Official Title of Study:

Induction Study #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction Therapy for Moderately to Severely Active Crohn's Disease

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INDUCTION STUDY #2 - A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ORAL OZANIMOD AS INDUCTION THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

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SPONSOR NAME/ ADDRESS:	Celgene International II Sàrl Rue du Pré-Jorat 14 2108 Couvet Switzerland Tel: [redacted]

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PROTOCOL SUMMARY

Study Title

Induction Study #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction 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 most recently 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 recent 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 considerable unmet medical need for safe, effective, and oral treatments for patients with CD.

Objectives

Primary objective:

- Demonstrate the efficacy of ozanimod compared to placebo on the induction of clinical remission

Secondary objectives:

- Demonstrate the efficacy of ozanimod compared to placebo on induction of clinical response, endoscopic response, endoscopic remission, and histologic improvement
- Evaluate the efficacy of ozanimod compared to placebo, in subjects who had previously received biologic therapy (eg, anti-IL-12, anti-IL-23, anti-TNF, or anti-integrin therapy)
- Characterize the population pharmacokinetics (PK) and PK/pharmacodynamics (PD) relationship of ozanimod
- Demonstrate the safety and tolerability of ozanimod as induction therapy

Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to determine the effect of oral ozanimod as an induction treatment for subjects with moderately to severely active CD, defined as a CDAI score ≥ 220 to ≤ 450. Approximately 600 subjects with active clinical symptoms and mucosal inflammation will be randomized in a 2:1 ratio to receive either ozanimod 0.92 mg or placebo. Subjects will be stratified [redacted]. Approximately 50% of subjects with a history of treatment with marketed biologic agents (eg, TNF antagonists, anti-IL-12/23 and anti-integrin therapy) will be recruited. This limit will ensure the enrollment of subjects who have failed or been intolerant to corticosteroids or immunomodulators but never failed a biologic agent. A futility analysis will be conducted when approximately 300 subjects have been enrolled, with a similar proportion of biologic naïve to biologic exposed population as that in the overall study population. [redacted]

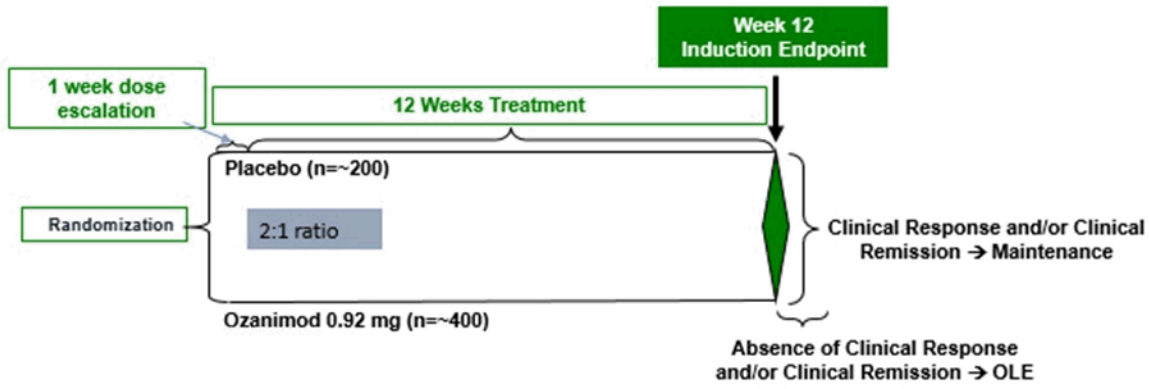
The primary endpoint of the study is the proportion of subjects in clinical remission (CDAI score < 150) at Week 12. Key secondary endpoints are presented in Section 2.

[redacted]

[redacted] Those subjects not meeting the criteria outlined above at the end of the Induction Study will be eligible to enter the Open-Label Extension (OLE) Study (RPC01-3204). Subjects receiving any medical or surgical intervention for the treatment of CD who meet the criteria for treatment failure will be discontinued from the study and will not be eligible for the Maintenance or OLE Studies.

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.

Overall Study Design



Abbreviations: OLE = Open-label Extension

Study Population

Subjects with moderately to severely active CD will be qualified based on clinical symptoms (CDAI ≥ 220 to ≤ 450 with an average stool frequency score ≥ 4 and/or an average abdominal pain score of ≥ 2) and endoscopic findings (Simple Endoscopic Score for Crohn's Disease [SES-CD] ≥ 6 or ≥ 4 for isolated ileal disease).

Length of Study

Subjects who complete the Induction Study are anticipated to receive 12 weeks of treatment (12-week Induction Study). Subjects not entering the Maintenance Study or Open-Label Extension Study will have [redacted]

The end of study (Induction Study RPC01-3202) is defined as either the date of the last visit of the last subject to complete the Safety Follow-up, 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.

Study Treatments

Following a 7-day dose escalation, subjects will receive a single 0.92 mg oral dose of ozanimod (equivalent to ozanimod HCl 1 mg) or matching placebo administered daily. The dose escalation regime is as follows:

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

Day 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)

Day 8 through Week 12: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg) (or matched placebo)

Overview of Key Efficacy Assessments

Note: All endpoints will evaluate subjects at Week 12 unless otherwise specified.

Primary Endpoint:

- Proportion of subjects with a CDAI score < 150 at Week 12

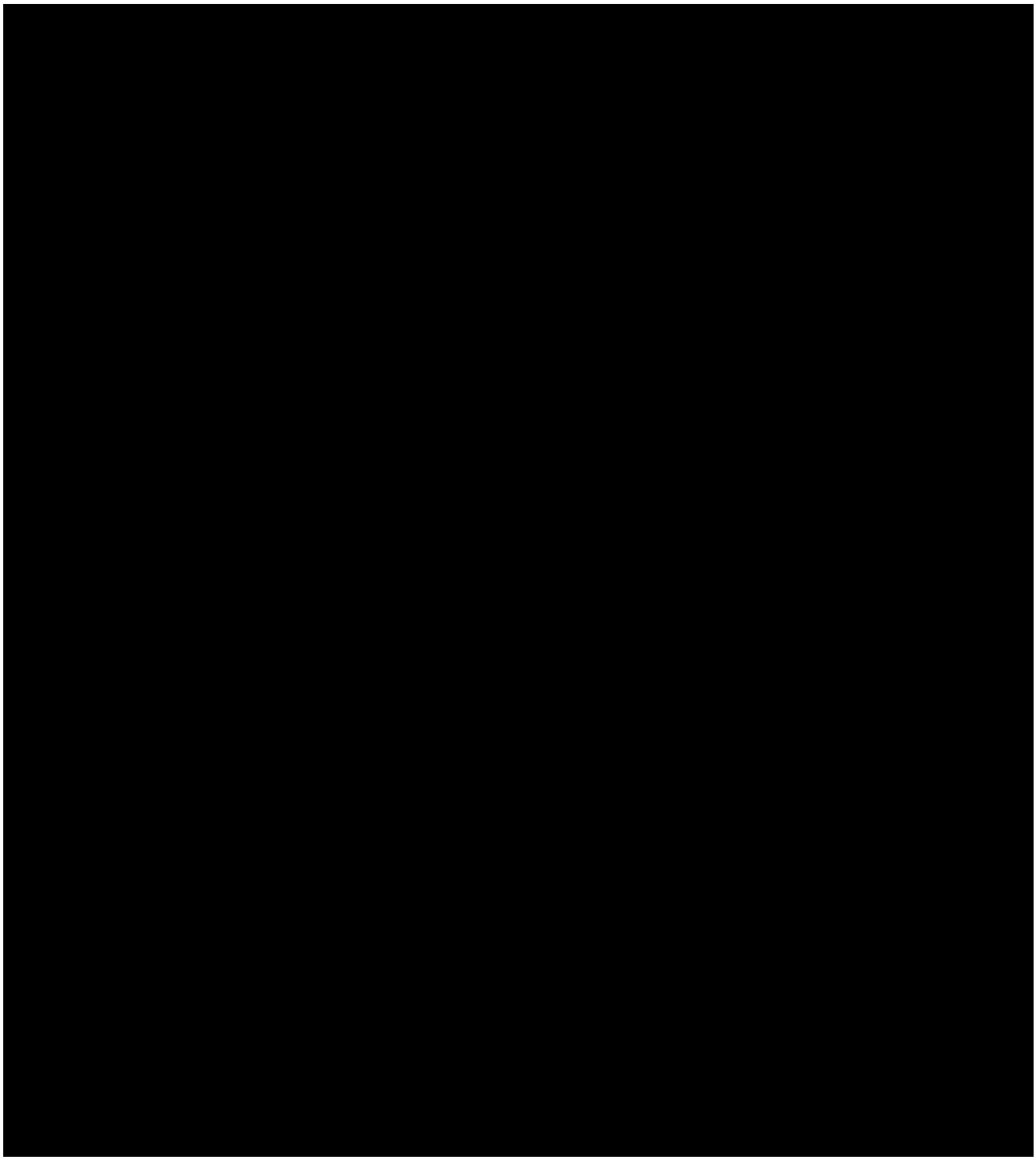
Major Secondary Endpoints:

- 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 at Week 12
- Proportion of subjects with a Simple Endoscopic Score for Crohn's Disease (SES-CD) score decrease from baseline of ≥ 50% at Week 12
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score < 150 at Week 12
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score < 150 and SES-CD decrease from baseline of ≥ 50% at Week 12

Other Secondary Endpoints:

- Proportion of subjects with CDAI score < 150 at Week 12 and SES-CD decrease from baseline of ≥ 50% at Week 12
- Proportion of subjects with an 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 an SES-CD ≤ 4 points and decrease ≥2 points at Week 12
- Proportion of subjects with an 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 an SES-CD decrease from baseline of ≥ 50% at Week 12
- Histologic Improvement based on differences between ozanimod and placebo in histologic disease activity scores (ie, Global Histologic Activity Score (GHAS) changes (Geboes, 2000) at Week 12

- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points at Week 12
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥ 10% at Week 12
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline of ≥ 50% at Week 12



[redacted]

Overview of Key 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 [redacted], clinical laboratory measures, vital signs, and electrocardiograms (ECGs).

Statistical Methods

This is a Phase 3, double-blind, randomized, placebo-controlled study to explore the effect of oral ozanimod as an induction treatment on clinical remission for 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.

- Per-protocol (PP): The PP population will consist of all subjects in the ITT population who do not have protocol deviations that may substantially affect the primary efficacy assessment. This population will be used in a sensitivity analysis of the primary endpoint.

Determination of Sample Size for the Primary Endpoint

The primary endpoint is CDAI clinical remission at Week 12. Subjects will be deemed a responder with respect to this endpoint if they meet the definition for CDAI clinical remission at Week 12. This study is designed to have at least a 90% power to correctly detect a statistically significant difference between placebo and ozanimod with respect to this endpoint.

Sample size determination was done separately for the two-group chi-square test of equal proportions with 2:1 unbalanced treatment arms. This yields an overall sample size of 600 with the assumption of a type I error rate of 5%. The overall type I error rate across all controlled endpoints will be maintained at 5%.

Efficacy Analyses

A futility analysis is planned to be performed when approximately 300 subjects (with a similar proportion of biologic naïve to biologic exposed subjects as that in the overall study population) from both Induction Studies, collectively, have completed the 12-week Induction Period. The analysis will occur after these subjects have completed the Induction Period and the data have been cleaned. The primary endpoint, CDAI remission (CDAI < 150) at Week 12 be used in the analysis.

[redacted] The Induction Studies (RPC01-3201 and RPC01-3202) may be stopped for futility if the observed treatment effect size in CDAI remission is at a low probability to demonstrate superiority. Additional efficacy endpoints including CDAI response, abdominal pain and stool frequency scores, SES-CD, [redacted] will be evaluated as supporting analyses. The futility boundary is "non-binding," implying that the boundary can be overruled if desired without inflating the type-1 error. The "non-binding" boundary is intended to allow the Sponsor or the independent Data Monitoring Committee (DMC) to continue the study to gather additional information, despite crossing the futility boundary.

The futility analysis will be conducted by the designated unblinded team (statistician and programmers) that supports the DMC and the results will be sent to the DMC and may also be sent to a Celgene internal review committee (IRC) for review. The Celgene IRC members will not play a role in the study conduct, and the blind will be maintained for persons responsible for the ongoing conduct and management of the study through the end of the Maintenance Study (RPC01-3203), until database lock.

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

The primary analysis of proportion of clinical remission (as well as clinical response) endpoints will be carried out using the Cochran-Mantel-Haenszel (CMH) test to account for [redacted] as randomization stratification factors.

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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 interleukin-12 and interleukin-23, was most recently 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 recent 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 considerable unmet medical need for safe, effective, and 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. 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 S1P2, > 5000 nM for S1P3, and > 2000 nM for S1P4. 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 S1P1, 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 S1P1 and S1P5 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 inflammatory bowel disease, 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 Investigator's Brochure 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 (RPC01-3102).

At the conclusion of the Induction Phase of RPC01-202, the proportion of subjects 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 signal observed.

RPC01-202 also had a maintenance phase and an open-label extension (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 induction of clinical remission at Week 10 and in maintenance at Week 52 (Sandborn, 2020). 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 in the Induction Period and up to 148 weeks in the Extended Period. 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 Investigator's Brochure 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 single ascending dose and multiple ascending dose studies in Phase 1 were utilized to select appropriate doses for Phase 2 studies. The Phase 2 study 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) in subjects with active CD treated with ozanimod 0.92 mg suggest clinical benefit based on clinical, endoscopic, histologic [redacted] 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 CD program.

A dose escalation regimen over the first 7 days is being utilized [redacted] 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 Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.2.4. Benefit Risk Assessment

Despite recent progress in CD treatment, there remains an unmet need for oral agents that are safe and convenient and that can provide effective induction and long term maintenance of clinical remission. The benefit risk profile for ozanimod has been evaluated for the indication of Crohn's disease. 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 generally well tolerated in patients with Crohn's disease and is consistent with that observed in other patient populations (UC and RMS). The overall data to date suggest that this ozanimod Induction Study (RPC01-3202) has a potential favorable benefit risk profile for patients with moderate to

severe Crohn's disease who have inadequate response or intolerance to corticosteroids, immunomodulators, or biologic therapy.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global health pandemic has been identified as a potential risk to clinical trial subjects in general and may particularly affect patients with underlying chronic disease. It is not known if taking ozanimod increases the risk of SARS-CoV-2 infection, or the duration or severity of coronavirus disease 2019 (COVID-19). The individual benefit risk considerations remain the responsibility of the Investigator. Investigators should apply clinical judgment and these risks should be considered when enrolling a subject.

