

- adverse event
- withdrawal by subject
- death
- [redacted]
- lack of efficacy
- pregnancy

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.

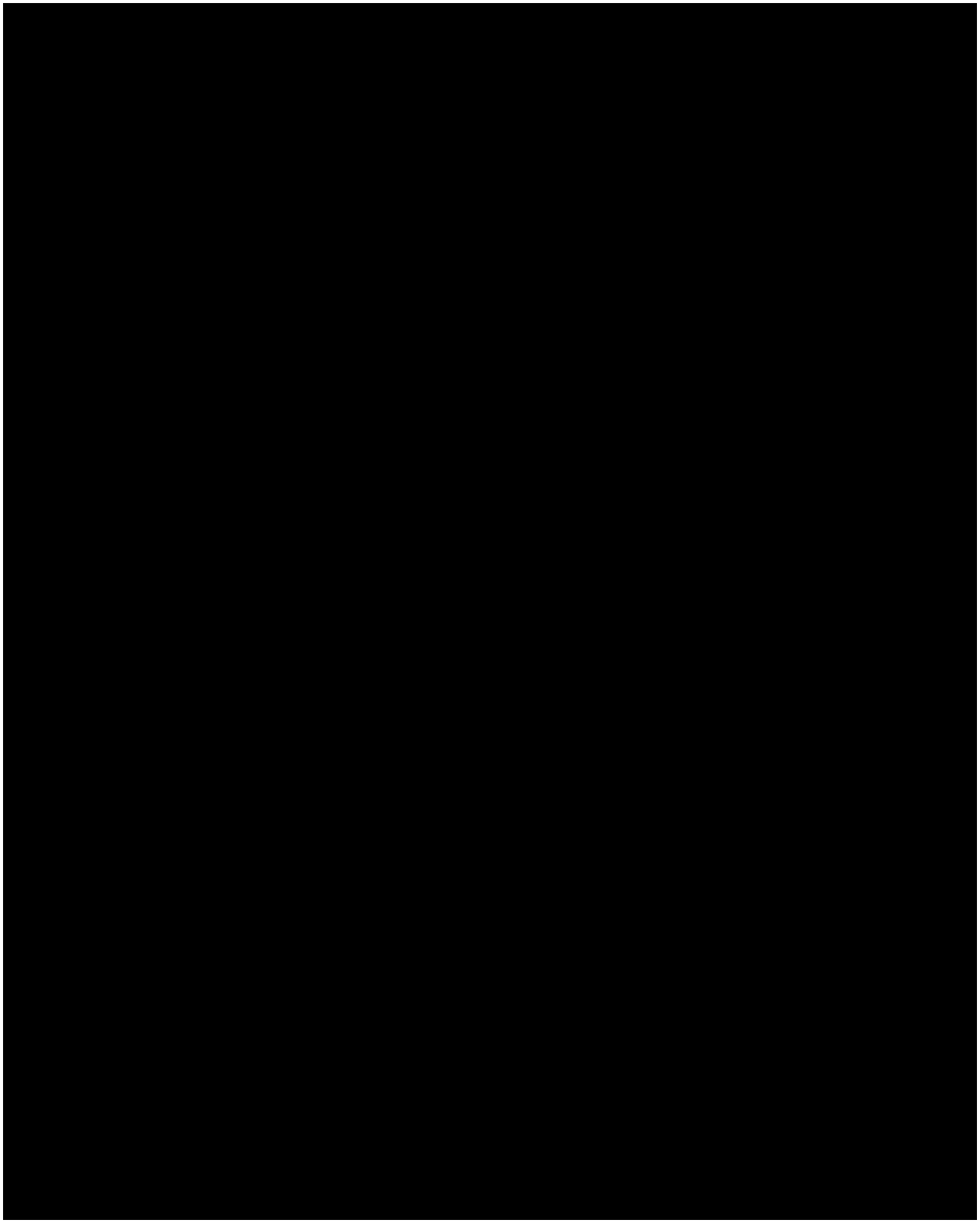
14.2 Study Discontinuation

Subjects may voluntarily withdraw from the study at any time. The investigator will provide a written explanation in the source documentation to be entered on the appropriate eCRF page describing the reason for discontinuation.

