Official Title of Study:

A Phase 3, Multicenter, Open-Label Extension Study of Oral Ozanimod for Moderately to Severely Active Crohn's Disease

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A PHASE 3, MULTICENTER, OPEN-LABEL EXTENSION STUDY OF ORAL OZANIMOD FOR MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

INVESTIGATIONAL PRODUCT:	Ozanimod (BMS-986374)
PROTOCOL NUMBER:	RPC01-3204
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SPONSOR NAME/ ADDRESS:	Celgene International II Sàrl Route de Perreux 1 2017 Boudry Switzerland Tel: [redacted]

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

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Date

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Printed Name of Celgene International II Sàrl Representative

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 6.0:

The main reason for this amendment is to extend the study duration so that all subjects might complete 264 weeks (5 years) of treatment. Additionally, this amendment serves to consolidate the protocol with the European Union Clinical Trials Regulations (EU-CTR) requirements, addressing the removal of the France-specific protocol. Other changes include simplification of the [redacted] after the first year; addition of benefit/risk assessment details; and updates to prohibited medications, discontinuation requirements, and ophthalmic monitoring language.

The Protocol Summary has been updated to align with the changes in the table below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Sponsor address updated.	Sponsor address change.
Medical Monitor/Emergency Contact Information	Medical Monitor and associated contact information updated.	Sponsor staff change.
Sponsor Therapeutic Area Lead Signature Page	Sponsor Therapeutic Area Lead updated.	Sponsor staff change.
Section 1.2.4: Benefit/Risk Assessment	Section removed (now Section 1.4.3: Overall Benefit/Risk Conclusion).	Integration of previously stand-alone Benefit/Risk document into body of protocol.
Section 1.4: Benefit/Risk Assessment [redacted] Section 1.4.2: Benefit Assessment Section 1.4.3: Overall Benefit Risk Conclusion	Sections added.	Integration of previously stand-alone Benefit/Risk document into body of protocol.
Section 2.2: Study Endpoints Section 3.2: Study Duration for Subjects	Extended study duration from 234 weeks to 264 weeks plus the Safety Follow-up Visits.	Study duration was extended to collect long-term safety and efficacy data for a full 5 years on study drug.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 2.2.1: Efficacy Endpoints Section 2.2.3: Overview of Safety Assessments	Removed the word "key" from section headings (previously Section 2.2.1: Key Efficacy Endpoints and Section 2.2.3: Overview of Key Safety Assessments).	Correction.
[redacted]		
Section 3.1: Study Design Section 14.2: Study Discontinuation	Updated language regarding Investigator discretion in discontinuation of subjects based on Crohn's Disease Activity Index (CDAI) score for clinical response and/or clinical remission.	To enable Principal Investigator discretion in terms of benefit/risk assessment and in alignment with real-world clinical practice.
Section 4.3.1: Exclusions Related to General Health	Added the following France-specific language: "In France, hypotension is exclusionary if it makes the implementation of the protocol or interpretation of the study difficult or would put the subject at risk by participating in the study."	To align with EU-CTR consolidation and removal of the France-specific protocol.
Section 4.3.2: Exclusions Related to Medications	Updated Exclusion Criterion 7 to remove "within the corresponding timeframe."	Correction.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 4.3.2: Exclusions Related to Medications	[redacted]	[redacted]

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]	[redacted]	[redacted]
Section 6.4.3: Electrocardiogram	[redacted]	Clarification.
[redacted] Section 6.3.2: Simple Endoscopic Score for Crohn's Disease	[redacted]	Clarification.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
[redacted]		
Section 8.1.3: COVID-19 Vaccination	Added language regarding non-live coronavirus disease 2019 (COVID-19) vaccination.	Moved language from Benefit/Risk section.
[redacted]		

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 6.0		
Section Number & Title	**Description of Change**	**Brief Rationale**
Appendix B: SARS-CoV-2 Guidelines	Updated language to indicate that testing for COVID-19 to inform decisions about clinical care during the study should follow local standard practice and to provide guidance on the evaluation and management of SARS-CoV-2 infections.	Moved language from Benefit/Risk section.
All	Minor formatting and typographical corrections.	Minor, therefore have not been summarized.

PROTOCOL SUMMARY

Study Title

A Phase 3, Multicenter, Open-Label Extension Study of Oral Ozanimod 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

The objective of this study is to demonstrate the long-term safety and explore long-term efficacy of ozanimod (BMS-986374) for the treatment of subjects with moderately to severely active CD.

Study Design

This is a Phase 3, open-label, multicenter extension study to evaluate safety and explore the long-term efficacy of ozanimod in subjects with moderately to severely active CD. It is anticipated that approximately [redacted] subjects who have participated in a prior study of ozanimod for CD will be eligible to participate in this study if they meet the eligibility criteria and have not met the discontinuation criteria as outlined in the prior studies (RPC01-3201, RPC01-3202, RPC01-3203, and RPC01-2201).

Subjects entering the study from RPC01-2201 will continue to receive ozanimod 0.92 mg/day (equivalent to ozanimod HCl 1 mg). Subjects entering the study from RPC01-3201, RPC01-3202, or RPC01-3203 will initiate ozanimod treatment in accordance with a 7-day dose escalation regimen as follows:

- Days 1 through 4: Ozanimod 0.23 mg daily (equivalent to ozanimod HCl 0.25 mg)
- Days 5 through 7: Ozanimod 0.46 mg daily (equivalent to ozanimod HCl 0.5 mg) (administered as two 0.23-mg capsules)
- Day 8 through End of Study: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg)

[redacted]

Subjects who discontinue from treatment due to lack of response, adverse events (AEs), or other reasons, even if alternative treatment is given, will be followed for [redacted] for collection of safety data, including lymphocyte recovery, and for assessment of their disease status. Refer to [redacted] and Section 11.1 for further details on lymphocyte recovery monitoring.

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 Practices (GCPs) and applicable regulatory requirements.

Study Population

Adult subjects with CD who have previously participated in a study of ozanimod for CD may be eligible for entry in this study if they met the eligibility criteria and have not met the discontinuation criteria outlined in the prior studies (eg, RPC01-3201, RPC01-3202, RPC01-3203, and RPC01-2201).

Length of Study

This study is expected to continue for a subject for approximately 264 weeks (5 years) plus the Safety Follow-up Visits. Subjects who do not meet discontinuation criteria or withdraw from the study may continue until they complete 264 weeks (5 years) on study treatment or until the study is discontinued, whichever comes first. Where applicable, the sponsor will provide IP after study discontinuation as per local or national requirements. The study may be discontinued early if the sponsor determines that the primary study objectives of demonstration of long-term safety and efficacy have been met, a significant safety and/or efficacy concern is identified, or the sponsor discontinues the development program.

Study Treatments

Subjects entering the study from RPC01-2201 will continue to receive ozanimod 0.92 mg/day (equivalent to ozanimod HCl 1 mg). Subjects entering the study from RPC01-3201, RPC01-3202, or RPC01-3203 will initiate ozanimod treatment in accordance with a 7-day dose escalation regimen as described above.

Overview of Efficacy Assessments

Note: Endpoints will be evaluated annually for up to 264 weeks.

Efficacy Endpoints:

- Proportion of subjects with a CDAI score of < 150
- Proportion of subjects with a Simple Endoscopy Score for Crohn's Disease (SES-CD) decrease from baseline of ≥ 50%
- Proportion of subjects with average daily abdominal pain score ≤ 1 point, and average daily stool frequency ≤ 3 points with abdominal pain and a stool frequency no worse than baseline
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score of < 150
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥ 10%
- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points
- Change from baseline in CDAI
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score of < 150 and SES-CD decrease from baseline of ≥ 50%
- Proportion of subjects with CDAI score of < 150 and SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points

- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points
- Proportion of subjects with SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points
- Proportion of subjects with a CDAI score < 150 in subjects off corticosteroids
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline of ≥ 50%

[redacted]

Overview of Safety Assessments

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

Statistical Methods

All subjects who receive at least 1 dose of IP in this study will comprise both the Intent-to-Treat population (ITT) and the Safety Population. These populations will be used to summarize all safety and efficacy data.

Each efficacy endpoint will be summarized and [redacted] around the estimates may also be presented. Due to the open-label nature of the study and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed. All efficacy data will be listed.