The exclusion criteria (Section 4.3) have been designed to exclude people with current and recent infections. Testing to exclude asymptomatic SARS-CoV-2 prior to enrollment should follow local practice.

The study has been designed with study visits that allow for close monitoring of subjects' safety throughout the clinical trial (Table 1), and subjects are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice.

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 consider holding dosing of investigational product and to consult the Medical Monitor.

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 benefit risk 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 authorized (ie, Emergency Use Authorization [FDA] or equivalent) by national health authorities.

1.3. Study Rationale

Given the mechanism of action of ozanimod, data from the preclinical animal model, the positive results from the Phase 2 (RPC01-202) and Phase 3 (RPC01-3101) UC studies, and preliminary results from the Induction Period of the Phase 2 study in CD (RPC01-2201), a Phase 3 program with ozanimod in CD is being initiated.

The current study is designed as a double-blind, placebo-controlled study to assess the efficacy and safety of ozanimod in inducing clinical remission and response in subjects with moderately to severely active CD.

Primary efficacy assessment of ozanimod 0.92 mg per day will be assessed at Week 12 based on the efficacy results seen in the RPC01-2201 study after 12 weeks of treatment with ozanimod 0.92 mg daily.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective:

- Demonstrate the efficacy of ozanimod compared to placebo on the induction of clinical remission

2.1.2. Secondary Objectives:

- Demonstrate the efficacy of ozanimod compared to placebo on induction of clinical response, endoscopic response, endoscopic remission, and histologic improvement
- Evaluate the efficacy of ozanimod compared to placebo, in subjects who had previously received biologic therapy (eg, anti-IL-12, anti-IL-23, anti-TNF, or anti-integrin therapy)
- Characterize the population pharmacokinetics (PK) and PK/pharmacodynamics (PD) relationship of ozanimod
- Demonstrate the safety and tolerability of ozanimod as induction therapy

2.2. Study Endpoints

Note: All endpoints will evaluate subjects at Week 12 unless otherwise specified.

2.2.1. Primary Endpoint:

- Proportion of subjects with a CDAI score < 150 at Week 12

2.2.2. Key Secondary Endpoints:

- 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 at Week 12
- Proportion of subjects with a Simple Endoscopic Score for Crohn's Disease (SES-CD) score decrease from baseline of ≥ 50% at Week 12
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score < 150 at Week 12
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score < 150 and SES-CD decrease from baseline of ≥ 50% at Week 12

2.2.3. Other Secondary Endpoints:

- Proportion of subjects with CDAI score < 150 at Week 12 and SES-CD decrease from baseline of ≥ 50% at Week 12
- Proportion of subjects with an 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 an SES-CD ≤ 4 points and decrease ≥ 2 points at Week 12

- Proportion of subjects with an average daily abdominal pain score ≤ 1 point, and average daily stool frequency score ≤ 3 points with abdominal pain and stool frequency score no worse than baseline and an SES-CD decrease from baseline of ≥ 50% at Week 12
- Histologic Improvement based on differences between ozanimod and placebo in histologic disease activity scores (ie, Global Histologic Activity Score (GHAS) changes) (Geboes, 2000) at Week 12
- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points at Week 12
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥10% at Week 12
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline of ≥ 50% at Week 12

[redacted]

2.2.7. Overview of Key Safety Assessments

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

3. OVERALL STUDY DESIGN

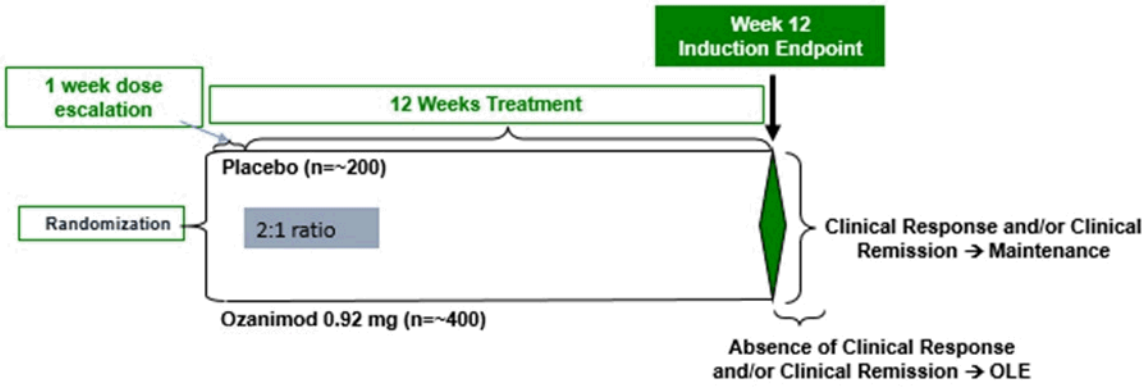
3.1. Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled study to explore the effect of oral ozanimod as an induction treatment for subjects with moderately to severely active CD, defined as a CDAI score ≥ 220 to ≤ 450. Approximately 600 subjects with active clinical symptoms and mucosal inflammation will be randomized in a 2:1 ratio to receive either ozanimod 0.92 mg or placebo. Subjects will be stratified [redacted]. A maximum of approximately 50% of subjects with a history of treatment with marketed biologic agents (eg, TNF antagonists, anti-IL-12/23, and anti-integrin therapy) will be recruited. This limit will ensure the enrollment of subjects who have failed or been intolerant to corticosteroids or immunodulators but never failed a biologic agent.

The primary endpoint of the study is the proportion of subjects in clinical remission (CDAI score < 150) at Week 12. Key secondary endpoints are provided in Section 2. A futility analysis will be conducted when approximately 300 subjects have been enrolled, with a similar proportion of biological naïve to biological exposed population as that in the overall study population. [redacted] Subjects who received placebo 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 at the end of this study will continue to receive placebo in a blinded fashion in the Maintenance Study. Those subjects not meeting the criteria outlined above at the end of the Induction Study will be eligible to enter the OLE Study (RPC01-3204). Subjects receiving any medical or surgical intervention for the treatment of CD that meet the criteria for treatment failure (Section 9.8) will be discontinued from the study and will not be eligible for the Maintenance or OLE Studies.

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



Abbreviations: OLE = Open-Label Extension.

3.2. Study Duration for Subjects

Subjects who complete the Induction Study are anticipated to receive 12 weeks of treatment (12-week Induction Study). Subjects not entering the Maintenance Study or Open-Label Extension Study will have [redacted]

3.3. End of Study

The end of study (Induction Study RPC01-3202) is defined as either the date of the last visit of the last subject to complete the [redacted] 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.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 600 subjects with moderately to severely active CD will be randomized in a 2:1 ratio to receive either ozanimod 0.92 mg or placebo.

4.2. Inclusion Criteria

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

1. Male or female subjects aged 18 to 75 years (at Screening)
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 with the Table of Events.
3. Subject has signs and symptoms consistent with a diagnosis of CD for at least 3 months (prior to first IP administration). The diagnosis should be confirmed by clinical and endoscopic evidence and corroborated by a histology report. (Note: endoscopy and local histopathology confirmation may be obtained during Screening if no prior report is readily available).
4. Subject has met each of the following 2 criteria:
   - a CDAI score ≥ 220 and ≤ 450
   - an average daily stool frequency ≥ 4 points and/or an abdominal pain of ≥ 2 points
5. Subject has a SES-CD score of ≥ 6 (or SES-CD ≥ 4 in subjects with isolated ileal disease).
6. Subject has an inadequate response or loss of response to or is intolerant of at least 1 of the following systemic CD treatments (see Appendix B for additional details):
   - corticosteroids
   - immunomodulators
   - biologic therapies (eg, ustekinumab, TNFα antagonists, or vedolizumab)
7. If the subject is taking the following background therapies for CD, a stable dose must be maintained throughout the study beginning from the screening period as indicated below:
   - oral aminosalicylates (eg, mesalamine, sulfasalazine, olsalazine, balsalazide) with a stable dose for at least [redacted] prior to Screening endoscopy
   - prednisone (doses [redacted]) or equivalent with a stable dose for at least [redacted] prior to Screening endoscopy
   - budesonide therapy (doses [redacted]) or beclomethasone (doses [redacted]) at a stable dose for at least [redacted] prior to the Screening endoscopy
8. Subject at high risk (ie, family history, CD duration) for colonic malignancy has documented evidence of having had a surveillance colonoscopy within the last 2 years or according to local and national medical guidelines to evaluate for polyps, dysplasia, or

malignancy. If there is no recent history of surveillance colonoscopy, this can be done as part of the colonoscopy performed during Screening. Any visualized adenomatous polyps must be removed and any suspicious lesion confirmed free of cancer and/or dysplasia prior to randomization.

9. Female subjects of childbearing potential (FCBP):

   Note: For the purposes of this study, a female subject is considered to be of childbearing potential if 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. The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence at Screening and Day 1, as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

10. Subject must have documentation of positive varicella zoster virus (VZV) [redacted] or complete VZV vaccination at least 30 days prior to randomization. See Section 11.3.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment or at the timepoint specified in the following criteria:

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.
2. Subject is likely to require, in the physician's judgment, bowel resection within 12 weeks of entry into the study.
3. Subject has a diagnosis of UC, indeterminate colitis, radiation colitis, or ischemic colitis, or has strictures with prestenotic dilatation, requiring procedural intervention, or with obstructive symptoms. In addition, subjects with colonic or ileal strictures that are not passable with an age-appropriate colonoscope that the endoscopist normally uses in clinical practice, or strictures in the ileum or ileocecal valve that are fibrotic in nature, will be excluded. Any other modality used in addition to the colonoscopy to assess this criterion must be discussed with the Medical Monitor.
4. Subject has current stoma, ileal-anal pouch anastomosis, fistula that is likely to require, in the physician's judgement, surgical or medical intervention within 12 weeks of entry into the study or need for ileostomy or colostomy.
5. Subject has extensive small bowel resection (> 100 cm) or known diagnosis of short bowel syndrome, or subject requires total parenteral nutrition.
6. Subject has suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated.
7. Subject has documentation of positive test for toxin producing *Clostridium difficile* (*C. difficile*), or polymerase chain reaction (PCR) examination of the stool. If positive, subjects may be rescreened after appropriate treatment and retested no earlier than 7 days after completion of treatment.
8. Subject has documentation of positive examination for pathogens (ova and parasites, and bacteria). If positive, subjects may be treated and rescreened.
9. Subject is pregnant, lactating, or has a positive serum beta human chorionic gonadotropin (β-hCG) test measured during Screening.
10. Subject has any condition that would make implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study, including history or presence of the following clinically relevant cardiovascular conditions:
    - Recent (within the last 6 months) occurrence of myocardial infarction, unstable angina, stroke, transient ischemic attack, symptomatic bradycardia, decompensated

heart failure requiring hospitalization, Class III/IV heart failure, or severe untreated sleep apnea

- Second degree (Mobitz type II) atrioventricular (AV) block, third degree AV block, sick sinus syndrome or sino-atrial block in subjects without a pacemaker in place (for subjects with a pacemaker in place, [redacted]); if second degree Type II or third degree AV block is due to concomitant medication, consult Medical Monitor prior to Screening
- Prolonged QT interval corrected for heart rate using Fridericia's formula (QTcF) (QTcF > 450 msec males, > 470 msec females) at either Screening or Day 1 Predose assessment.
- Resting [redacted] when taking vitals as part of the physical examination at either Screening or Day 1 Predose assessment. One recheck is allowed for subjects with [redacted] per visit (ie, during the Screening and/or Day 1 Predose assessment visit).

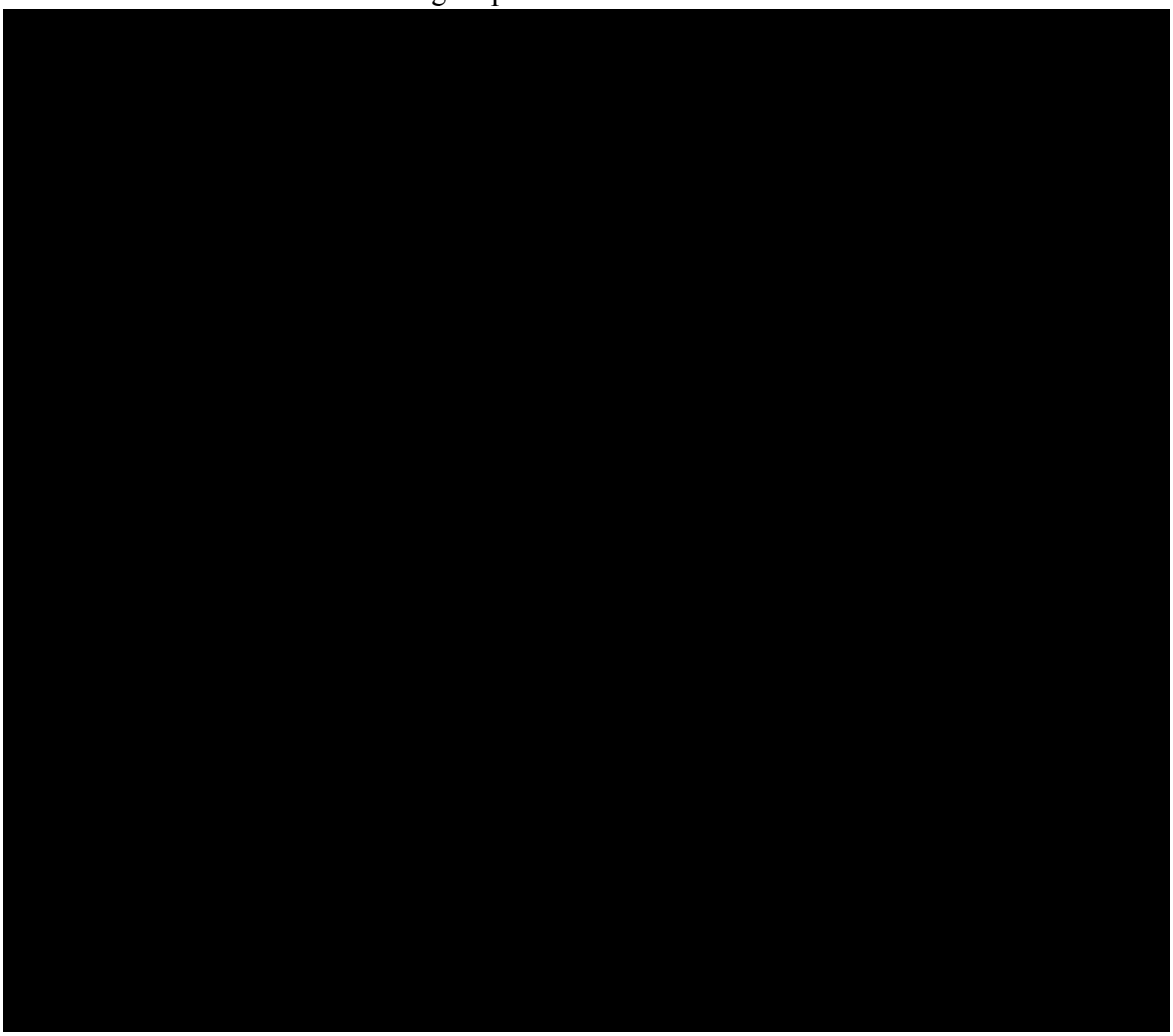
Note: Subjects with certain preexisting cardiac conditions, as detailed [redacted], may be considered for participation in the trial.