The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, the Medical Monitor must be contacted, and that subject will be withdrawn from the study if continuation is determined to be a safety risk.

Reasons for discontinuation include, but are not limited to, the following:

- Physician decision: The investigator must discontinue IP if it is determined that it is not safe or in the subject's best interest to receive further treatment. The Medical Monitor should be promptly notified of the decision.
- Noncompliance with IP: After consultation between the investigator, the Medical Monitor, and the sponsor when appropriate, a subject may be discontinued from the study for failure to comply with dosing regimen as specified by the protocol.
- Noncompliance with protocol/protocol deviation: After consultation between the investigator, the Medical Monitor, and the sponsor when appropriate, a subject may be discontinued from the study for failure to follow protocol procedures, or other event or decision that stands in contrast to the guidelines set in the protocol.
- Adverse event: A subject must be discontinued from IP if, in the judgment of the investigator or if specified in the protocol, the subject develops an AE such as an intercurrent illness or complication that justifies discontinuation of IP.



[1] International Normalized Ratio (INR) is part of the coagulation panel and may be obtained at the discretion of the investigator via central or local laboratory testing.

[redacted]

- Lack of efficacy: Decision by the subject and/or the investigator to discontinue IP due to a lack of expected or desired effect related to a therapy.
- Withdrawal by subject: The subject may choose to discontinue IP at any time. Every effort should be made within the bounds of safety and subject choice to have each subject complete the Early Termination Visit [redacted]. If a subject withdraws consent, the only additional investigational data to be collected will be the [redacted] of SAEs as mandated by the protocol.
- Pregnancy: If a female subject becomes pregnant, IP must be discontinued (see Section 12).
- Study termination by sponsor
- Other

[redacted]

15 EMERGENCY PROCEDURES

15.1 Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research 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/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 sponsor/designee 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) or Medical Monitor or designee for emergency calls.

15.2 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 IRT by using an emergency unblinding personal identification number (PIN). The investigator should log into IRT for unblinded dose information.

16 REGULATORY CONSIDERATIONS

16.1 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 sponsor, its authorized representative, and investigator abide by GCP, as described in 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/IEC 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.

16.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. The sponsor's 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 sponsor 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 ICF for the study.

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 the sponsor on public registry websites) is considered sponsor confidential information. Only information that is previously disclosed by sponsor on a public registry website may be freely disclosed by the investigator or its institution, or as outlined in the Clinical Study Agreement. Sponsor's 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 the sponsor. Information proposed for posting on the investigator's or their institution's website must be submitted to the sponsor 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, sponsor 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 his/her caregiver as agreed by the subject.

16.3 Subject Information and Informed Consent

The investigator must obtain informed consent from a subject and/or a subject's legal representative prior to any study-related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF 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 the content of the informed consent, the ICF 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. The revised ICF 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.

16.4 Confidentiality

Sponsor 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). Sponsor requires the investigator to permit sponsor'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.

16.5 Protocol Amendments

Any amendment to this protocol must be approved by the sponsor's Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/IEC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/IEC 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.

16.6 Institutional Review Board/Independent Ethics Committee Review and Approval

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

IP can only be supplied to an investigator by sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/IEC and their occupation, and qualifications. If the IRB/IEC 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/IEC 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. The formal approval 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/IEC 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 should also be revised.

The investigator must keep a record of all communications with the IRB/IEC and, if applicable, between a coordinating investigator and the IRB/IEC. 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 sponsor and the IRB/IEC prior to use.

16.7 Ongoing Information for Institutional Review Board/Independent Ethics Committee

If required by legislation or the IRB/IEC, the investigator must submit to the IRB/IEC:

- Information on serious or unexpected AEs 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.