All safety data will be listed and summarized. All TEAEs will be coded and tabulated by system organ class and preferred term. Incidence of TEAEs, SAEs, and AEs leading to discontinuation will be summarized and presented in descending order of frequency. Associated clinical laboratory parameters such as hepatic profile, renal function, and hematology values will be grouped and presented together. For each laboratory test, individual subject values outside standard reference range will be flagged and listed. Shift tables and analyses of changes from baseline will be produced. The change from baseline for each of the vital signs and ECG parameters will be

summarized. Incidence of abnormal vital signs parameters will be tabulated, and an outlier analysis of ECG results will be conducted.

Determination of Sample Size

As this is an open-label extension study for subjects who previously participated in a study of ozanimod for CD, there is no statistical basis for the sample size. It is anticipated that approximately [redacted] subjects who participated in prior studies of ozanimod in CD will be eligible for treatment in this study.

TABLE OF CONTENTS

LIST OF TABLES

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 (BMS-986374) 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 (EC50) 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 include 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 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 50% 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 (RPC01-202) study 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 signals 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 sub-scores 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, 2021). All 3 key secondary endpoints in the Induction Period (clinical response, endoscopic improvement, and mucosal healing), and all 6 key secondary endpoints in the Maintenance Period (clinical response, endoscopic improvement, maintenance of remission, corticosteroid-free remission, mucosal healing, and durable clinical remission) were achieved by a statistically significantly greater proportion of subjects in the ozanimod 0.92 mg treatment group compared with placebo. The treatment effects for the primary and key secondary endpoints consistently supported a favorable treatment effect for ozanimod in multiple demographics, prior and concomitant medication, disease characteristics, and geographic subgroups.

1.2.2.2 Crohn's Disease

RPC01-2201, a Phase 2 study was conducted in CD, to examine endoscopic and clinical outcomes following treatment with ozanimod 0.92 mg daily for 12 weeks. Simple Endoscopic Score for Crohn's Disease (SES-CD) reductions of ≥ 50% from baseline were seen in 28.6% of subjects (observed cases) as measured by paired segments, with greater endoscopic response in subjects with baseline SES-CD score ≤ 12 and a shorter disease duration. At week 52, the proportion of subjects achieving reductions of ≥ 50% was maintained at 26.7%. Clinical response was seen in 68.5% and 93.8% of subjects (observed cases) at Week 12 and Week 52, respectively. Clinical remission was seen in 46.3% and 65.6% of subjects (observed cases) at Week 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 trial of ozanimod in UC was conducted comparing 0.92 mg and 0.46 mg of ozanimod with placebo. Safety was comparable across both ozanimod arms, and the 0.92 mg/day dose arm demonstrated better efficacy as compared to the 0.46 mg/day dose arm across various clinical and endoscopic endpoints (Sandborn, 2016). Results suggested a dose dependent efficacy response, making 0.92 mg more favorable for future investigation.

The favorable clinical results and the available safety data from the Phase 2 and Phase 3 UC studies as described above, as well as supportive clinical and safety data from the completed Relapsing Multiple Sclerosis (RMS) program provide additional data to support the 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 and [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.

[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.

1.3 Study Rationale

Given the mechanism of action of ozanimod, data from the preclinical animal model, the positive results from the Phase 2 UC study, RPC01-202, and preliminary results from the Induction Period

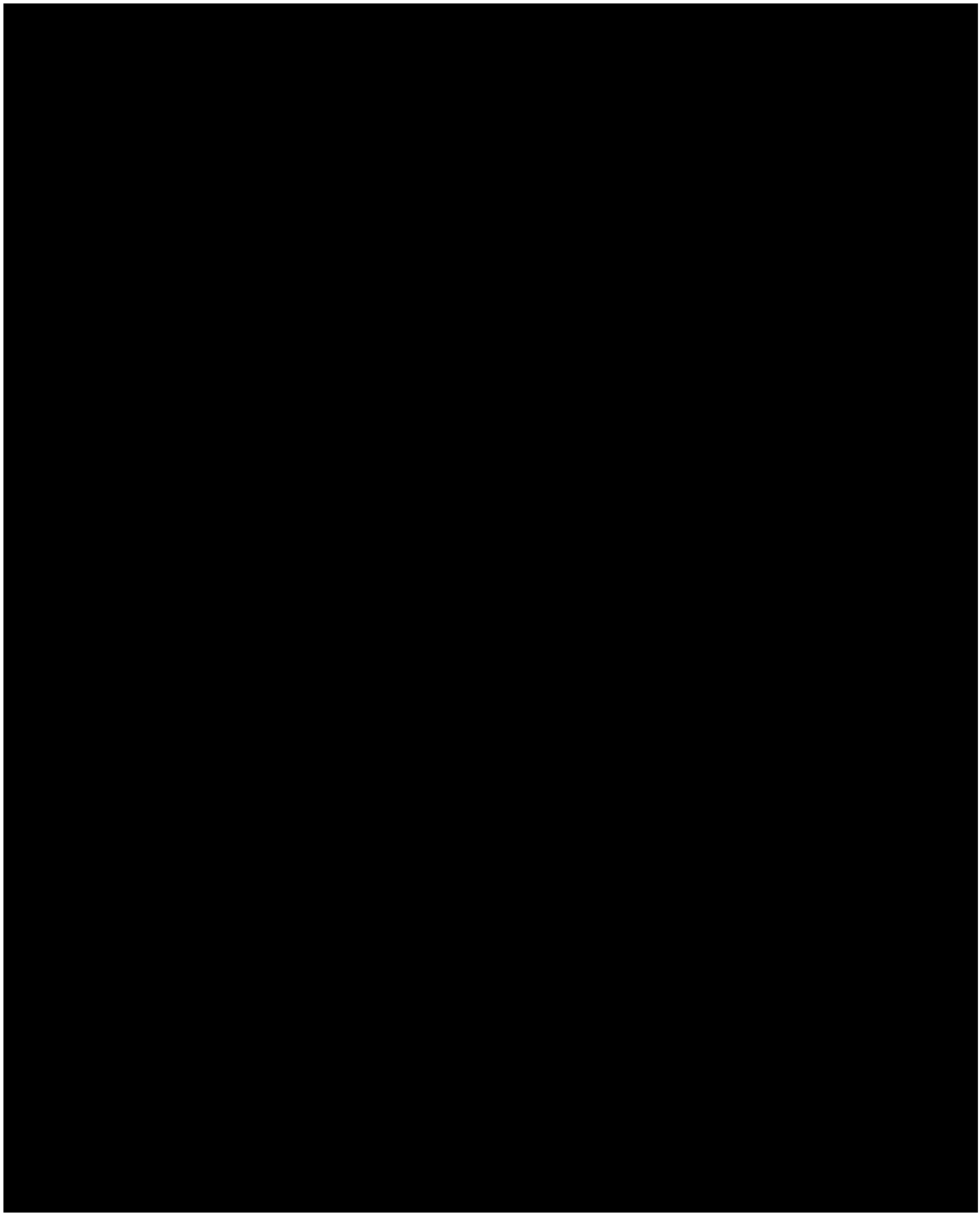
of the Phase 2 study in CD, RPC01-2201, a Phase 3 program with ozanimod in CD is being conducted.