11. Subject has a history of diabetes mellitus type 1, or uncontrolled diabetes mellitus type 2 with hemoglobin A1c (HbA1c) > 9% or is a diabetic subject with significant comorbid conditions such as retinopathy or nephropathy.
12. Subject has a history of uveitis (within the last year prior to Screening) or a history of macular edema.
13. Subject has a known active bacterial, viral, fungal (excluding fungal infection of nail beds, minor upper respiratory tract infections, and minor skin infections), mycobacterial infection (including tuberculosis [TB] or atypical mycobacterial disease) or any major episode of infection that either required hospitalization, treatment with intravenous (IV) antibiotics within 30 days of Screening, or treatment with oral antibiotics within 14 days of Screening
    - Note: In the case of a known SARS-CoV-2 infection, symptoms must have completely resolved and based on Investigator assessment in consultation with the Clinical Trial Physician / Medical Monitor, there are no sequelae that would place the subject at a higher risk of receiving investigational treatment. [redacted] See Appendix C for more details.
14. History or known presence of recurrent or chronic infection (eg, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV); recurrent urinary tract infections are allowed.
15. Subject has a history of 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.

16. Subject has a history of alcohol or drug abuse within 1 year prior to initiation of Screening.

Exclusions Related to Medications:

17. Hypersensitivity to active ingredients or excipients of ozanimod or placebo
18. Prior participation in an ozanimod clinical study.
19. Subject has a history of primary nonresponse to 2 or more approved biologic agents or has been treated with 4 or more biologics for CD. Subjects who have received biologic therapy at sub-therapeutic doses, or durations, should be discussed with the Medical Monitor to assess eligibility.
20. Subject has been treated with a biologic agent within 8 weeks or 5 elimination half-lives (whichever is shorter) prior to the first dose of IP.
21. Subject has a history of treatment with an investigational agent within 5 elimination half-lives of that agent prior to the first dose of IP.



Exclusions Related to Laboratory Results and Other Assessments:

Note: Approval from the Medical Monitor or designee must be obtained if retest is required to be repeated > 2 times for assessing the following criteria:

36. Subject has screening ECG results showing any clinically significant abnormality.
37. Subject has serum creatinine results > 1.4 mg/dL (128 µmol/L) for female or > 1.6 mg/dL (145 µmol/L) for male.
38. Subject has liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) results > 2 x the upper limit of normal (ULN), or direct bilirubin > 1.5 x ULN.
39. Subject has a platelet count < 100,000/µL (100 GI/L).
40. Subject has hemoglobin < 7.5 g/dL (75 g/L).
41. Subject has neutrophils < 1500/µL (1.5 GI/L).
42. Subject has an absolute white blood cell (WBC) count < 3500/µL (3.5 GI/L).
43. Subject has an absolute lymphocyte count (ALC) < 800 cells/µL (0.80 GI/L).
44. Subject has a forced expiratory volume at 1 second (FEV1) or forced vital capacity (FVC) < 70% of predicted values at screening.

5. TABLE OF EVENTS

Table 1: Table of Events

	Study Procedures	Screening	Initiation of Dose Escalation	Treatment				Early Termination (ET)	[redacted]
			Day 1[a,b]	Day 8	Week 4[b]	Week 8[b]	Week 12[b]		
		Day -35 to 0	Day 1 (Baseline)	Day 8	Day 28 ±3 [aa]	Day 56 ±3 [aa]	Day 84 ±3 [aa]	Day ET	
[redacted]									

Table 1: Table of Events (Continued)

	Study Procedures	Screening	Initiation of Dose Escalation	Treatment				Early Termination (ET)	[redacted]
			Day 1[a,b]	Day 8	Week 4[b]	Week 8[b]	Week 12[b]		
		Day -35 to 0	Day 1 (Baseline)	Day 8	Day 28 ±3 [aa]	Day 56 ±3 [aa]	Day 84 ±3 [aa]	Day ET	
[redacted]									

Table 1: Table of Events (Continued)

	Study Procedures	Screening	Initiation of Dose Escalation	Treatment				Early Termination (ET)	[redacted]	
			Day 1[a,b]	Day 8	Week 4[b]	Week 8[b]	Week 12[b]			
		Day -35 to 0	Day 1 (Baseline)	Day 8	Day 28 ±3 [aa]	Day 56 ±3 [aa]	Day 84 ±3 [aa]	Day ET		
Efficacy Assessments	Electronic diary[w]	X	X		X	X	X	X		
	[redacted]									
	CDAI	X[q]	X		X	X	X[r]	X		
	Colonoscopy/SES-CD/ CDEIS/colonic biopsy[s]	X					X	X		
[redacted]										

Abbreviations:

CDAI = Crohn's Disease Activity Index; CDEIS = Crohn's Disease Endoscopic Index of Severity;
ET = early termination;

[redacted]

[a] [redacted]

[b] Study visits should be scheduled in the morning, where possible, and on study visit days, subjects should be instructed to withhold the dose until the study visit and the dose should be administered during the visit after the PK draw.

[redacted]

[s] Colonoscopy should be performed upon confirmation of eligibility based on CDAI at Screening and other entry criteria, if possible. A subject's colonoscopy from a previous screening in this study may be used if within 35 days of randomization. If early termination visit is less than 4 weeks after Baseline, no further colonoscopy is required. At Week 12, a colonoscopy should be performed either on day of visit or no more than 7 days prior to the visit date. Intestinal mucosal biopsies will be performed when the ileocolonoscopies are done as indicated in Table 1, except in countries or sites with local restrictions.

[redacted]

[w] The electronic daily diary will be provided to subjects at the Screening Visit. Subject compliance with the completion of the diary data should be assessed at each study visit.

[redacted]

6. PROCEDURES

[redacted]

6.1. Screening Period

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).

Screening procedures must be completed within 35 days prior to receiving the first dose of IP. All screening assessments and procedures as per Table 1 are to be performed by the Investigator or a qualified designee. During the screening period, [redacted]

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

A screen failure is defined as a subject who has given informed consent and failed to meet the inclusion and/or exclusion criteria. Subjects who fail to meet the inclusion/exclusion criteria can be rescreened per Investigator discretion. Additional screening attempts beyond the first should be approved by the Medical Monitor prior to rescreening.

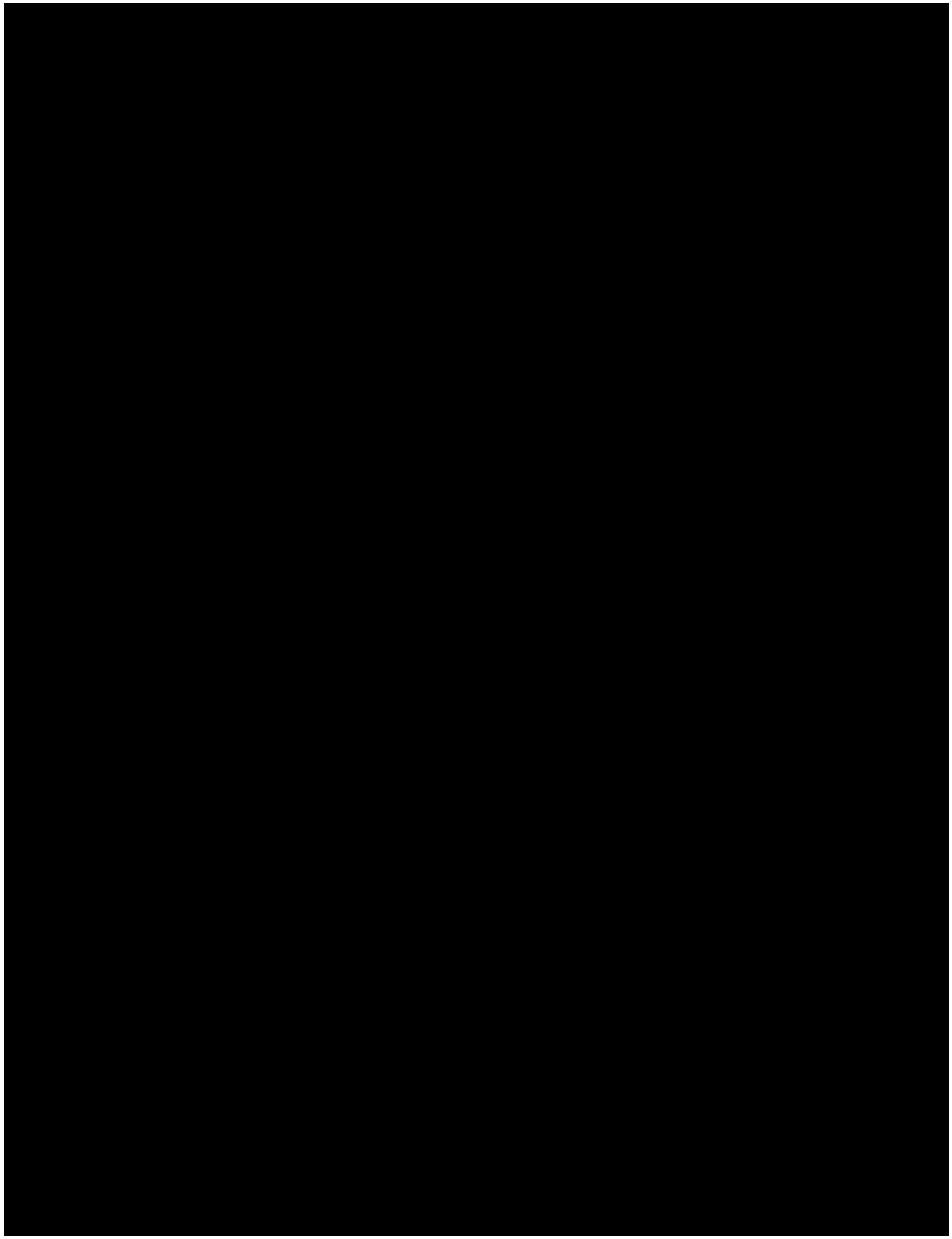
During Screening, the subject's prior use of medications to treat CD and whether he/she responded to adequate treatment with each medication will be assessed and documented.

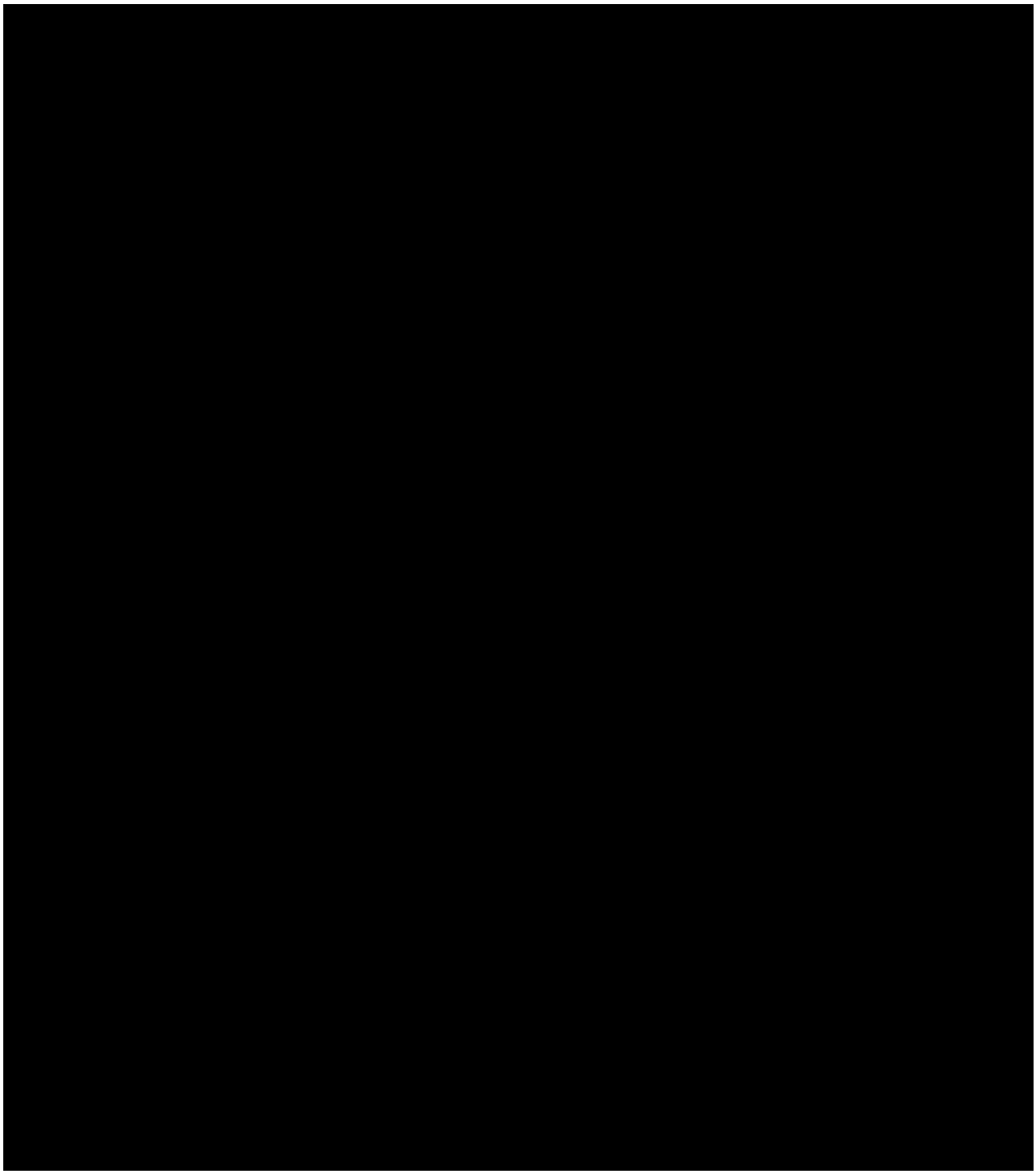
It will also be documented when the subject has been intolerant to 1 of these therapies (eg, unable to achieve doses as indicated in Appendix B, dose levels, or treatment durations because of treatment-related side effects and/or laboratory abnormalities).