16.8 Termination of the Study

The sponsor has the right to terminate the study for safety reasons. In addition, the sponsor may terminate the study for administrative reasons. In all cases, all necessary measures have to be taken to guarantee appropriate safety [redacted] of all subjects already included in the study.

The IRB/IEC and the Regulatory Authorities will be informed in writing about any termination of the study.

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

- unsatisfactory enrollment
- GCP noncompliance
- inaccurate or incomplete data collection
- falsification of records
- failure to adhere to the study protocol

17 DATA HANDLING AND RECORDKEEPING

17.1 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 or CD-ROM.

17.2 Data Management

Data will be collected via eCRF and entered into the clinical database. This data will be electronically verified through use of edit checks and manual review. 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.

17.3 Record Retention

Essential documents must be retained by the investigator according to the period of time outlined in the clinical study 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 for all subjects
- subject identification code list and enrollment log
- record of all communications between the investigator and the IRB/IEC
- composition of the IRB/IEC
- record of all communications between the investigator, Sponsor, 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
- 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 the sponsor 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 the sponsor prior to destruction of any records. If the investigator is unable to meet this obligation, he or she must ask the sponsor 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.

18 QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures (SOPs).

18.1 Study Monitoring and Source Data Verification

The sponsor 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 investigator's meeting. Prior to enrolling subjects into the study, a sponsor 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.

18.2 Product Quality Complaint

Issues that call into question 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 IP 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 and labeling.

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

18.3 Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exist within sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with the sponsor SOPs to evaluate compliance with GCP 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/IECs, Regulatory Authorities (eg, Food and Drug Administration [FDA], European Medicines Agency [EMA], and 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 or she should contact the sponsor immediately.

19 PUBLICATIONS

As described in Section 16.2, all protocol- and amendment-related information, with the exception of the information provided by sponsor on public registry websites, is considered sponsor's confidential information and is not to be used in any publications. Sponsor's protocol-related information proposed for use in a publication must be submitted to sponsor for review and approval, and should not be utilized in a publication without express written approval from sponsor, or as described in the Clinical Trial Agreement.

Sponsor will ensure sponsor-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 1 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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[redacted]

21 APPENDICES

APPENDIX A TABLE OF ABBREVIATIONS

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6-MP	6-mercaptopurine
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase (SGPT)
[redacted]	
AP	Abdominal pain
AST	Aspartate aminotransferase (SGOT)
[redacted]	
AZA	Azathioprine
[redacted]	
β-hCG	β-subunit of human chorionic gonadotropin
[redacted]	
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CYP	Cytochrome P450
[redacted]	
DMC	Data Monitoring Committee
EC	European Committees
eCRF	Electronic case report form
EMA	European Medicines Agency
IEC	Independent Ethics Committee
ECG	Electrocardiogram
EEA	European Economic Area