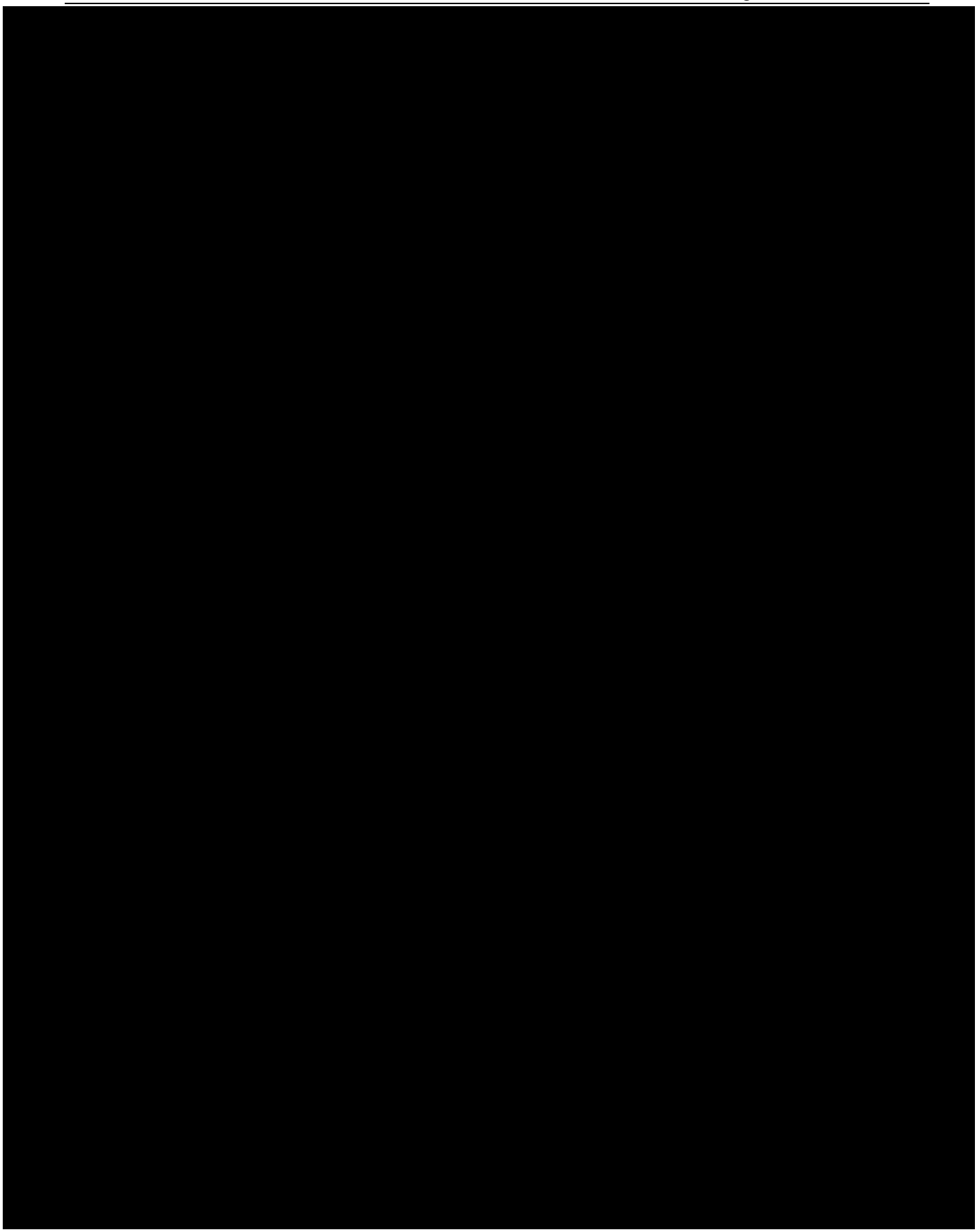
The current study is designed to assess the long-term safety and explore long-term efficacy of ozanimod in subjects with moderately to severely active CD. This study will allow subjects who are receiving clinical benefit from ozanimod the opportunity to continue to receive IP and experience potential long-term endoscopic benefit. For subjects who are not in clinical response and/or clinical remission after completing 12 weeks in the Induction Studies, this study provides an opportunity for potential delayed clinical benefit.

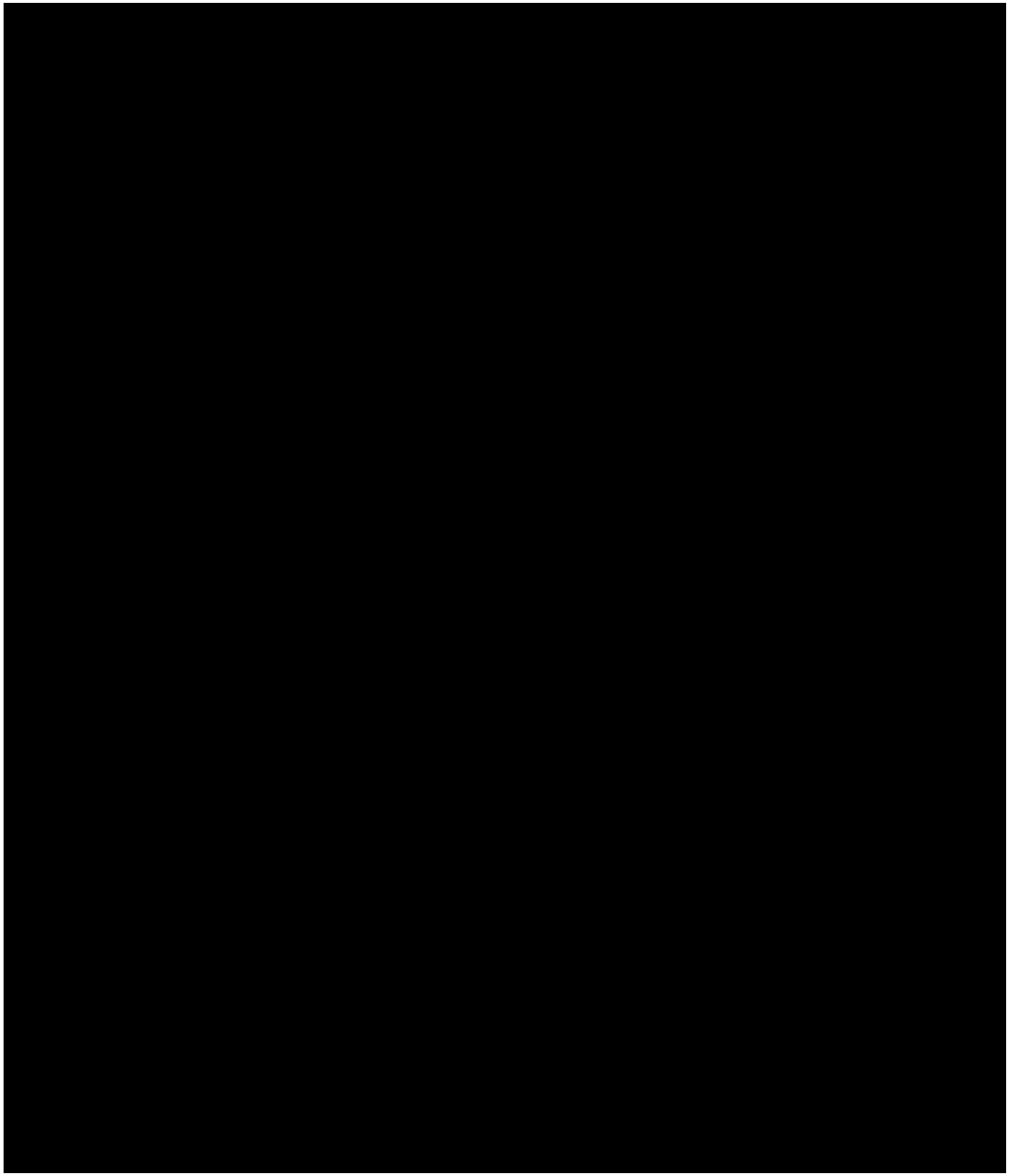
1.4 Benefit/Risk Assessment

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

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







1.4.2 Benefit Assessment

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

1.4.3 Overall Benefit Risk Conclusion

Despite recent progress in CD treatment, there remains an unmet need for agents that are safe and convenient oral treatments and can provide effective induction and long-term maintenance of clinical remission. The benefit/risk profile for ozanimod has been evaluated for the indication of CD. Results from subjects with moderate to severe disease who previously failed prior therapy and were treated with ozanimod 0.92 mg daily for at least 12 weeks suggested clinical and endoscopic benefit. In addition, the safety results suggest that ozanimod is well tolerated in patients with CD and is consistent with that observed in other patient populations (UC and RMS). The overall data to date suggest that this ozanimod Open-Label Extension Study (RPC01-3204) has a potential favorable benefit/risk profile for patients with active CD.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objective

- Demonstrate the long-term safety and explore long-term efficacy of ozanimod for the treatment of subjects with moderate to severely active CD.

2.2 Study Endpoints

Note: Endpoints will be evaluated annually for up to 264 weeks.