Screening period schedule and procedures are provided in the Table of Events (Table 1). Each subject must be re-consented prior to each screening attempt. A subject's colonoscopy from a previous screening in this study may be used if within 35 days of randomization.

6.2. Treatment Period

Eligible subjects will be randomized to treatment on Day 1. Visits, assessments, and procedures will be performed as per the Table of Events in Table 1. [redacted]





6.2.4. 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 safety follow-up 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.

6.3. [redacted]

[redacted]

6.3.2. Efficacy Assessments

See Section 2 for a description of study endpoints.

6.3.2.1. Primary Efficacy Assessment

The CDAI will be used to evaluate the primary efficacy endpoint.

6.3.2.1.1. 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 3. The definitions of mild, moderate, and severe CD are provided in Table 4.

[redacted]

[redacted]

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 screening 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 Screening and throughout the study.

Table 3: Crohn's Disease Activity Index Assessment

Clinical or Laboratory Variable	**Weighting Factor, ×**
Number of liquid or soft stools each day for 7 days[redacted]	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[b]	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 4: Crohn's Disease Severity Definitions

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

Abbreviations: CDAI = Crohn's Disease Activity Index.

6.3.2.1.2. Abdominal Pain and Stool Frequency

The abdominal pain and stool frequency scores are based on 2 components of the CDAI (Khanna 2015). See Section 6.3.2.1 above for more details.

Stool frequency and abdominal pain, as described in Section 6.3.2.1, will be obtained and calculated without a weighting factor for use as part of the inclusion criteria. These un-weighted subject-reported assessments will also be used as efficacy endpoints (Section 2).

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

[redacted]

6.3.2.2. Simple Endoscopic Score for Crohn's Disease

The SES-CD assesses the degree of inflammation. The SES-CD assesses the following four 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 5.

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. [redacted], the same endoscopist and the same diameter colonoscope as used in screening should be used throughout the study wherever possible. [redacted] 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.

Local colonoscopy may be used for baseline assessments in the Induction Study if within 35 days of baseline, consent was obtained from the subject for use in a clinical study, and video quality and format is considered adequate for evaluation by centralized reading facility.

Table 5: Definitions of Simple Endoscopic Score for Crohn's Disease (SES-CD)

	SES-CD 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

6.3.2.3. Histology

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

Table 6: GHAS Grading System

GHAS Descriptors and Levels	
Epithelial damage	0: Normal 1: Focal Pathology 2: Extensive Pathology
Architectural changes	0: Normal 1: Moderately disturbed (< 50%) 2: Severely disturbed (> 50%)
Infiltration of mononuclear cells in the lamina propia	0: Normal 1: Moderate increase 2: Severe increase
Infiltration of polymorphonuclear cells in the lamina propria	0: Normal 1: Moderate increase 2: Severe increase
Polymorphonuclear cells in epithelium	0: Absent 1: In surface epithelium 2: Cryptitis 3: Crypt abscess
Presence of erosion and/or ulcers	0: No 1: Yes

Table 6: GHAS Grading System (Continued)

GHAS Descriptors and Levels	
Presence of granuloma	0: No 1: Yes
Number of biopsy specimens affected[a]	0: None 1: ≤ 33% 2: > 33%-66% 3: > 66%

Abbreviations: GHAS = Global Histologic Activity Score

[a] For individual segments with only one biopsy segment available, determine if the sample is entirely involved or not. If the fragment is not involved, score as '0 – None'. If ≤ 33% of the fragment is involved, score as '1 - ≤ 33%'. If 34 to 66% of the fragment is involved, score as '2 - 34%-66%'. If > 66% of the fragment is involved, score as '3 - > 66%'.

[redacted]

6.3.3. Other Assessments

6.3.3.1. Physical Examination

A complete physical examination will be performed to evaluate the heart, lungs, head and neck, abdomen, skin, extremities, weight, as well as to check for visual symptoms (eg, blurred vision or decreased visual acuity as reported by the patient). Height should be measured and recorded at

screening. 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 patient. See Table 1 for additional details and assessment time points.

6.3.3.2. Vital Signs

Systolic and diastolic blood pressure and pulse will be assessed in a supine and standing position at every visit. An automated validated device may be used, if available. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Subjects will be carefully monitored after the first dose of investigational drug with a 6 hour post-dose monitoring period of hourly recording of pulse and blood pressure as described in [redacted].

6.3.3.3. Electrocardiogram

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the study. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the study-specific manual and provided to the site before the start of the study. 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. Electrocardiograms will be performed before the first dose of IP in all subjects and 2, 4 and 6 hours after the first dose of investigational drug administration for at-risk subjects (as outlined [redacted]), or in all subjects if deemed necessary by national and local requirements, on Day 1 while the subject is in the clinic.

All ECGs will be evaluated by the treating physician, with input from a local cardiologist (upon approval from a Medical Monitor) or a central reader to confirm if additional monitoring is required. If a local cardiologist is not available upon discharge, discharge criteria were evaluated by the treating physician, and the central results are assessed as abnormal or unmeasureable then the subject will need to return for further evaluation.

[redacted]

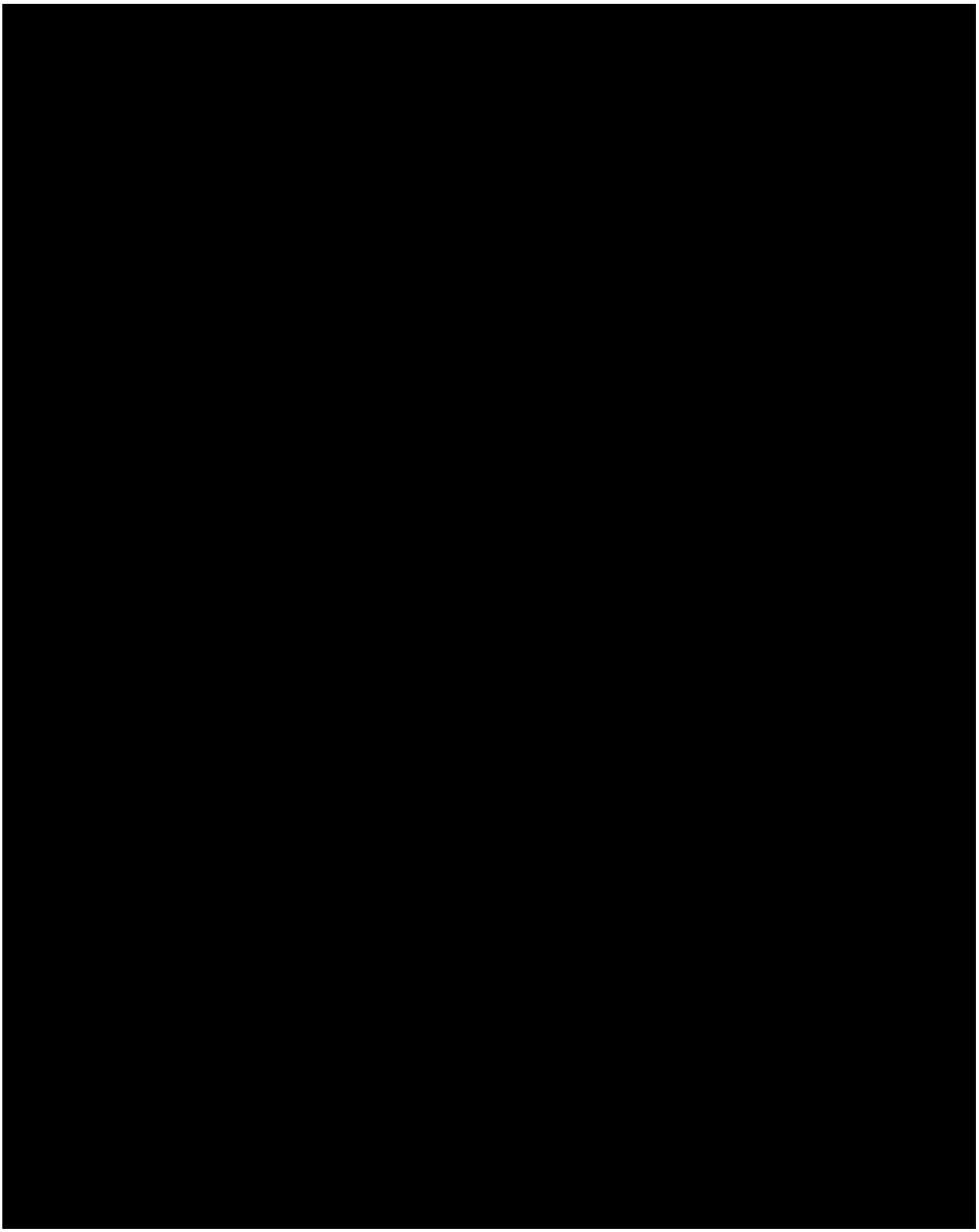
Only clinically significant abnormalities should be reported in the medical history/current medical conditions or the AE eCRF.