Table 9: Abbreviations and Specialist Terms

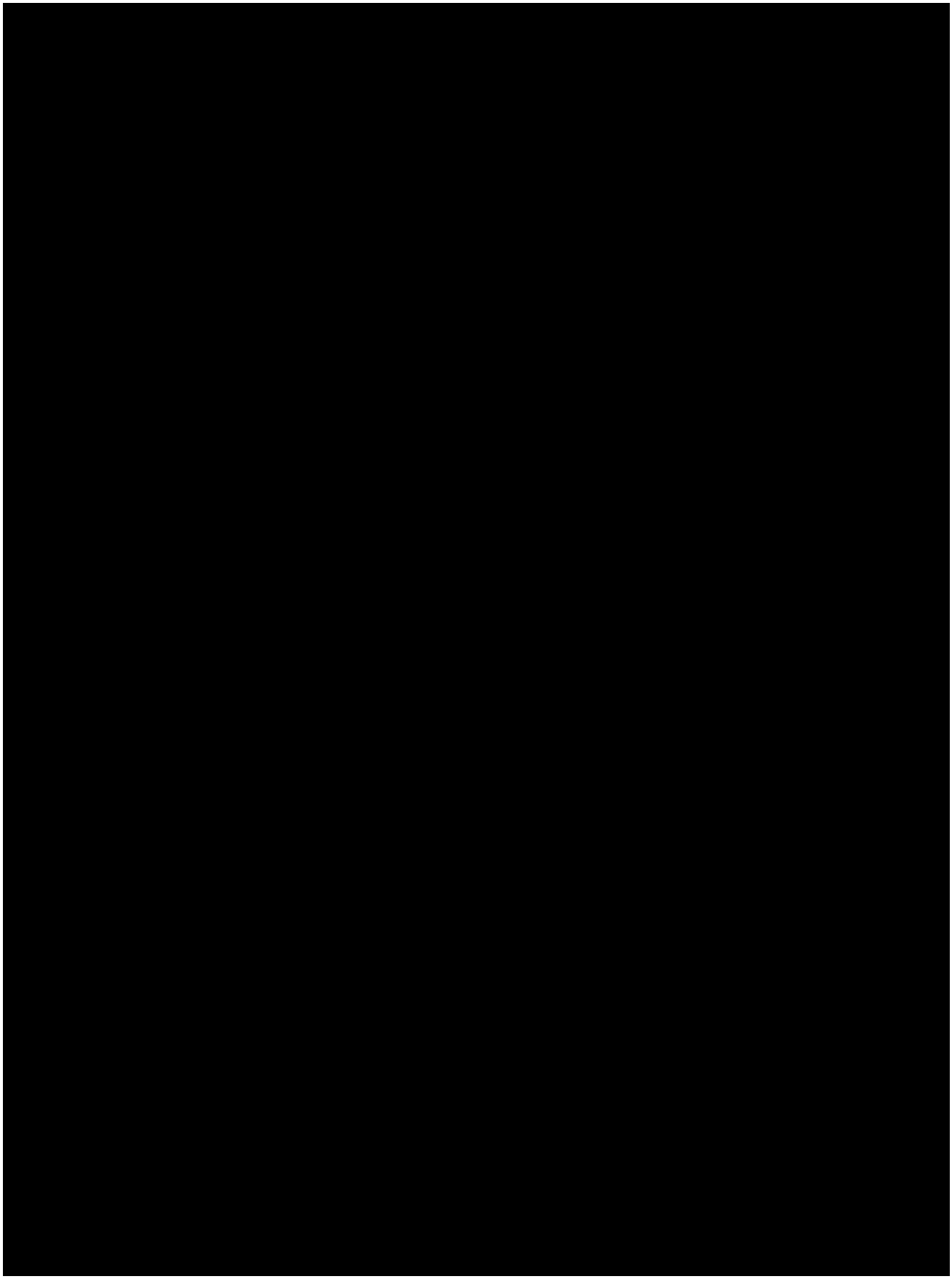
Abbreviation or Specialist Term	Explanation
[redacted]	
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
[redacted]	
FDA	Food and Drug Administration
[redacted]	
FCBP	Female of childbearing potential
[redacted]	
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
[redacted]	
GI	Gastrointestinal
HBV	Hepatitis B virus
HCl	Hydrochloride
HIV	Human immunodeficiency virus
[redacted]	
HRU	Healthcare resource utilization
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
[redacted]	
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
[redacted]	
IL	Interleukin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
[redacted]	
IRT	Interactive Response Technology

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ITT	Intent-to-treat
IV	Intravenous
[redacted]	
ME	Macular edema
MERS-CoV	Middle East respiratory syndrome coronavirus
[redacted]	
MTX	Methotrexate
[redacted]	
OLE	Open-Label Extension
[redacted]	
PFT	Pulmonary function test
[redacted]	
PP	Per protocol
[redacted]	
PYE	Patient years of exposure
QoL	Quality of life
[redacted]	
RHI	Robarts Histologic Index
RMS	Relapsing multiple sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease

Table 9: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
[redacted]	
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	
TNF	Tumor necrosis factor
TFR	Treatment failure rules
TRT	Treatment
UC	Ulcerative colitis
[redacted]	
WBC	White blood cell
[redacted]	