2.2.1 Efficacy Endpoints:

- Proportion of subjects with a CDAI score of < 150
- Proportion of subjects with a SES-CD decrease from baseline of ≥ 50%
- Proportion of subjects with average daily abdominal pain score ≤ 1 point, and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than baseline
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score of < 150
- Proportion of subjects with absence of ulcers ≥ 0.5 cm with no segment with any ulcerated surface ≥ 10%
- Proportion of subjects with CDAI reduction from baseline of ≥ 70 points
- Change from baseline in CDAI
- Proportion of subjects with CDAI reduction from baseline of ≥ 100 points or CDAI score of < 150 and SES-CD decrease from baseline of ≥ 50%
- Proportion of subjects with CDAI score of < 150 and SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points
- Proportion of subjects with average daily abdominal pain score ≤ 1 point and average daily stool frequency ≤ 3 points with abdominal pain and stool frequency no worse than baseline and SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points
- Proportion of subjects with SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points
- Proportion of subjects with a CDAI score < 150 in subjects off corticosteroids
- Proportion of subjects with a Crohn's Disease Endoscopic Index of Severity (CDEIS) decrease from baseline of ≥ 50%

[redacted]

2.2.3 Overview of Safety Assessments

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

3 OVERALL STUDY DESIGN

3.1 Study Design

This is a Phase 3, open-label, multicenter extension study to evaluate safety and explore the long-term efficacy of ozanimod 0.92 mg in subjects with moderately to severely active CD. It is anticipated that approximately [redacted] subjects who have participated in a prior study of ozanimod for CD will be eligible to participate in this study if they meet the eligibility criteria and have not met the discontinuation criteria as outlined in the prior studies (eg, RPC01-3201, RPC01-3202, RPC01-3203, and RPC01-2201).

Subjects entering the study from RPC01-2201 will continue to receive ozanimod 0.92 mg/day (equivalent to ozanimod HCl 1 mg). Subjects entering the study from RPC01-3201, RPC01-3202, or RPC01-3203 will initiate ozanimod treatment in accordance with a 7-day dose escalation regimen as follows:

- Days 1 through 4: Ozanimod 0.23 mg daily (equivalent to ozanimod HCl 0.25 mg)
- Days 5 through 7: Ozanimod 0.46 mg daily (equivalent to ozanimod HCl 0.5 mg) (administered as two 0.23-mg capsules)
- Day 8 through End of Study: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg)

[redacted]

Subjects who discontinue from treatment due to lack of response, AEs, or other reasons, even if alternative treatment is given, will be followed for [redacted] for collection of safety data, including lymphocyte recovery, and for assessment of their disease status. Refer to [redacted] and Section 11.1 for further details on lymphocyte recovery monitoring.

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

3.2 Study Duration for Subjects

This study is expected to continue for a subject for approximately 264 weeks (5 years) plus the Safety Follow-up Visits. Subjects who do not meet discontinuation criteria or withdraw from the study may continue until they complete 264 weeks (5 years) on study treatment, or until the study is discontinued, whichever comes first. Where applicable, the sponsor will provide IP after study

discontinuation as per local or national requirements. The study may be discontinued early if the Sponsor determines that the primary study objectives of demonstration of long-term safety and efficacy have been met, a significant safety and/or efficacy concern is identified, or the sponsor discontinues the development program.

3.3 End of Study

The end of study is defined as either the date of the last visit of the last subject to complete the [redacted] 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 and is subject to provisions in Section 3.2, whichever is the later date.

4 STUDY POPULATION

4.1 Number of Subjects

It is anticipated that approximately [redacted] subjects who participated in prior studies of ozanimod in CD (RPC01-2201, RPC01-3201, RPC01-3202, RPC01-3203) will be eligible for treatment in this study.

4.2 Inclusion Criteria

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

1. Subjects who are not in clinical response and/or clinical remission after completing 12 weeks in the Induction Studies RPC01-3201 or RPC01-3202, subjects who experience relapse in the Maintenance Study RPC01-3203, subjects who complete the Maintenance Study RPC01-3203, subjects who complete at least 1 year of RPC01-2201.
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 [redacted]
3. Female subjects of childbearing potential (FCBP):

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

   Must agree to practice a highly effective method of contraception throughout the study until completion of the [redacted] Safety Follow-up Visit. 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. Female condom and male condom should not be used together.

[redacted]

4.3 Exclusion Criteria

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

4.3.1 Exclusions Related to General Health:

1. Subject has any clinically relevant cardiovascular (See [redacted] hepatic, neurological, pulmonary [severe respiratory disease (pulmonary fibrosis or chronic obstructive pulmonary disease)], ophthalmological, endocrine, psychiatric, or other major systemic disease making implementation of the protocol or interpretation of the study difficult or that would put the subject at risk by participating in the study. In France, hypotension is exclusionary if it makes the implementation of the protocol or interpretation of the study difficult or would put the subject at risk by participating in the study.
2. Subject is pregnant, lactating, or has a positive urine beta human chorionic gonadotropin (β-hCG) test.
3. Subject has suspected or diagnosed intra-abdominal or perianal abscess that has not been appropriately treated.

4.3.2 Exclusions Related to Medications:

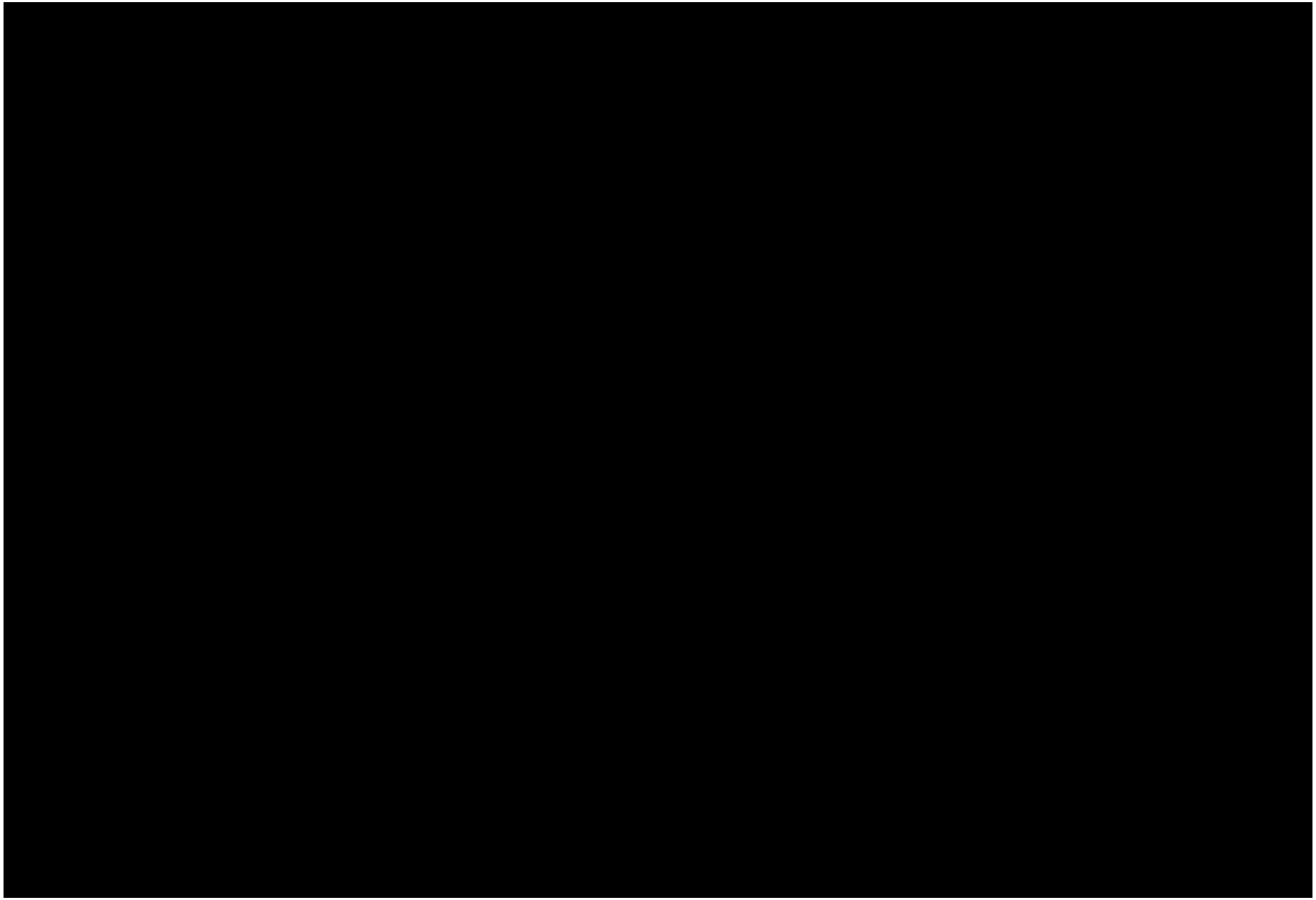
4. Hypersensitivity to active ingredients or excipients of ozanimod