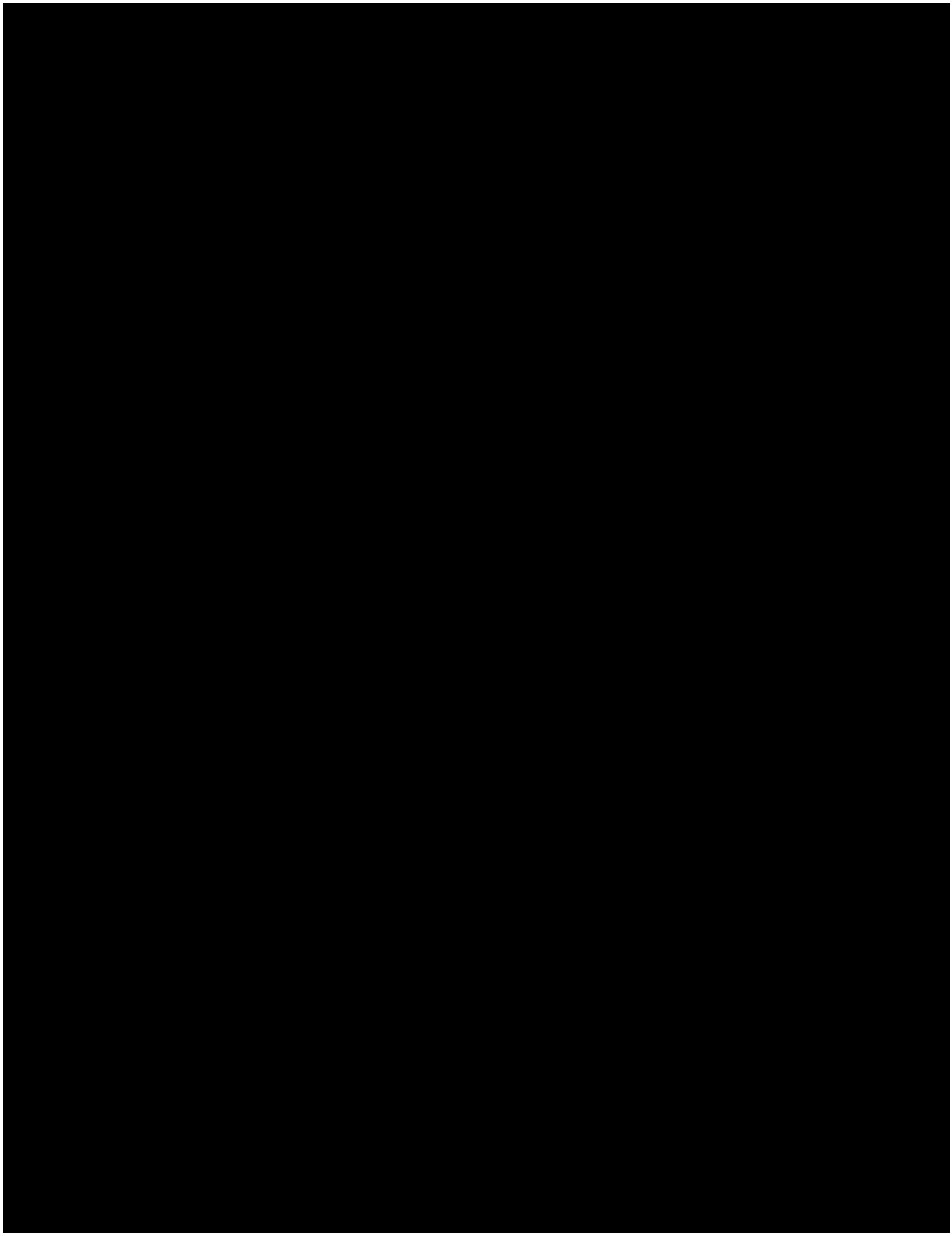
6.3.3.4. Pulmonary Function Test

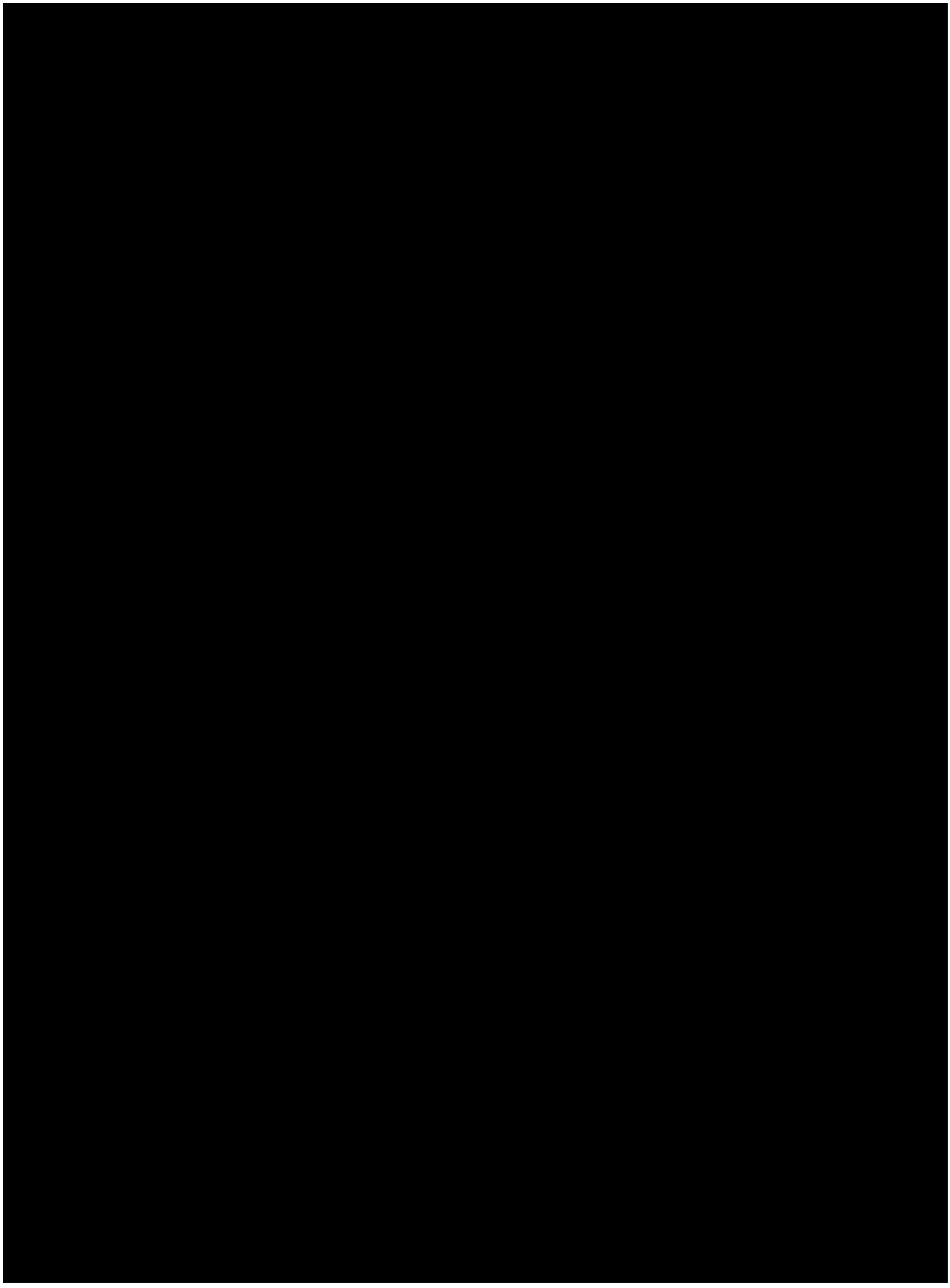
The pulmonary function test (PFT) refers to "pulmonary function test – no bronchodilator" (eg, spirometry which includes total and timed vital capacity, and expiratory flow rate measurement). [redacted]

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).







7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product

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. Both 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

Following the 7-day dose escalation, subjects will receive a single 0.92 mg oral dose of ozanimod (equivalent to ozanimod HCl 1 mg) or matching placebo administered daily. The dose escalation regime is as follows:

- Day 1 through 4: Ozanimod 0.23 mg (equivalent to ozanimod HCl 0.25 mg) (or matched placebo)
- Day 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)
- Day 8 through Week 12: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg) (or matched placebo)

[redacted]

If subjects miss dosing for more than 14 days, they are required to complete the 7-day dose escalation regimen as outlined above, including [redacted].

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 Medical Monitor or other designated Drug Safety Center. The overdose should be recorded in the study exposure eCRF. AEs associated with an overdose should be reported on relevant AE/SAE sections in the eCRF.

Please refer to the Investigator's Brochure 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. 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 a single dose is missed during the first 2 weeks of treatment, or for more than 7 consecutive days during Days 15 to 28, treatment must be reinitiated using the [redacted] If a subject misses a dose during dose escalation, the Medical Monitor should be contacted to discuss completing the dose escalation schedule. The missed dose and extended days for escalation need to be documented as appropriate in the eCRFs.

If a subject misses more than 14 consecutive doses for any reason, the Medical Monitor must be contacted to discuss procedures for resuming therapy, [redacted].

7.3. Method of Treatment Assignment

Subjects will be assigned as follows:

- ozanimod 0.92 mg capsule orally starting with a 7-day dose escalation
- matching placebo capsule orally starting with a 7-day dose escalation

7.4. Packaging and Labeling

[redacted]

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

IP 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 the 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 Trial 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. IP and all medication containers will be returned to the clinical supply distribution vendor and documentation will be returned to the Clinical Research Organization. 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 to 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. A complete history of all previous treatments for CD must be documented. All diagnostic, therapeutic, or surgical procedures and/or past biologic exposure relating to CD should be recorded. Histories of all other prior medications taken during the 30 days prior to the date of informed consent, must also be documented.

Administration of concomitant medications must be reported along with dosage information, dates of administration, and reasons for use. For 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.

[redacted]

8.1.1. Corticosteroids

During the Induction Study, subjects are to maintain their stable baseline corticosteroid dose, if applicable. Corticosteroids may be tapered starting after completion of the Induction Study at Week 12 for subjects after entering either the Maintenance Study or the OLE Study. Please see protocols RPC01-3203 and RPC01-3204 for details on the tapering regimen in these studies.

8.1.2. Aminosalicylates and Purified Medicinal Probiotics

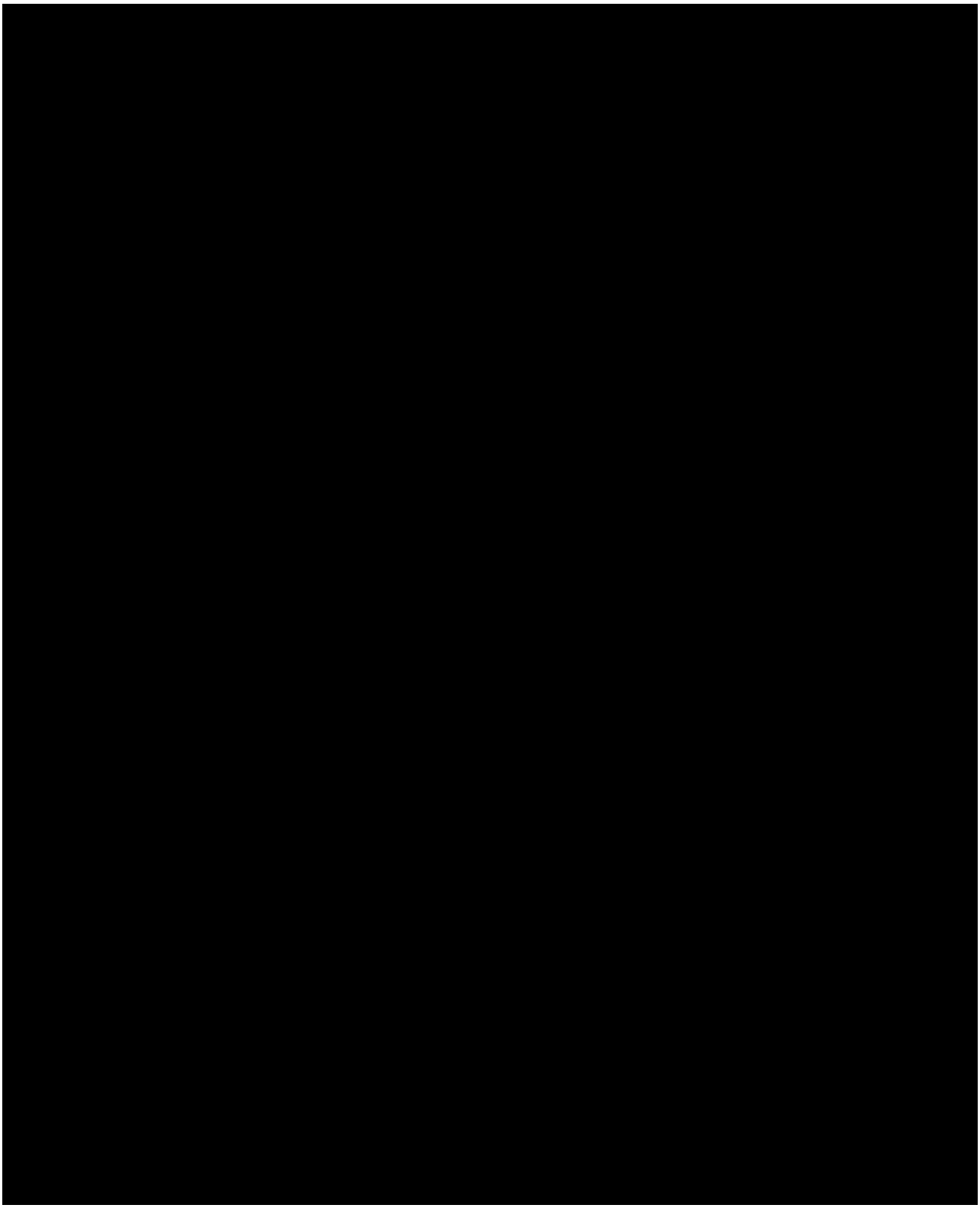
Subjects who are receiving oral 5-ASA, or purified medicinal probiotics prior to randomization should, if possible, keep their prescribed dosage steady through Week 12 unless reduction or discontinuation is clinically indicated. Oral 5-ASAs or probiotics should only be discontinued or reduced in dose if required based on Investigator's judgment. Oral 5-ASA or purified medicinal probiotics should not be started in subjects who are not receiving them.

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 prior to or during the study, including during treatment with IP and after the last dose of IP. In the instance of COVID-19 vaccination given during the screening period, both doses (if applicable) should be given prior to randomization.

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

8.2. Prohibited Concomitant Medications and Procedures



[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 multicenter, double-blind, randomized, Phase 3, placebo-controlled study to determine the effect of oral ozanimod as induction therapy on clinical remission in subjects with moderately to severely active CD. Approximately 600 subjects with active clinical symptoms and mucosal inflammation will be randomized in a 2:1 ratio to receive either ozanimod 0.92 mg or placebo. Subjects will be stratified [redacted].

Interactive response technology (IRT) will be utilized to ensure a central randomization based on a stratified block randomization. See Section 9.3.4 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.
- Per-protocol (PP): The PP population will consist of all subjects in the ITT population who do not have protocol deviations that may substantially affect the primary efficacy assessment. This population will be used in a sensitivity analysis of the primary endpoint.

Additional analysis populations are defined and their use described in the SAP.

9.3. Sample Size and Power Considerations

9.3.1. Primary Endpoint

The primary endpoint is CDAI clinical remission at Week 12. Subjects will be deemed responders with respect to this endpoint if they meet the definition for CDAI clinical remission at Week 12. Rejection of the null hypothesis associated with the primary endpoint will lead to the conclusion that the proportion of Week 12 CDAI clinical remission responders in the ozanimod arm is statistically significantly different from the proportion of Week 12 CDAI clinical remission responders in the placebo arm.

9.3.2. Placebo Response Rates for the Primary Endpoint

The Week 12 placebo response rate(s) were developed from a literature search (Jairath, 2017; Vermeire, 2016; Sandborn, 2013). The Week 12 ozanimod response rate for the primary endpoint [redacted] was derived from data obtained from Protocol RPC01-2201 (see Section 1.2.2 for a summary of the RPC01-2201 study). Table 9 summarizes this information:

Table 9: Placebo Response Rates from Selected Literature

	Placebo Rates from Literature
CDAI < 150	18% (95% confidence interval: 16% - 21%)
	23%
	6.80%

Abbreviations: CDAI = Crohn's Disease Activity Index.

9.3.3. Power Calculations

For the primary endpoint (CDAI < 150 clinical remission) the ozanimod remission rate is assumed to be [redacted] and the placebo remission rate is assumed to be [redacted] Using nQuery Advisor® 7.0, the two-group chi-square test of equal proportions for 2:1 unbalanced treatment arms was applied, and the following sample sizes were obtained (Table 10):

Table 10: Sample Size Calculation for the Primary Endpoint (CDAI Remission)

[redacted]

Abbreviations: CDAI = Crohn's Disease Activity Index.

To account for subject drop-out during the study, we plan to enroll approximately 600 subjects in each study (RPC01-3201 and RPC01-3202) separately.

[redacted] the following is known from Study RPC01-2201 (ozanimod rate) and also from the published FITZROY study (placebo rate; Vermeire, 2016):

[redacted]

It is often true that response rates in randomized blinded studies are smaller than in open-label studies. To provide a conservative sample size estimate, the assumed ozanimod and placebo rates for endoscopic response are therefore [redacted] and [redacted] respectively. This yields the following sample size calculations:

[redacted]

In order to provide at least [redacted] power to detect a difference of at least [redacted] between the ozanimod and placebo arms with respect to the endoscopic response endpoints (proportion of subjects with [redacted] at Week 12 and proportion of subjects with CDAI reduction from baseline of ≥ 100 points [redacted] at Week 12), the data from RPC01-3201 and RPC01-3202 will be pooled for those endpoints

Additional power and sample size details regarding the endoscopic response major secondary endpoints, as well as a discussion around the power associated with the collection of primary and major secondary endpoints, are provided in the SAP.

Note: The overall type I error rate across all controlled endpoints will be maintained at 5% using methods discussed in Section 9.6.3.