APPENDIX C SARS-COV-2 GUIDELINES

[redacted] Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

If the subject receives a positive SARS-CoV-2 test result and is asymptomatic during the pre-randomization period, the subject may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

1. At least 10 days have passed since positive test result, and
2. In the opinion of the investigator, there are no COVID-19 sequelae that may confound the assessment of safety or efficacy within the study and place the subject at a higher risk of receiving investigational treatment

If the subject receives a positive SARS-CoV-2 test result and is symptomatic during the pre-randomization period, the subject may be considered eligible for the study after meeting all inclusion/exclusion criteria related to active infection, and after meeting the following criteria:

1. At least 10 days (7 days if initial test was performed 5 days after symptom onset, 20 days for severe/critical illness) have passed since symptoms first appeared or positive test result, and
2. At least 24 hours have passed since last fever without the use of fever-reducing medications, and
3. Symptoms (eg, cough, shortness of breath) have resolved, and
4. In the opinion of the investigator or in consultation with sponsor, there are no COVID-19 sequelae that may confound the assessment of safety or efficacy within the study and place the subject at a higher risk of receiving investigational treatment.

Each study visit will include an assessment for AEs including SARS-CoV-2 and other infections. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS CoV-2 should be reported from the time of consent until the final study visit (Section 10).

Procedures related to COVID-19 identification (eg, MERS-CoV test, SARS-CoV-2 antibody test, SARS-CoV-2 ELISA test), and treatment (eg, intubation, dialysis) must be reported on the appropriate section of the eCRF.

Evaluation and management of SARS-CoV-2 infections arising during the course of the trial are left to the discretion and expertise of the Investigator. For subjects who are exhibiting symptoms consistent with SARS-CoV-2, the Sponsor advises the Investigator to consult the Medical Monitor.

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur during the study, including during treatment with IP and after the last dose of IP. Administration of vaccinations must be reported along with dosage information, dates of administration and vaccine name/trade name on the appropriate section of the eCRF. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.

APPENDIX D PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 6.0, 16-Mar-2023:

The overall rationale for this protocol amendment is to consolidate the protocol with the European Union (EU)/Clinical Trials Regulations (CTR) requirements, particularly to address the removal of the France-specific protocol. Other changes include the addition of risk/benefit assessment details, correction of Exclusion Criteria timeframes and updates to prohibited medications, as well as updates to cardiac and ophthalmic monitoring language.

The Protocol Summary was updated with all relevant changes.

Summary of Changes For Protocol Amendment 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Sponsor address updated.	Sponsor address change.
Medical Monitor/Emergency Contact Information	Medical Monitor and associated contact information updated.	Sponsor staff change.
Sponsor Therapeutic Area Lead Signature Page	Sponsor Therapeutic Area Lead information updated.	Sponsor staff change.
Section 1.2.4: Risk/Benefit Assessment	Section removed (now Section 1.4.3: Overall Risk/Benefit Conclusion).	Integration of previously stand-alone Risk/Benefit document into body of protocol.
Section 1.4: Risk/Benefit Assessment; [redacted] Section 1.4.2: Benefit Assessment; Section 1.4.3: Overall Risk/Benefit Conclusion	Sections added.	Integration of previously stand-alone Risk/Benefit document into body of protocol.
[redacted]		

Summary of Changes For Protocol Amendment 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 4.3.1: Exclusions Related to General Health	Added France-specific language to indicate that hypotension is mentioned as being exclusionary if it makes the implementation of the protocol or interpretation of the study difficult or would put the subject at risk by participating in the study.	To align with EU/CTR consolidation and removal of the France-specific protocol.
Section 4.3.2: Exclusions Related to Medications	[redacted]	Corrected to align with timeframe as stated in Induction protocol.