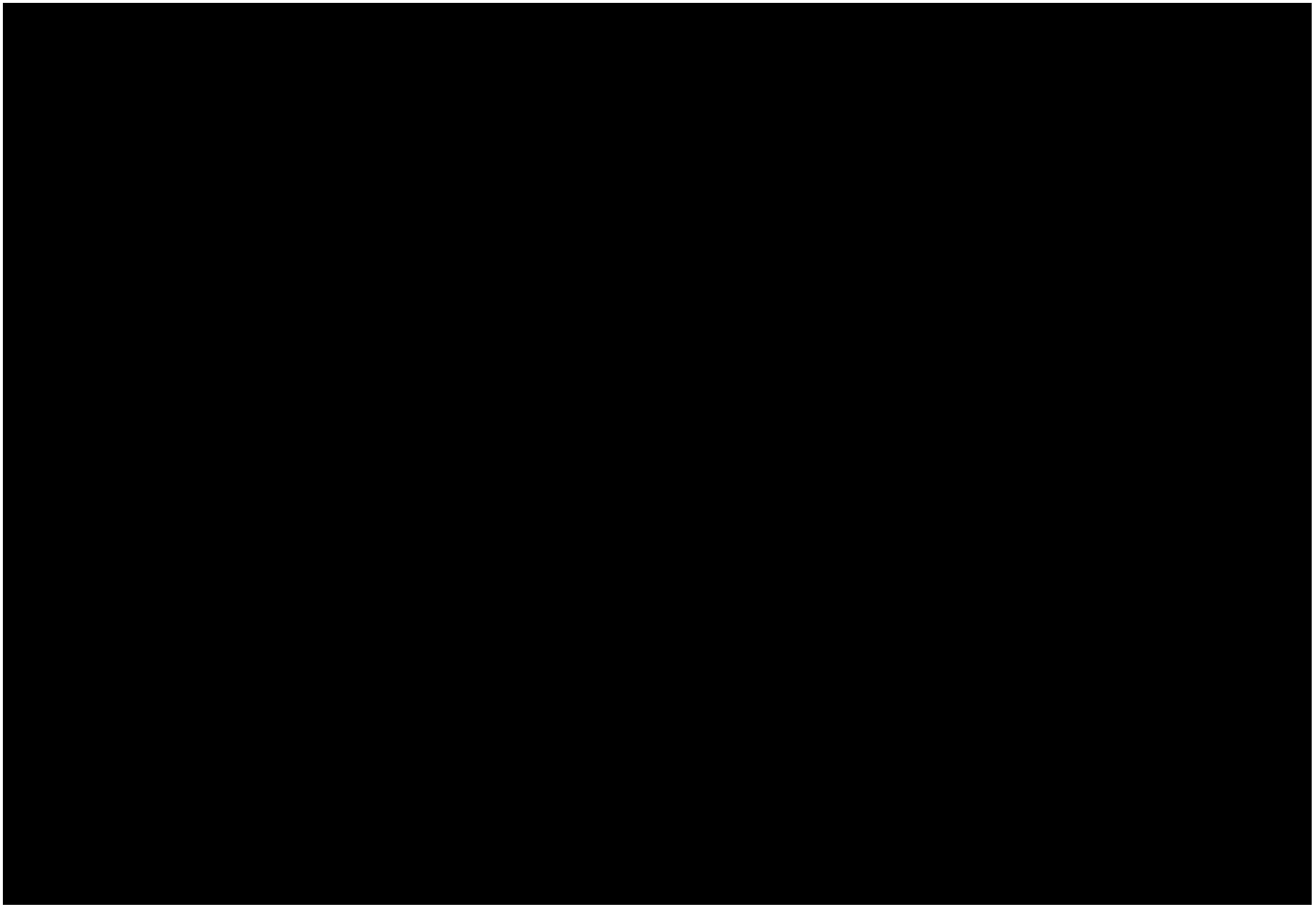
[redacted]

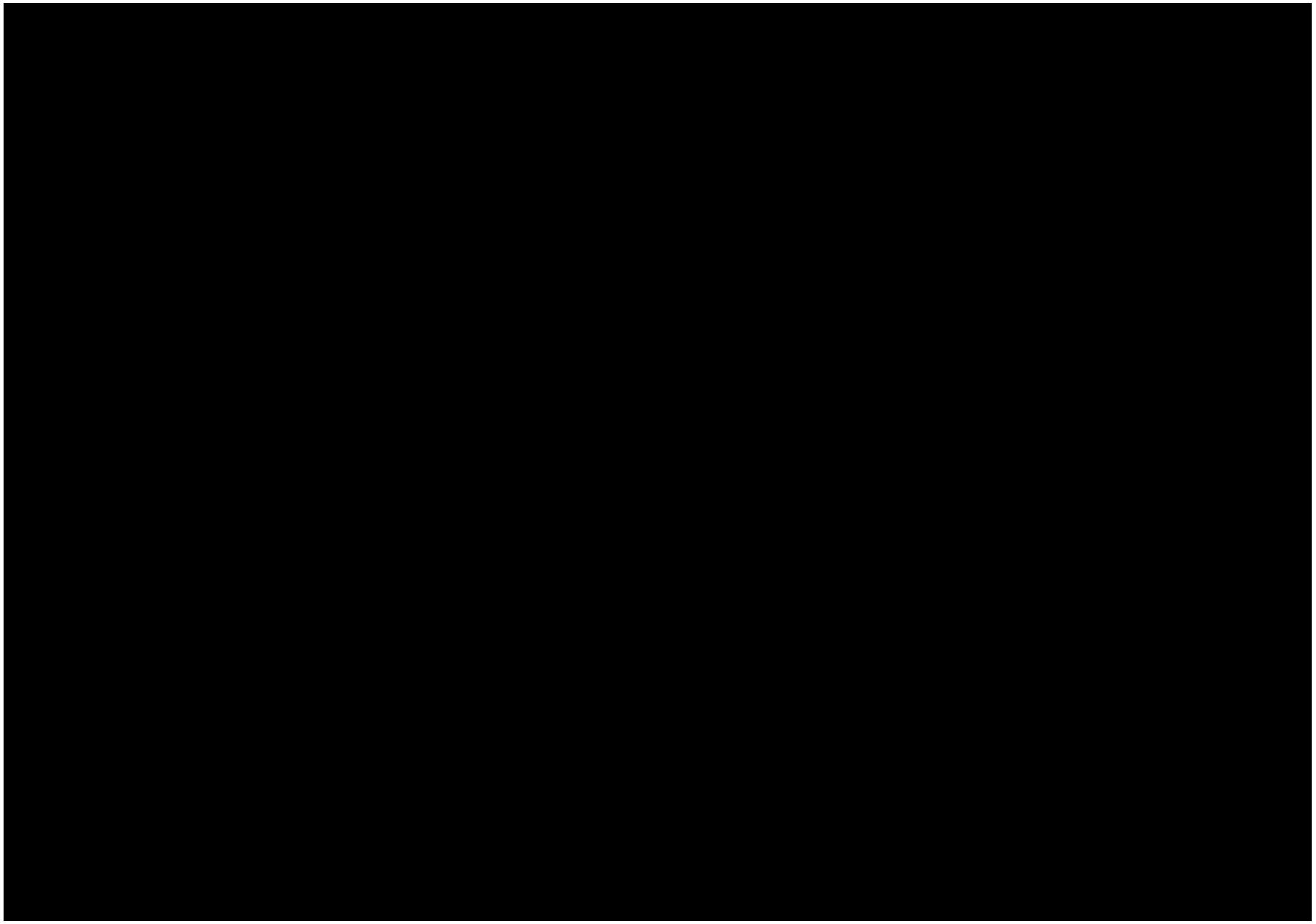
[redacted]