9.3.4. Stratified Block Randomization

Subjects enrolled in this protocol will be randomized using stratified block randomization in order to account for the study design. Subjects will be stratified [redacted] and then randomized to either ozanimod 0.92 mg or placebo in a 2:1 allocation ratio.

9.4. Background and Demographic Characteristics

Descriptive summaries will be presented for all collected baseline and demographic information. Continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Baseline characteristics subject demographics will include, at minimum, age, sex, race, ethnicity, height, weight, body mass index, 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, baseline stool frequency and abdominal pain score[redacted]

9.5. Subject Disposition

Subject disposition will be based on the following:

- number of subjects screened
- number of subjects randomized
- number of subjects dosed
- number of subjects completing the Induction Study
- number of subjects not completing the Induction Study by reason for dropout
- number of subjects entering the OLE Study
- number of subjects entering the Maintenance Study

9.6. Efficacy Analysis

Because all primary and secondary endpoints for this study are either remission or responder endpoints (ie, proportions of subjects meeting the criteria to be classified as remitters or responders for the 2 treatment groups), the analysis of endpoints using a continuous measure will not be described here, but rather discussed in the SAP. For the primary analysis of remission or responder endpoints, the ITT analysis population will be used. Furthermore, for the primary analysis of remission or responder endpoints and for a given timepoint or study visit, ITT subjects who have insufficient data for remission or response determination will be considered non-remitters/non-responders for that timepoint or study visit. Sensitivity analyses, missing data imputation and continuous endpoint efficacy analyses are discussed in the SAP.

9.6.1. Futility Analysis

A futility analysis is planned to be performed when approximately 300 subjects (with a similar proportion of biologic naïve to biologic exposed subjects as that in the overall study population) from both Induction studies, collectively, have completed the 12-week Induction Period. The analysis will occur after these subjects have completed the Induction Period and the data have been cleaned. The primary endpoint, CDAI remission (CDAI < 150) at Week 12 will be used in the analysis.

[redacted] The Induction studies (RPC01-3201 and RPC01-3202) may be stopped for futility if the observed treatment effect size in CDAI remission is at a low probability to demonstrate superiority. Additional efficacy endpoints including CDAI response, abdominal pain and stool frequency scores, SES-CD, [redacted] will be evaluated as supporting analyses. The futility boundary is "non-binding," implying that the boundary can be overruled if desired without inflating the type-1 error. The "non-binding" boundary is intended to allow the Sponsor or the independent DMC to continue the study to gather additional information, despite crossing the futility boundary.

The futility analysis will be conducted by the designated unblinded team (statistician and programmers) that supports the DMC and the results will be sent to the DMC for review, and

may also be sent to a Celgene internal review committee (IRC) for review. The Celgene IRC members will not play a role in the study conduct, and the blind will be maintained for persons responsible for the ongoing conduct and management of the study through the end of the Maintenance Study (RPC01-3203), until database lock.

9.6.2. 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 12 will be each carried out using the Cochran-Mantel-Haenszel (CMH) method. The stratifying factors of [redacted] 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.

The primary analysis of the primary and key secondary endpoints will be performed with the missing data imputed using non-responder imputation (NRI) method. Sensitivity analyses will also be performed using other missing data handling rules.

9.6.3. Control of Family-Wise Type I Error Rate and Data Pooling

The primary endpoint and major secondary endpoints of this study (RPC01-3202) will be tested statistically using a closed, hierarchical testing procedure in order to control the overall type I error rate for multiple endpoints in the current study. In parallel, this procedure is also applied to RPC01-3202 trial.

If an endpoint in this pre-specified hierarchy fails to reach statistical significance, all subsequent major secondary endpoints will be considered exploratory. Only the primary and major secondary endpoints will have type I error rates controlled at the family-wise level. All other endpoints will be tested at a nominal α=0.05 level.

9.7. Safety Analysis

All safety analysis will be carried out on the Safety Population. No inferential testing for statistical significance is planned.

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 [redacted], 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. AEs 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:

[redacted]

- 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 for lack of therapeutic effect before the Week 12 efficacy evaluations

9.9. Other Topics

9.9.1. Population Pharmacokinetics and Pharmacokinetics/Pharmacodynamics Analyses

[redacted]

9.9.2. Data Monitoring Committee

An independent, external 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 [redacted] to review aggregate analyses by treatment group concerning enrollment, treatment compliance, adherence to follow-up schedule, and safety data, etc. 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 CRF 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 are 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 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 10.1.1 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 as an SAE 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. The 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, 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. After the initial AE/SAE report, the Investigator is required to follow up proactively with each subject and provide further information to the Sponsor's Drug Safety or designee on the subject's condition. During the study, all AE/SAEs should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the subject's underlying disease, or the subject is lost to follow-up. 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. AEs 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

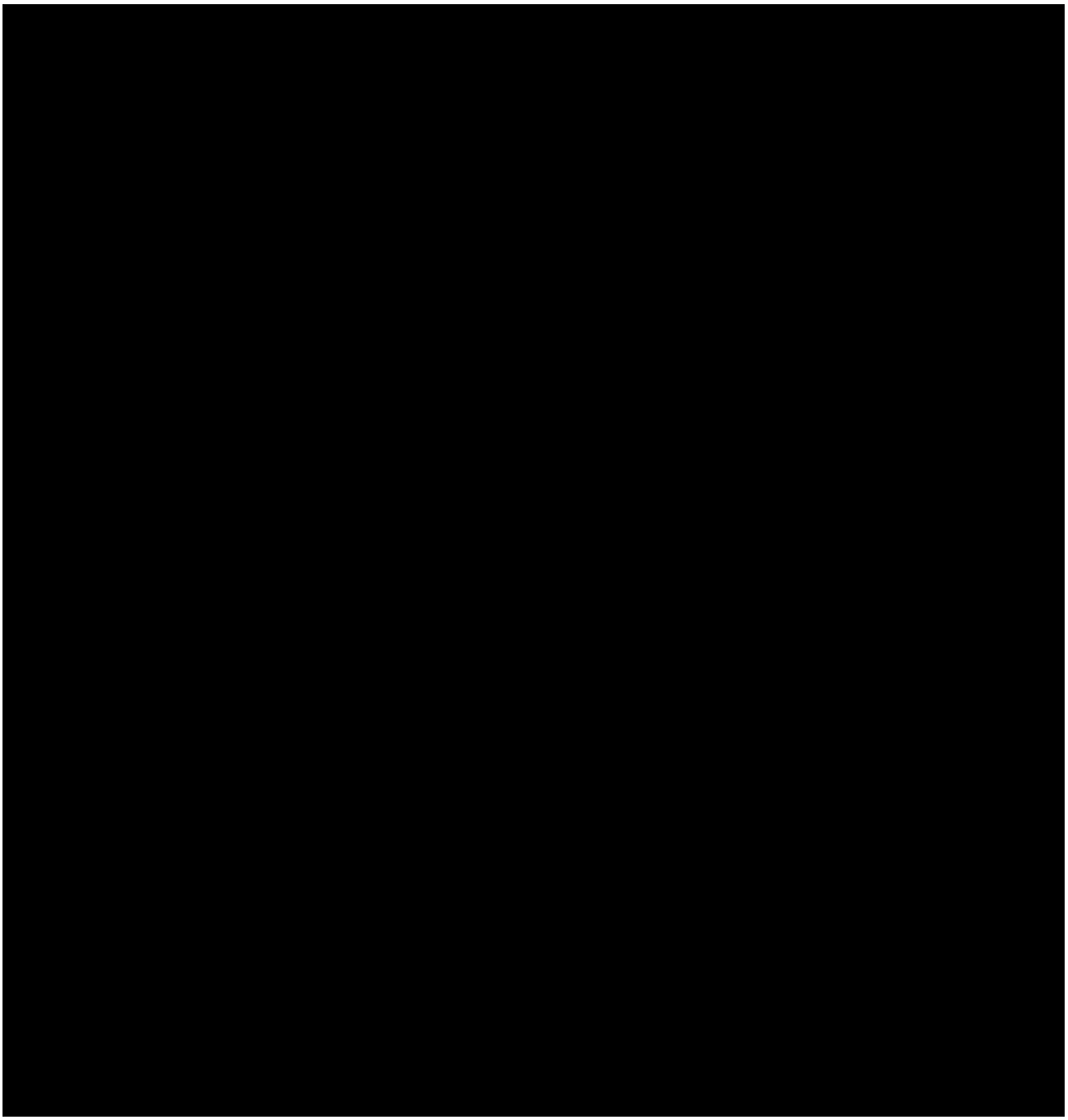
An SAE (experience) or reaction is any untoward medical occurrence that at any dose (ICH E2A, II.B):

- 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

[redacted]



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

[redacted]

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 trial. [redacted] The Sponsor may request additional medical information concerning AESIs that are non-serious.

[redacted]

[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 the Medical Monitor or designee must be informed. 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 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 at Screening: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, HbA1c, albumin, alkaline phosphatase, creatinine, ALT, 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 12 or early termination (ET) visit. [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.
- Pregnancy test: Serum β-hCG must be performed at screening in FCBP; urine β-hCG will be performed monthly in FCBP potential at each subsequent visit up until the [redacted], and if positive, the subject's dose should be held, and pregnancy status should be confirmed with a serum pregnancy test, including after the [redacted], if needed.

11.3. Serology

Serology testing will be performed at Screening to determine the subject's immune status with respect to the following viral infections:

- VZV
  - A VZV titer will be performed to determine if the subject has immunity (positive IgG result to varicella zoster virus). If the titer is negative, and there are no antibodies detected against VZV, the subject should therefore be offered to receive VZV vaccination. If the subject receives a VZV vaccination, randomization can only occur at a minimum of 30 days after vaccination has been completed. Note: Should the treating physician decide to vaccinate, the Sponsor will reimburse for the vaccine (and office visit if necessary), regardless of choice of vaccine. However, it is the responsibility of the treating physician to treat each patient in accordance with the approved prescribing information (package insert) and local and national guidelines. The Sponsor will not be involved in the supply of the vaccine.
- HIV
  - An HIV antibody test will be performed. Subjects testing positive for HIV (enzyme-linked immunosorbent assay [ELISA] test result, confirmed by Western blot) will be excluded from the study.
- HAV
  - An anti-hepatitis A virus (HAV) antibody (anti-HAV IgM) test will be performed. Subjects testing positive will be excluded from the study, unless they are indicative of prior hepatitis A that is considered cured and accompanied by normal liver function tests.
- HBV
  - Hepatitis B surface antigen (HBsAg) screening test and Hepatitis B core antigen (HBcAg) test will be performed.
  - Subjects who test positive for HBsAg will be excluded from the study. For subjects who test positive only for HBc antigen, an HBV DNA test must be performed. If the HBV DNA test is positive, the subject will be excluded from the study. If the HBV DNA test is negative (without anti-viral therapy) and the

LFTs are normal, the subject will be eligible for this trial. These subjects will undergo periodic monitoring for HBV DNA during the trial.

- HCV
  - A HCV antibody (anti-HCV IgG or IgM test) will be performed.
  - Subjects testing positive for HCV antibody and a positive confirmatory test will be excluded from the study.

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 female subjects of childbearing potential (FCBP). The Investigator will educate all FCBP about the different options of contraceptive methods or abstinence at Screening and Day 1, as appropriate. The subject will be re-educated every time her contraceptive measures/methods or ability to become pregnant changes. The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on IP, [redacted] are considered immediately reportable events. IP 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 the 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 Investigator's Brochure.

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 an expedited manner 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 Investigator's Brochure), 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), the Sponsor or authorized representative will report in an expedited manner to Regulatory Authorities and IECs concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical studies on IPs for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or 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's 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 investigational product(s):

- adverse event
- withdrawal by subject
- death
- lost to follow-up
- 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

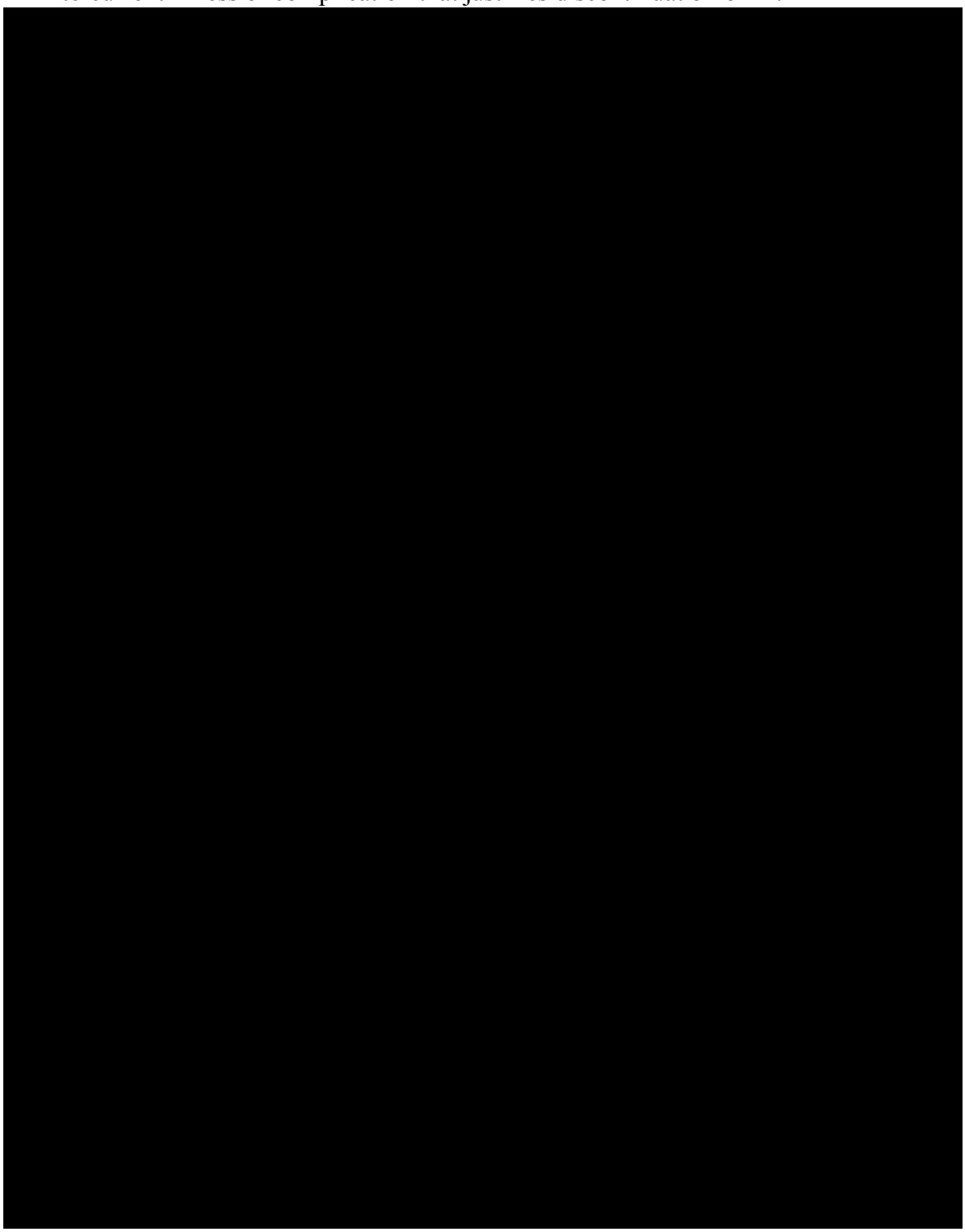
Subjects may voluntarily withdraw from the study at any time. The Investigator will provide a written explanation in the source documentation to be entered on the appropriate eCRF page describing the reason for discontinuation.