Summary of Changes For Protocol Amendment 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.3.2: Exclusions Related to Medications; [redacted]	[redacted]	
[redacted]		
Section 7.2.2: Guidelines for Monitoring Subjects at Risk for Cardiac Events During Re-Initiation of Treatment with Investigational Product; [redacted]	Cardiac monitoring language updated.	Correction/clarification.
Section 8.1.3: COVID-19 Vaccination	Non-live coronavirus disease 2019 (COVID-19) vaccination language added.	Moved language from Risk/Benefit section.
[redacted]	[redacted]	Clarification.

Summary of Changes For Protocol Amendment 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	
Appendix C: SARS-CoV-2 Guidelines	Language updated to indicate that testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice and to provide guidance on the evaluation and management of SARS-CoV-2 infections.	Moved language from Risk/Benefit section.
All	Minor formatting and typographical corrections/edits.	Minor, therefore have not been summarized

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Update of Summary of Clinical Studies in Inflammatory Bowel Disease (IBD)**

The Summary of Clinical Studies in IBD has been revised to align with the updated Investigator's Brochure and the recent results from the phase 3 RPC01-3101 study in ulcerative colitis.

Revised sections: **Section 1.2.2**, Summary of Clinical Studies in Inflammatory Bowel Disease; and **Section 1.2.3**, Rationale for Dose Selection

- **Refinement of Per-Protocol Population**

To ensure data integrity, the per-protocol population has been further defined to ensure subjects included in analysis of primary endpoints are compliant with study treatments and protocol requirements.

Revised sections: Protocol Summary and **Section 9.2**, Study Population Definitions

- **Update and Re-ordering of Endpoints**

Key secondary [redacted] endpoints were revised [redacted] to align with the clinical relevance for evaluating the efficacy in the Crohn's Disease (CD) population.

The endoscopic remission endpoints at Week 52 were previously defined as the proportion of subjects with Simple Endoscopic Score for Crohn's Disease (SES-CD) = 0. [redacted]

The proportion of subjects with a Crohn's Disease Activity Index (CDAI) reduction from baseline of ≥ 100 points or CDAI score < 150 at Week 52 was elevated to the position of the first major secondary endpoint, given its high clinical relevance in evaluating efficacy in the CD population.

Revised sections: Protocol Summary; **Section 2.2.2**, Major Secondary Endpoints; [redacted] and **Section 6.4.1.2**, Simple Endoscopic Score for Crohn's Disease

- **Update of Secondary Objective**

The corticosteroid-free remission objective was revised to align with the corresponding endpoint. It is important to demonstrate that patients on corticosteroids at baseline are able to achieve clinical remission off CSs, as well as demonstrate that the use of corticosteroids was prevented when achieving clinical remission.

Revised sections: Protocol Summary; **Section 2.1.2**, Secondary Objectives

- **Removal of 0.46 mg Treatment Arm from the Maintenance Study**

The results from previous trials to date support the benefit risk profile of a 0.92 mg dose in both CD and ulcerative colitis. Therefore, in an effort to simplify the protocol and complete the evaluation of ozanimod for CD patients in as efficient a manner as possible, the 0.46 mg treatment arm was removed. In addition, the randomization scheme and sample size were

readjusted to reflect the number of subjects needed based on the estimated treatment effects of ozanimod and placebo.

Revised sections: Protocol Summary; **Section 1.2.3**, Rationale for Dose Selection; **Section 2.2.9**, Dose-Ranging Substudy Endpoints (now removed); **Section 3.1**, Study Design; **Section 4.1**, Number of Subjects; **Section 7.1**, Description of Investigational Product(s); **Section 7.2**, Treatment Administration and Schedule; **Section 7.3**, Method of Treatment Assignment; **Section 7.4**, Packaging and Labeling; **Section 9.1**, Overview; **Section 9.3.2**, Power Calculations; **Section 9.3.3**, Sample Size Consideration for the Ozanimod 0.46 mg Group (now removed); and **Section 9.3.3** (previously Section 9.3.4), Stratified Block Randomization

[redacted]

- **CDAI Calculation**

Details on CDAI calculation were removed and will be specified in the Statistical Analysis Plan (SAP).