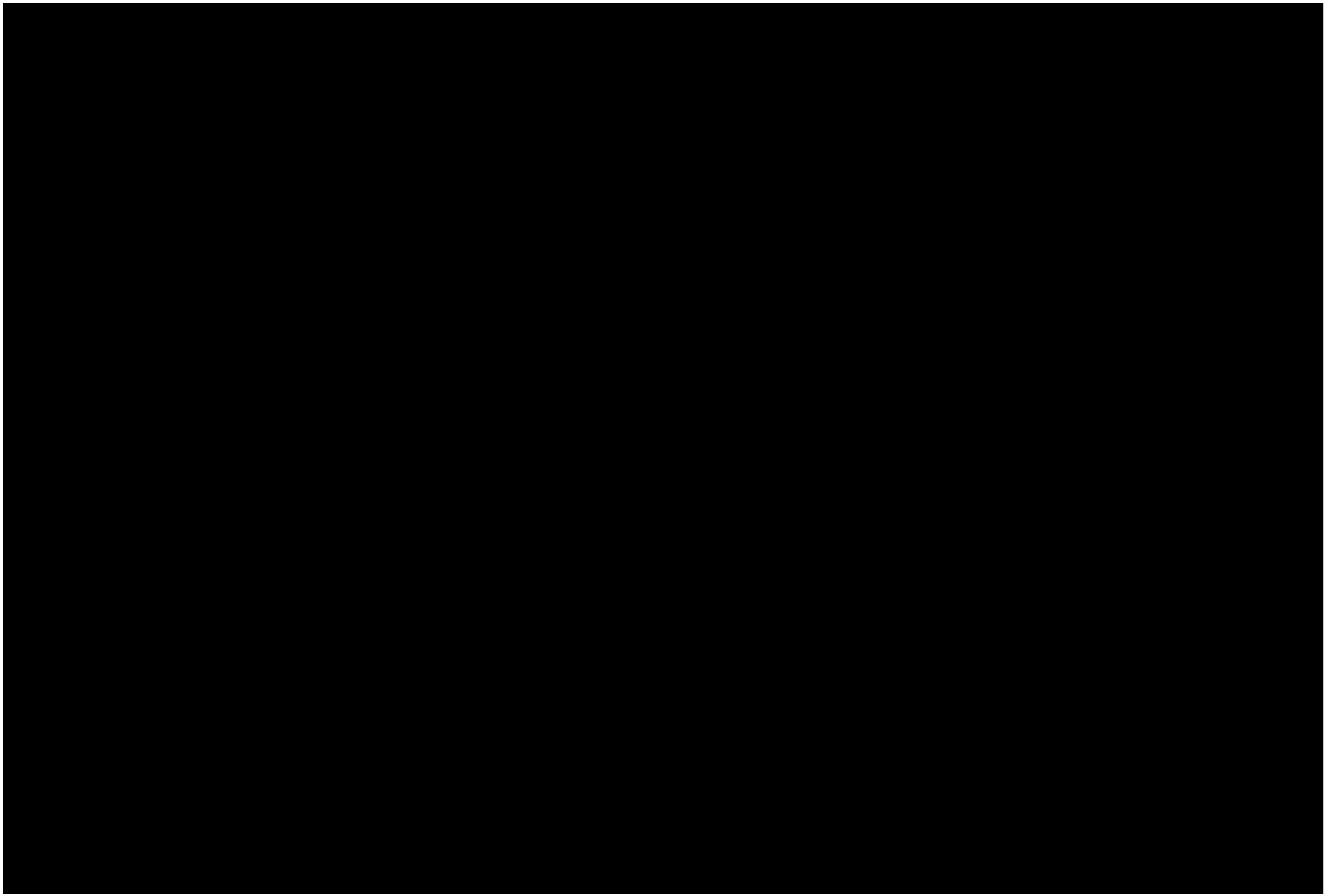
4.3.3 Exclusions Related to Laboratory Results and Other Assessments:

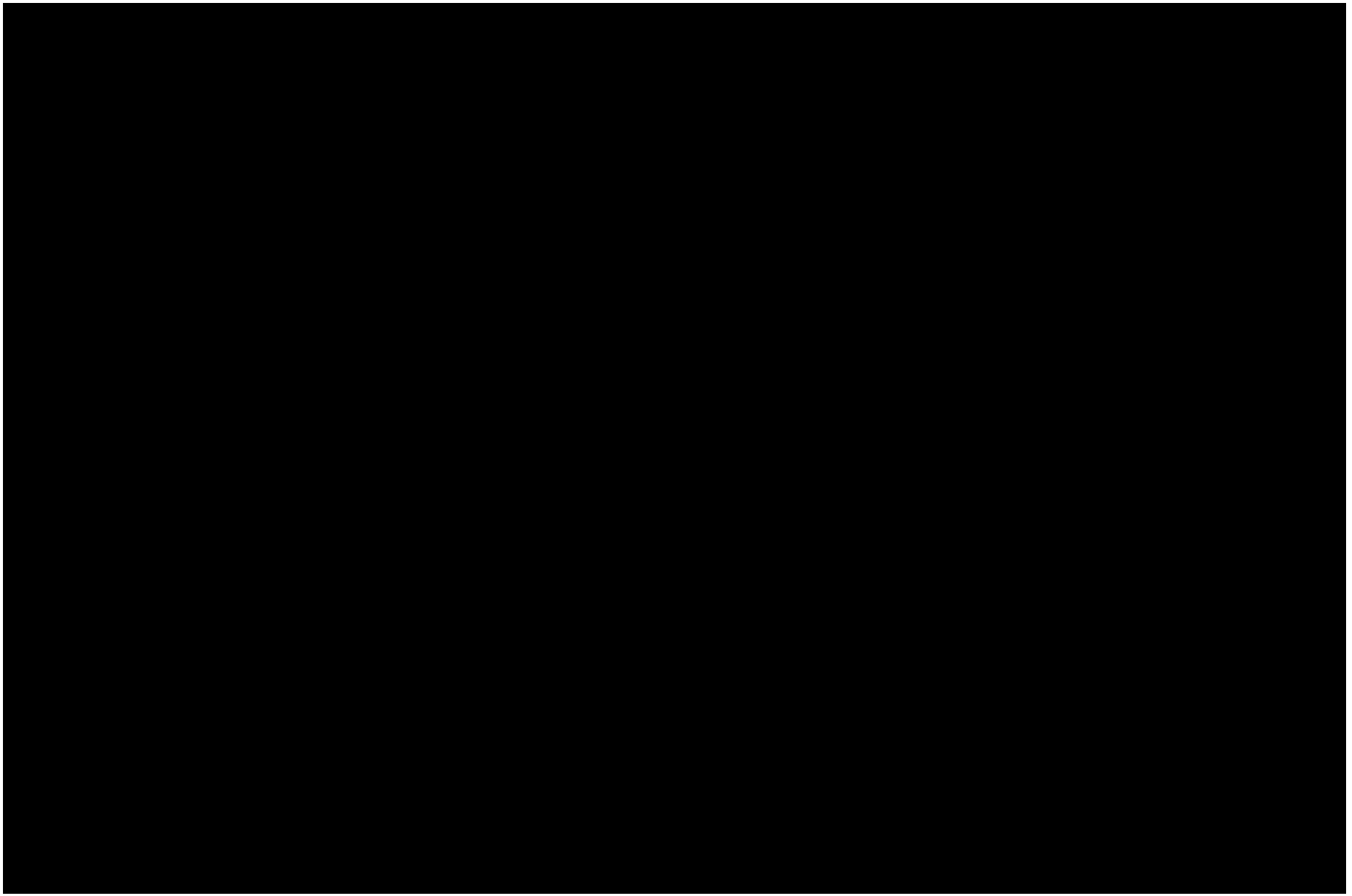
8. Subject has any clinically significant abnormal results (eg, labs or ECG) which, in the opinion of the Investigator, may put the subject at risk.
9. Subjects has a pre-dose resting [redacted]. One recheck is allowed at the Day 1 visit. If [redacted] remains [redacted] at Day 1, one additional recheck is allowed at a later date within the available window for roll-over from the previous study.