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. Subjects receiving any medical or surgical intervention for the treatment of CD that meet the criteria for treatment failure will be discontinued from the study and will not be eligible for the Maintenance or OLE studies. See Section 9.8.
- Withdrawal by subject (or subject's parent/guardian): The subject (or subject's parent/guardian) may choose to discontinue IP at any time. Every effort should be made within the bounds of safety and subject (or subject's parent/guardian) choice to have each subject complete the Early Termination Visit [redacted]. If a subject (or subject's parent/guardian) withdraws consent, the only additional investigational data to be collected will be the follow-up 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 or designee/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) 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. 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 and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

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

The information contained in the protocol and amendments (with the exception of the information provided by Sponsor on public registry websites) is considered Sponsor confidential information. Only information that is previously disclosed by the 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 protocol, amendment, and Investigator's Brochure information is not to be made publicly available (eg, 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/assent signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF/assent must be revised. Study subjects participating in the study when the amended protocol is implemented must be re- consented with the revised version of the ICF/assent. The revised ICF/assent signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

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 follow-up 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 may 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.

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 Investigators' 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, labeling.

In the event of a suspected product quality issue, the immediate action to be taken by the site is to quarantine the affected product. Do not dispose of the product. 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 or other representatives exist within the Sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with 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], Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

19. PUBLICATIONS

As described in Section 16.4, all protocol- and amendment-related information, with the exception of the information provided by Sponsor on public registry websites, is considered Sponsor confidential information and is not to be used in any publications. Sponsor 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 that 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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21. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 13: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6-MP	Mercaptopurine
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
[redacted]	
AP	Abdominal pain
AST	Aspartate aminotransferase (SGOT)
AV	Atrioventricular
AZA	Azathioprine
[redacted]	
β-hCG	β-subunit of human chorionic gonadotropin
[redacted]	
BMI	Body Mass Index
[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
[redacted]	
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ECG	Electrocardiogram

Table 13: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
EEA	European Economic Area
EEN	Exclusive Enteral Nutrition
[redacted]	
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
[redacted]	
ET	Early termination
FCBP	Female subject of childbearing potential
FDA	Food and Drug Administration
FEV1	Forced expiratory volume 1
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GHAS	Global Histologic Activity Score
GI	Gastrointestinal
GMP	Good Manufacturing Practices
HAV	Anti-hepatitis A virus
HbA1c	Hemoglobin A1c
HBcAg	Anti-hepatitis B core antigen
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C vaccine
HIV	Human immunodeficiency virus
[redacted]	
ICF	Informed consent form

Table 13: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
[redacted]	
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INR	International Normalised Ratio
IP	Investigational product
IRB	Institutional Review Board
[redacted]	
IRT	Interactive response technology
ITT	Intent to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
[redacted]	
LFT	Liver function test
MERS-CoV	Middle East respiratory syndrome coronavirus
[redacted]	
MTX	Methotrexate
[redacted]	
NRI	Non-responder imputation
[redacted]	
OLE	Open-Label Extension
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFT	Pulmonary function test

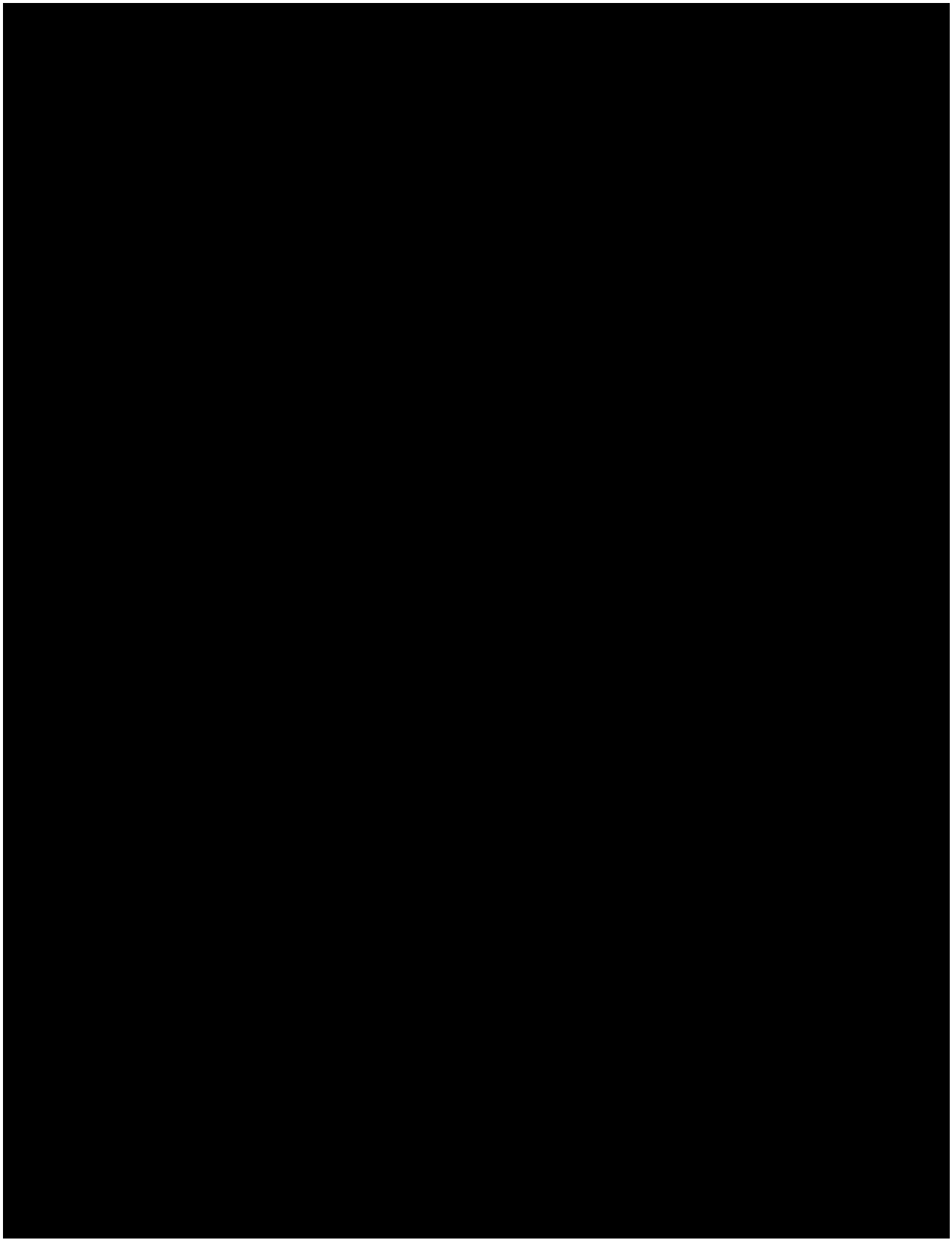
Table 13: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
PIN	Personal identification number
PK	Pharmacokinetics
[redacted]	
PP	Per protocol
[redacted]	
PYE	Patient years of exposure
QTcF	Fridericia's Correction Formula
[redacted]	
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SES-CD	Simple Endoscopic Score for Crohn's Disease
[redacted]	
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
[redacted]	
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TFR	Treatment failure rules
TNBS	Trinitrobenzenesulfonic acid
TNF	Tumor necrosis factor
TRT	Treatment
UC	Ulcerative colitis
ULN	Upper limit of normal

Table 13: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
[redacted]	
VZV	Varicella zoster vaccine
WBC	White blood cell
[redacted]	

APPENDIX B. INCLUSION CRITERIA DRUG SPECIFICATIONS



APPENDIX C. SARS-COV-2 GUIDELINES

[redacted]

If the subject receives a positive SARS-CoV-2 test result and is asymptomatic during the screening 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 screening 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.

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

COVID-19 vaccines that are NOT live are allowed and should be handled in the same manner as other vaccines. Administration may occur prior to and during the study, including during treatment with IP and after the last dose of IP. In the instance of COVID-19 vaccination given during the screening period, both doses (if applicable) should be given prior to randomization. Administration of vaccinations must be reported along with dosage information, dates of administration and vaccine name/trade name on the appropriate sections of the eCRF. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Thursday, 24 June 2021, 11:12 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

– SUMMARY OF CHANGES –

AMENDMENT NO. 5

INDUCTION STUDY #2: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLED STUDY OF ORAL OZANIMOD AS INDUCTION THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

INVESTIGATIONAL PRODUCT (IP):	Ozanimod
PROTOCOL NUMBER:	RPC01-3202
PREVIOUS VERSION DATE:	03 Sep 2020
AMENDMENT No. 5 DATE:	14 Jun 2021
EudraCT NUMBER:	2017-004293-33
IND NUMBER:	126,740

Contact Information:

Name: [redacted]

Title: [redacted] Clinical Trial Physician, [redacted]

Address: 3033 Science Park Road, Suite 300
San Diego, California, 92121, USA

Tel (office): [redacted]

Tel (cell): [redacted]

E-mail: [redacted]

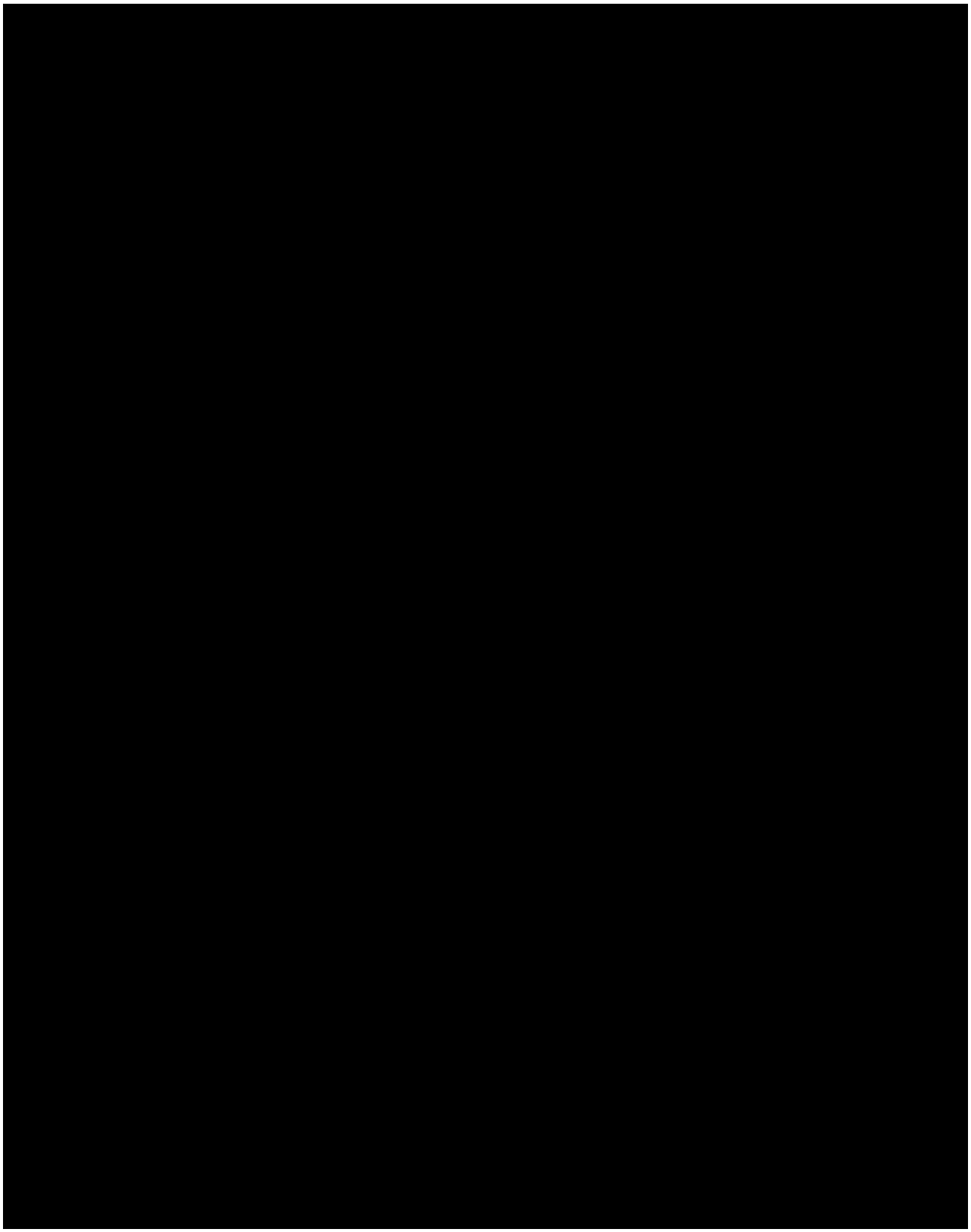
SPONSOR THERAPEUTIC AREA LEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature **Date**
[redacted]
Name and Title
By my signature, I indicate I have reviewed this summary of changes and find its content to be acceptable.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