Revised sections: **Section 6.4.1.1**, Crohn's Disease Activity Index

- [redacted] **Pulmonary Function Tests Will Only Be Required in Subjects Identified as At Risk**

[redacted] Baseline and subsequent pulmonary function tests (PFTs) will be conducted in subjects with a history of respiratory disease not considered to be severe. Additional guidance is also provided for subjects without preexisting respiratory disease who experience a decline in pulmonary function during the study. These revisions are aligned with the prescribing information for ozanimod.

Revised sections: [redacted] **Section 6.5.4**, Pulmonary Function Test; and [redacted]

- **Treatment Re-initiation Monitoring Will Be Required Only in Subjects Identified as at Risk for Cardiac Events**

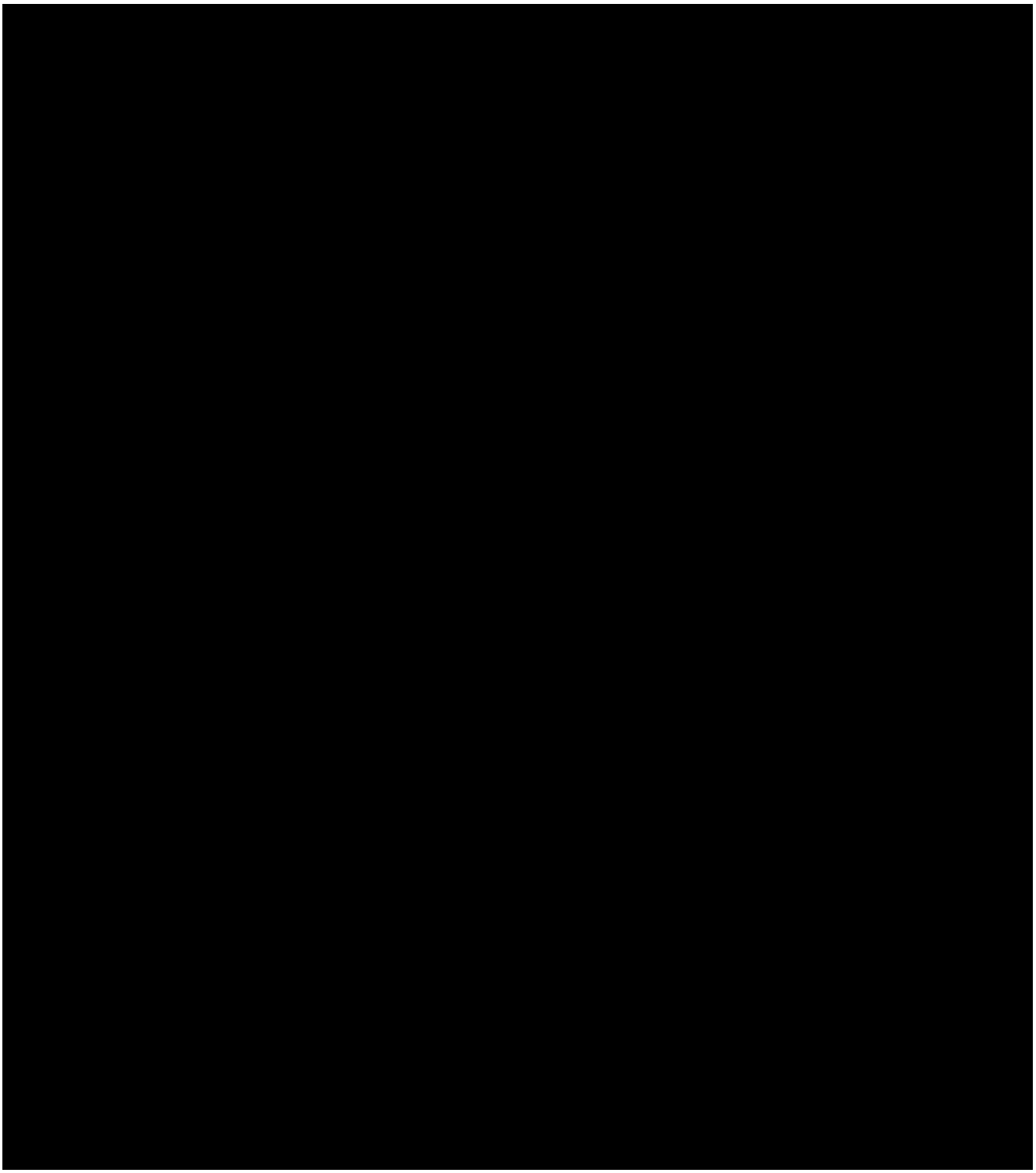
The criteria for cardiac monitoring during re-initiation of treatment have been revised to align with the prescribing information for ozanimod.