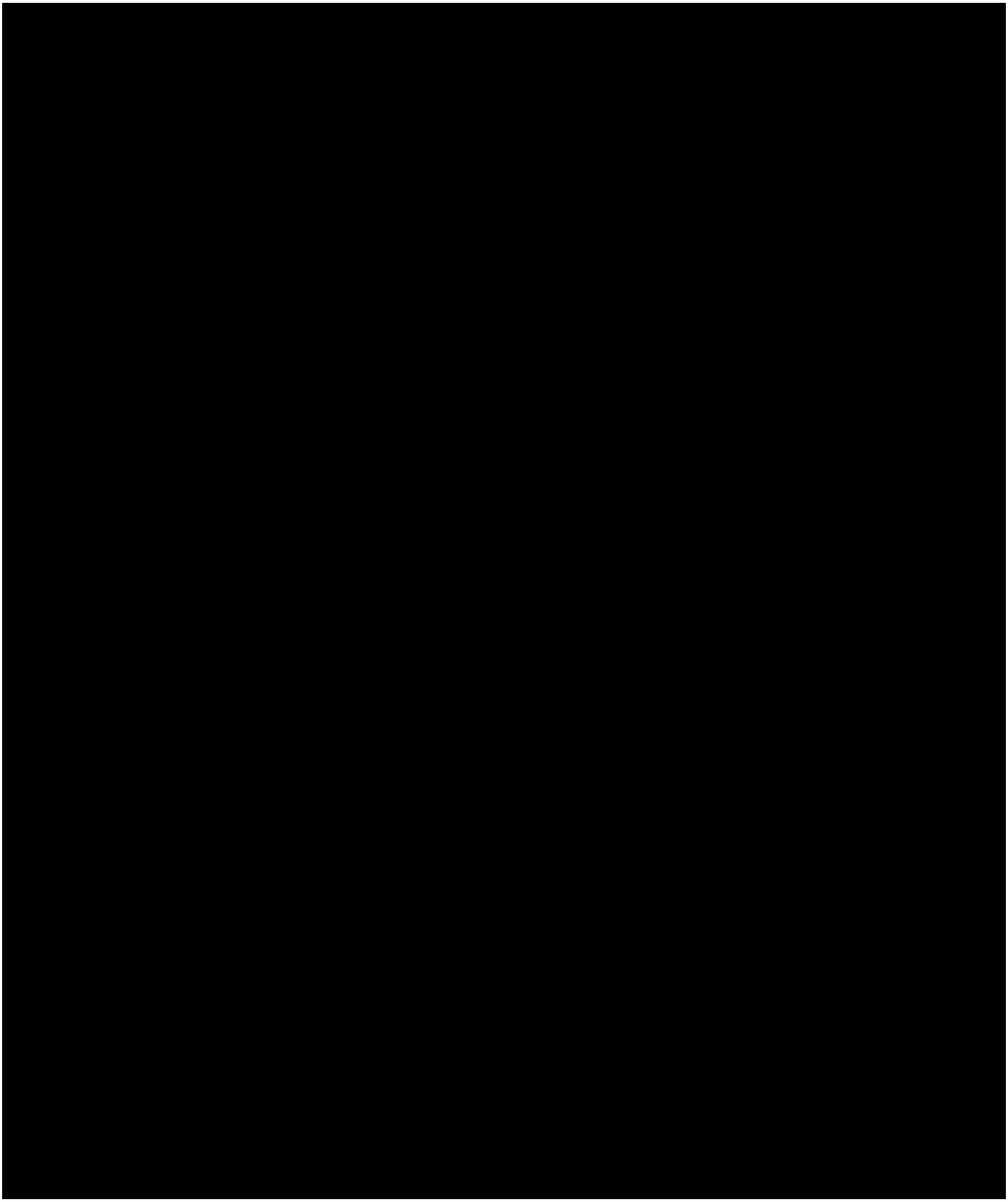
6 PROCEDURES

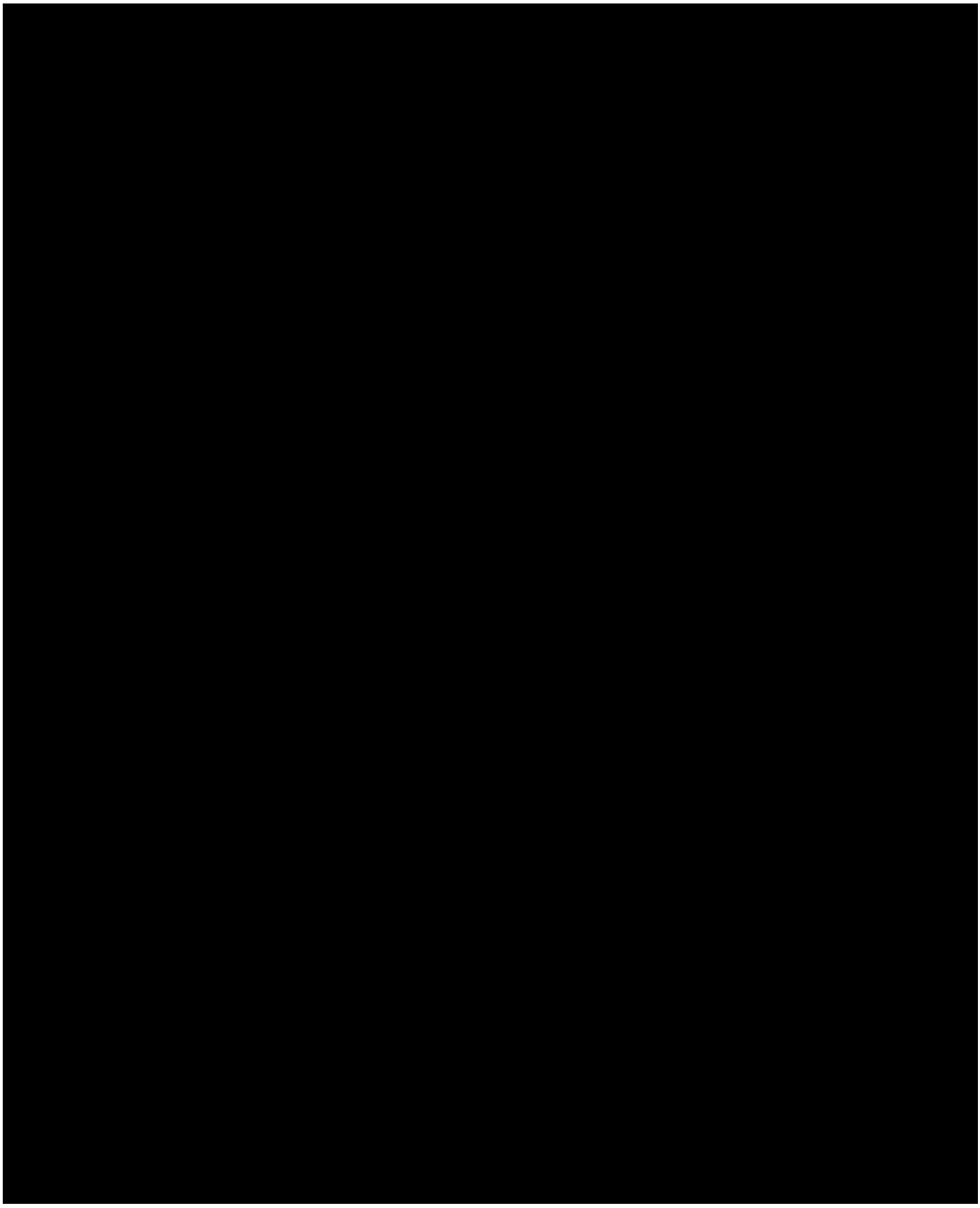
[redacted]

6.1 Treatment Period

Visits, assessments, and procedures will be performed as per the [redacted] instructions for missed doses are in Section 7.2.

[redacted]





[redacted]

6.1.2 Pre-Baseline Assessments/Day 1 Visit

[redacted]

For these at-risk subjects, the duration of the visit on Day 1 will be approximately 7 hours. [redacted]

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

6.1.3 Study Visits

Visits, assessments, and procedures will be performed according to [redacted]

Subjects who have previously received ozanimod for at least 1 year in an open-label study such as RPC01-2201 do not return for visits at [redacted].

[redacted]

6.1.5 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 have to 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.

[redacted]

[redacted]

6.3 Efficacy Assessments

See Section 2 for a description of study endpoints.

6.3.1 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]

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 Pre-baseline 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 pre-baseline 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	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	

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 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. Endoscopic remission has not yet been validated and may be defined as SES-CD ≤ 4 points and a SES-CD decrease ≥ 2 points, an absence of large ulcers, absence of ulcers, or SES-CD = ≤ 2.

To ensure quality data and standardization, the same endoscopist and the same diameter colonoscope as used in screening should be used throughout the study wherever possible.

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. Biopsies are not required in this study.

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

	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

6.3.3 Abdominal Pain and Stool Frequency

The abdominal pain and stool frequency scores are based on 2 components of the CDAI (Khanna, 2015). See Section 6.3.1 above for more details.

Stool frequency and abdominal pain, as described in Section 6.3.1, will be obtained and calculated without a weighting factor for use as part of the inclusion criteria. These unweighted subject-reported assessments will also be used as efficacy endpoints (Section 2).