[redacted]



SUMMARY OF CHANGES

INDUCTION STUDY #2 - A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ORAL OZANIMOD AS INDUCTION THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

INVESTIGATIONAL PRODUCT (IP):	**OZANIMOD**
PROTOCOL NUMBER:	**RPC01-3202**
VERSION & DATE:	**5.0 03 Sep 2020**
REPLACES VERSION:	**4.0 10 Jul 2019**
EudraCT NUMBER:	**2017-004293-33**
IND NUMBER:	**126,740**

Contact Information:

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Title: [redacted] Clinical Trial Physician, [redacted]

Address: 3033 Science Park Road, Suite 300, San Diego, California 92121 USA

Phone: Tel (office): [redacted] Tel (cell): [redacted]

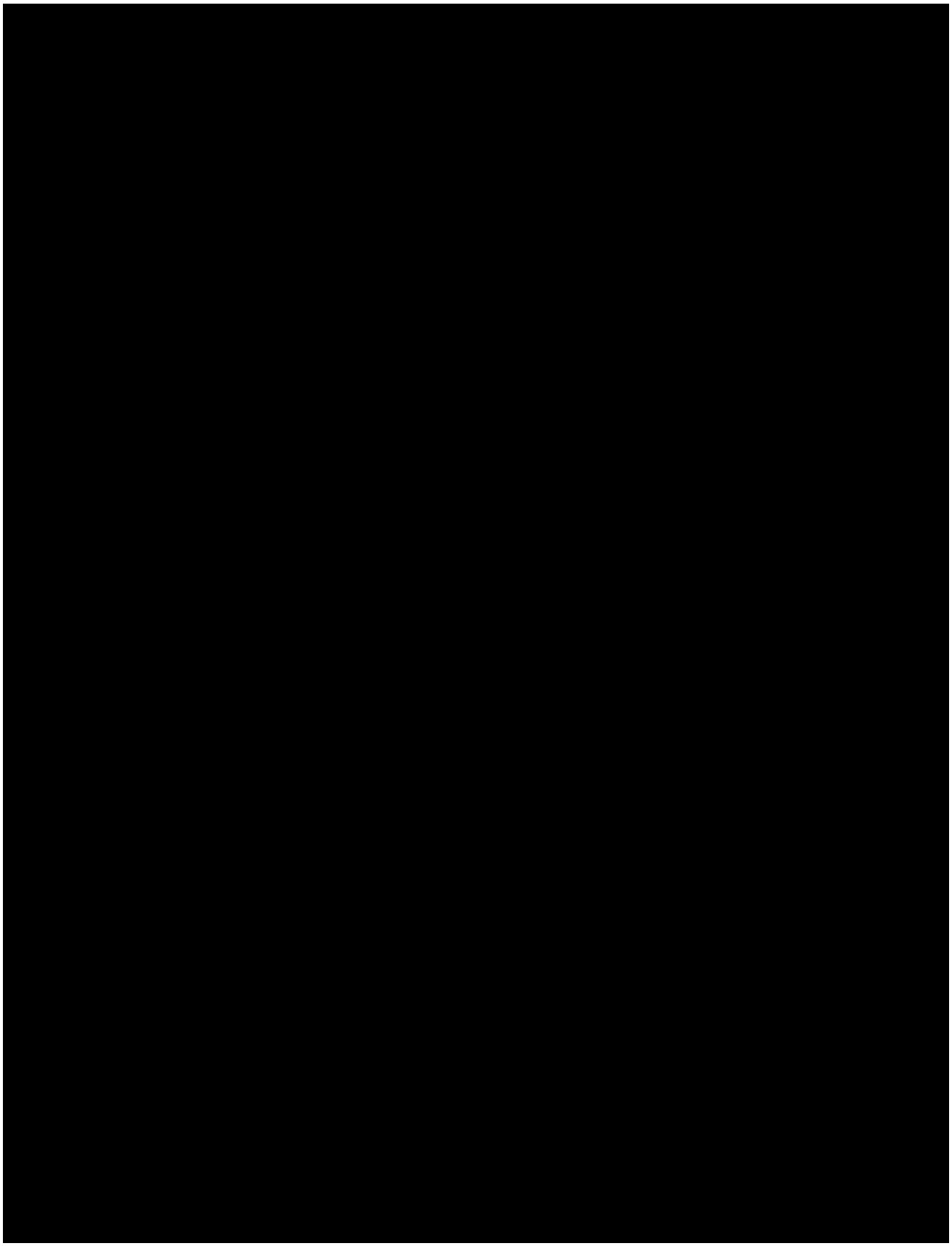
E-mail: [redacted]

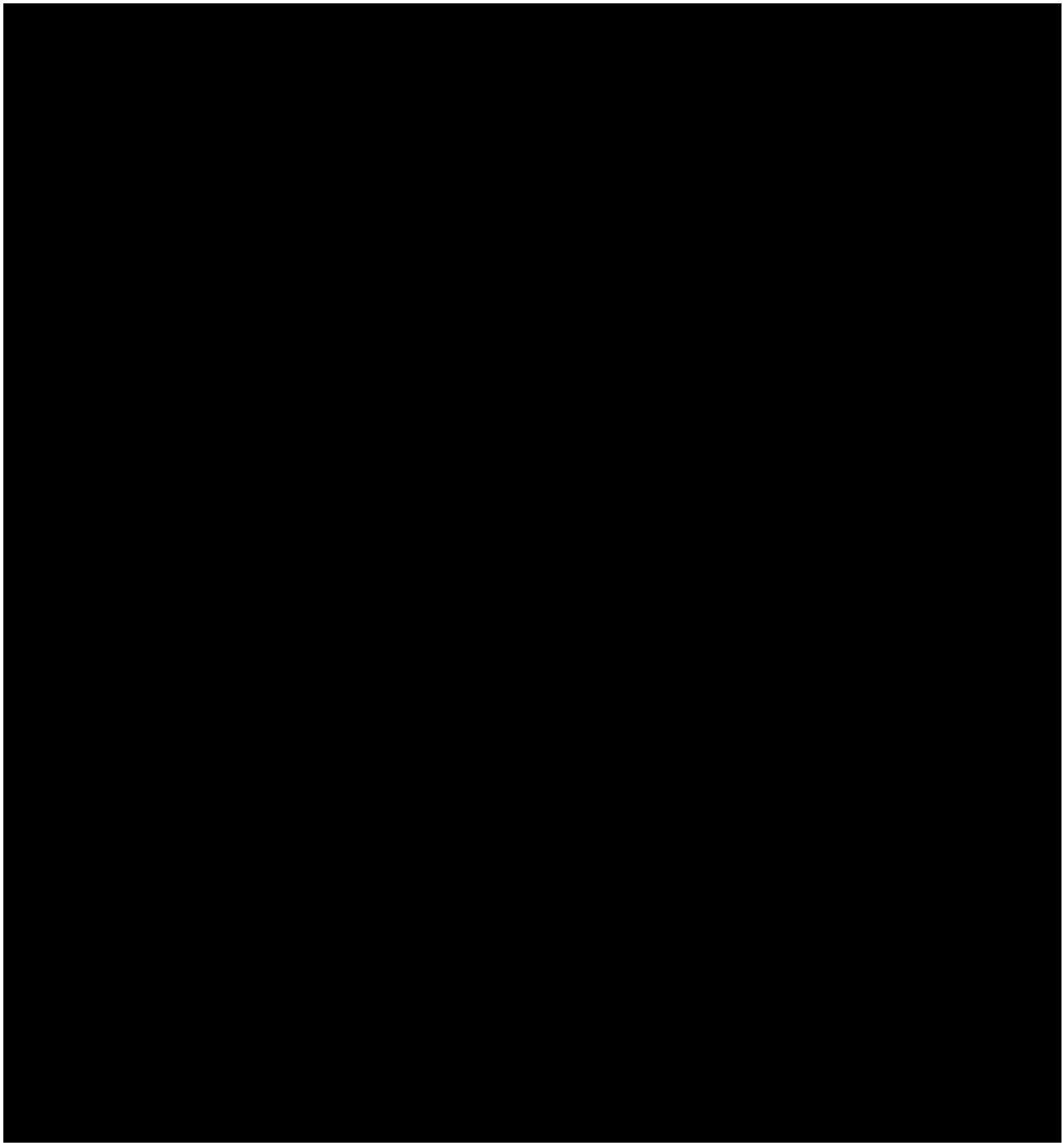
This document summarizes the changes that were made between Protocol RPC01-3202 Version 5 (27 Aug 2020) and Version 4 (dated 10 June 2019).

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

[redacted]





SUMMARY OF CHANGES

INDUCTION STUDY #2 - A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ORAL OZANIMOD AS INDUCTION THERAPY FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

Test Drug:	Ozanimod
Protocol Number:	RPC01-3202
Study Phase:	Phase 3
IND/EudraCT number:	126,740/2017-004293-33
Version and Date:	4 dated 10 July 2019
Replaces Version:	3 dated 18 June 2018

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LIST OF TABLES

This document summarizes the changes that were made between Protocol RPC01-3201 Version 4 (dated 10 July 2019) and Version 3 (dated 18 June 2018).

1. OVERVIEW OF KEY CHANGES

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

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

SUMMARY OF CHANGES

INDUCTION STUDY #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction Therapy for Moderately to Severely Active Crohn's Disease

Test Drug:	Ozanimod
Protocol Number:	RPC01-3202
Study Phase:	Phase 3
IND/EudraCT number:	126,740/2017-004293-33
Version and Date:	3 dated 18 June 2018
Replaces Version:	2 dated 19 December 2017

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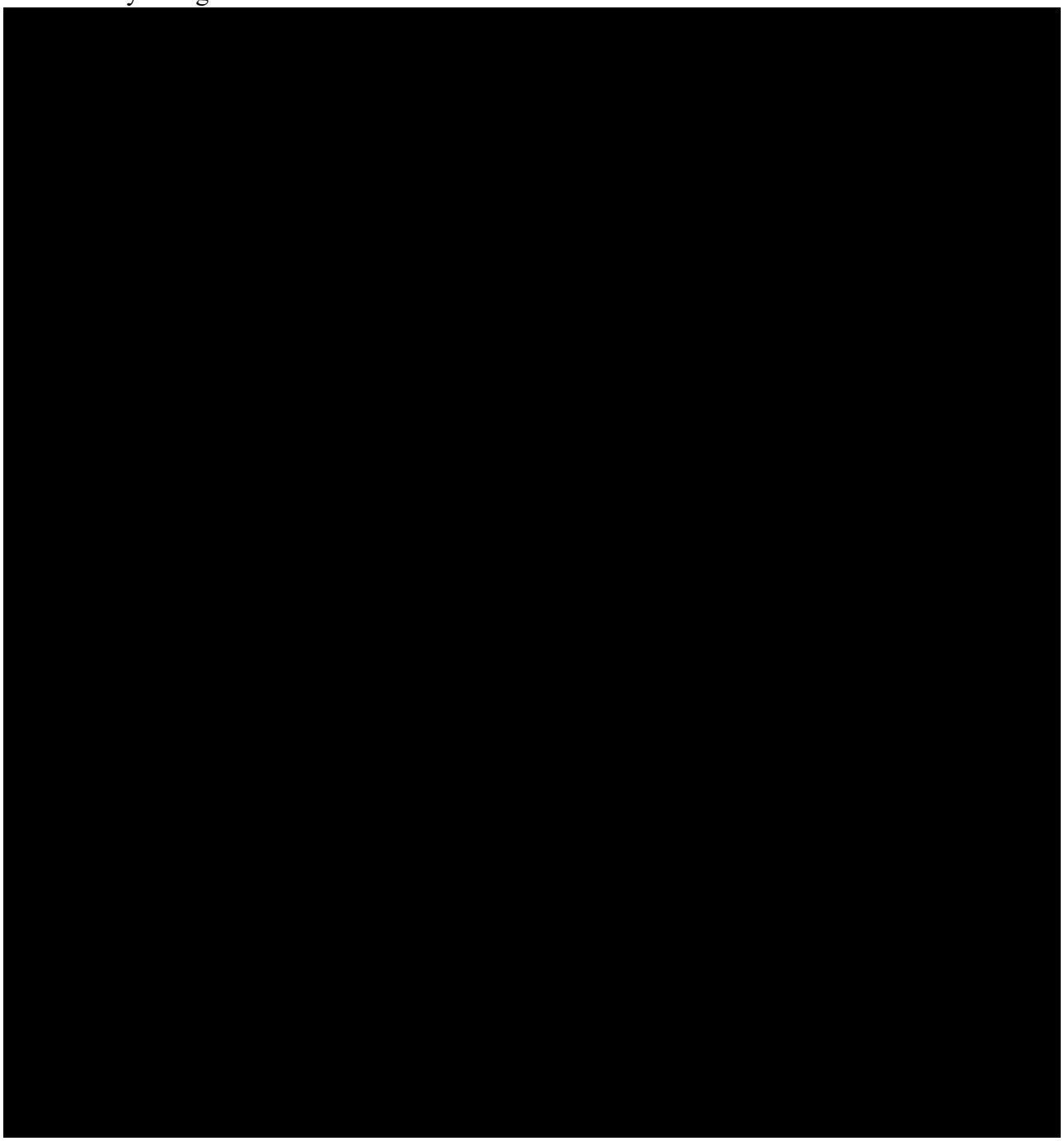
LIST OF TABLES

This document summarizes the changes that were made between Protocol RPC01-3202 Version 3 (dated 18 June 2018) and Version 2 (dated 20 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:



SUMMARY OF CHANGES

INDUCTION STUDY #2 - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Oral Ozanimod as Induction Therapy for Moderately to Severely Active Crohn's Disease

Test Drug:	Ozanimod
Protocol Number:	RPC01-3202
Study Phase:	Phase 3
IND/EudraCT number:	126,740/2017-004293-33
Version and Date:	2 dated 19 December 2017
Replaces Version:	1 dated 26 September 2017

TABLE OF CONTENTS

LIST OF TABLES

This document summarizes the changes that were made between Protocol RPC01-3202 Version 2 (dated 19 December 2017) and Version 1 (dated 26 September 2017).

1. OVERVIEW OF KEY CHANGES

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

[redacted]

The following bulleted list identifies global changes to the protocol:

[redacted]