Revised sections: **Section 7.2.2** [redacted], Guidelines for Monitoring Subjects at Risk for Cardiac Events During Re-Initiation of Treatment with Investigational Product; and [redacted]

- **Instructions for Missed Doses**

Additional instructions for missed doses were included in accordance with the prescribing information for ozanimod. The instructions for dose escalation upon treatment re-initiation were updated to account for the removal of the 0.46 mg treatment arm.

Revised sections: **Section 7.2**, Treatment Administration and Schedule and **Section 7.2.1**, Instructions for Missed Doses



- **Minor editorial changes to enhance clarity of the protocol, and update study personnel names, abbreviations, and references.**

This document summarizes the changes to Protocol RPC01-3203 from Version 3.0 (dated 18 Jun 2018) to Version 4.0 (dated 10 June 2019).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- Revisions to reflect the addition of adolescent subjects
- Addition of a dose ranging sub-study with a 0.46 mg dose arm

- Minor editorial changes to enhance clarity of the protocol, and update study personnel names.

This document summarizes the changes that were made between Protocol RPC01-3203 Version 3 (dated 18 June 2018) and Version 2 (dated19 December 2017).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each key change:

- A change has been made to provide further guidance to investigators on the management of patients with symptomatic bradycardia, including a reference to local guidelines.

- The protocol was updated to add new protocol template language regarding handling of product quality complaints for any drug product manufactured by or on behalf of Celgene Corporation.

The following bulleted list identifies global changes to the protocol:

- The term “patient” was changed to “subject” throughout the document in order to maintain consistency throughout the protocol.

- The terms “investigational drug” and “study drug” were changed to “investigational product” throughout the document to comply with regulatory guidances and maintain consistency throughout the protocol
- The term “Screening” was changed to “Randomization” throughout the document to maintain consistency and correctness with the study design
- Abbreviations lists in footnotes were updated.
- The list of references has been updated based on changes in this amendment.
- Minor typographical corrections have been made.
- Minor editorial changes and changes for clarification were made.

This document summarizes the changes that were made between Protocol RPC01-3203 Version 1.0 (dated 26 September 2017) and Version 2.0 (dated 19 December 2017).

1. OVERVIEW OF KEY CHANGES

The following bulleted list identifies the key changes to the protocol and provides the rationale for each change:

- The CDEIS is being introduced as an additional secondary endpoint because it is an established endoscopic measure.
- A change has been made to provide further guidance to investigators on the management of patients with symptomatic bradycardia, including a reference to local guidelines.
- Changes have been made to provide further guidance to investigators on cardiac monitoring.
- The section on the evaluation of adverse events was modified since the investigator will not determine whether an adverse event is an adverse event of special interest (AESI). This change was made to better align with the planned designation of AESIs by the sponsor and to align with the Medical Monitoring plan.

[redacted]

The following bulleted list identifies global changes to the protocol:

- A general statement was made to note that additional detailed statistical information can be found in the study Statistical Analysis Plan. Therefore, details were removed from Section 9 (Statistical Considerations).
- Abbreviations lists in footnotes were updated.
- The list of references has been updated based on changes in this amendment.
- Edits were made throughout the document for the purposes of clarity and protocol consistency.
- Minor typographical corrections have been made.