6.4 Other Assessments

6.4.1 Physical Examination

A complete physical examination will be performed to evaluate the heart, lungs, head and neck, abdomen, skin, extremities, and weight as well as to check for visual symptoms (eg, blurred vision or decreased visual acuity as reported by the subject). A full examination of the skin should be repeated every 24 weeks. An interim physical examination will include weight and a check for visual symptoms, and an evaluation of body systems with previously noted abnormalities and/or those body systems associated with any new complaints from the subject. See [redacted] for additional details and [redacted]

6.4.2 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 subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Subjects entering from a blinded study and deemed as high risk due to cardiac conditions 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]

6.4.3 Electrocardiogram

The 12-lead digital ECG devices will be provided to each clinical site by the central ECG laboratory for the duration of the trial. Detailed instructions describing the process for recording and transmission of the digital ECGs will be outlined in the trial-specific manual and provided to the site before the start of the trial. Paper versions of ECG tracings will be printed and photocopied to preserve the ink if necessary and kept at the site as source documentation. An ECG will be performed while resting. 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 in [redacted] or in all subjects if deemed necessary by national or 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 was evaluated by the treating physician, and the central results are assessed as abnormal or unmeasurable 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 electronic case report form (eCRF).

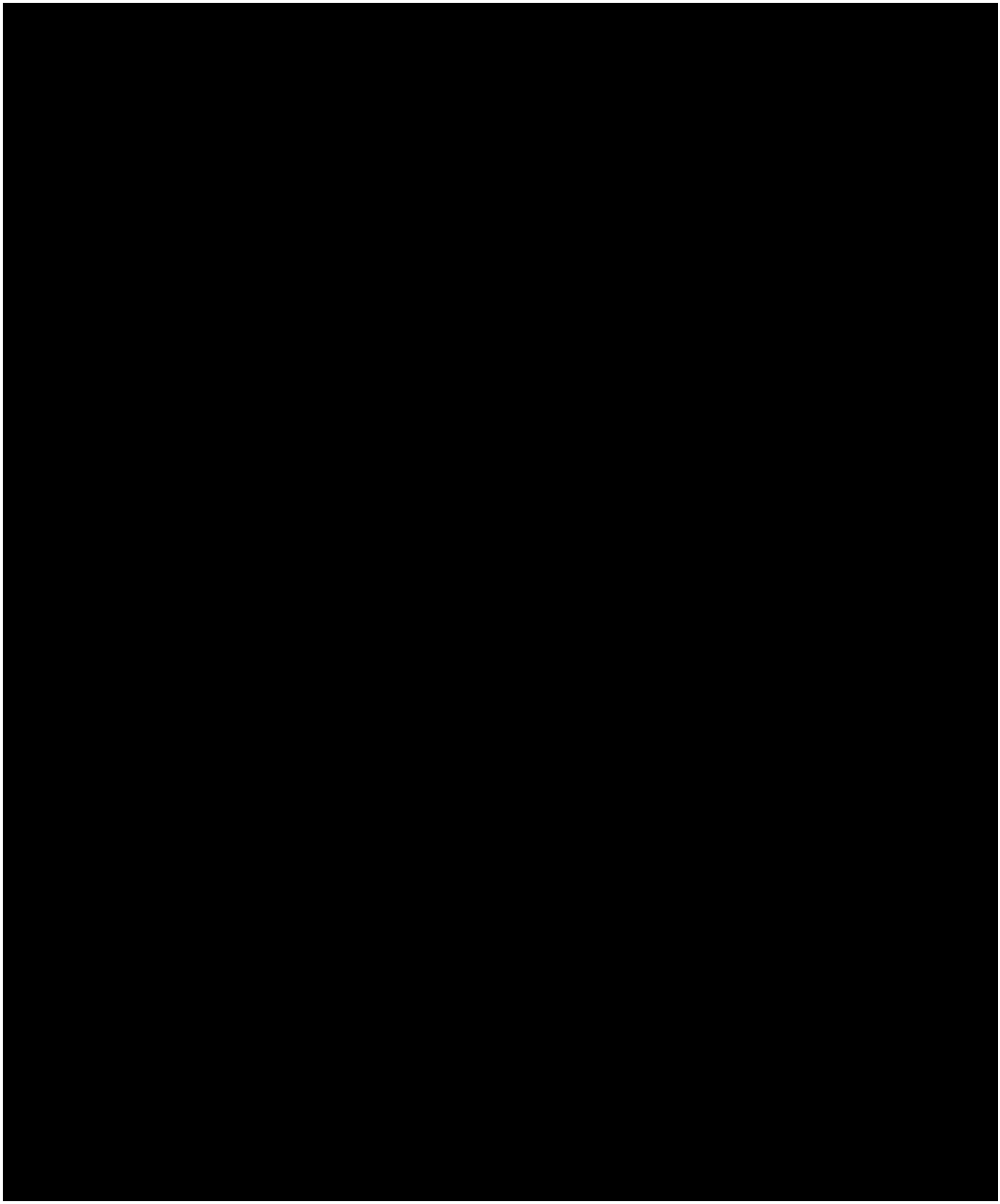
At the [redacted] Safety Follow-up Visit, an ECG should be repeated if the ECG at the ET/EoT visit shows a new abnormal result.

6.4.4 Pulmonary Function Tests

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

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

[redacted]



7 DESCRIPTION OF STUDY TREATMENTS

7.1 Description of Investigational Product(s)

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

Ozanimod 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. Ozanimod doses and strengths are expressed as the HCl salt form of ozanimod. Two ozanimod dosage strengths have been prepared for the clinical investigations: 0.23 mg (size 4 capsule; equivalent to ozanimod HCl 0.25 mg) and 0.92 mg (size 4 capsule; equivalent to ozanimod HCl 1 mg).

The capsules will be orally administered singularly, or in varying combinations, to achieve the desired dose for clinical studies.

There is no provision for dose adjustments in this study. Subjects who cannot tolerate IP must be withdrawn from the study.

7.2 Treatment Administration and Schedule

Subjects entering the study from RPC01-2201 will continue to receive ozanimod 0.92 mg/day (equivalent to ozanimod HCl 1 mg). Subjects entering the study from RPC01-3201, RPC01-3202, or RPC01-3203 will initiate ozanimod treatment in accordance with a 7-day dose escalation as follows:

- Days 1 through 4: Ozanimod 0.23 mg daily (equivalent to ozanimod HCl 0.25 mg)
- Days 5 through 7: Ozanimod 0.46 mg daily (equivalent to ozanimod HCl 0.5 mg) (administered as two 0.23-mg capsules)
- Day 8 through End of Study: Ozanimod 0.92 mg daily (equivalent to ozanimod HCl 1 mg)

[redacted] Subjects should be instructed to take IP at approximately the same time each day with or without food.

If subjects miss dosing for more than 14 days, they are required to complete the [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. There is no information regarding overdose with ozanimod. Any overdose, with or without associated AEs, must be promptly reported to the Medical Monitor or other designated Drug Safety Center. The overdose should be recorded in the Overdose eCRF. Any 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 7-day titration regimen (4 days of dosing at 0.23 mg daily [ozanimod HCl 0.25 mg] and 3 days of dosing at ozanimod 0.46 mg daily [ozanimod HCl 0.5 mg]). 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 doses 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

A single 0.92 mg oral daily dose of ozanimod will be administered.

7.4 Packaging and Labeling

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

The label(s) for IP will include sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5 Investigational Product Accountability and Disposal

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

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

lock. The Clinical Monitor will periodically check the supplies of IP held by the Investigator or pharmacist to verify accountability of all IP used.

The Investigator will provide the IP only to the identified subjects of this study, according to the procedures described in this study protocol. After the end of the study, the Clinical Monitor will perform final accountability, package, seal, and prepare for shipment. Investigational product and all medication containers will be returned to the clinical supply distribution vendor and documentation will be returned to the contract research organization (CRO). The CRO will verify that a final report of IP accountability is prepared and maintained in the Investigator's Trial Center File.

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

7.6 Investigational Product Compliance

It is the Investigator's responsibility to ensure that subjects are correctly instructed on how to take their IP, and that each subject is fully compliant with his/her assigned dosage regimen. Records of IP used and 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 medication 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 as assessed by medication counts (ie, 2 or more missed medication days in 1 week) and their response to a medication compliance question at each visit should be counseled on the importance of good compliance to the study dosing regimen. Subjects who are persistently noncompliant (< 80% or > 120%) should be discussed with the Medical Monitor to determine whether they should be withdrawn from the study.

8 CONCOMITANT MEDICATIONS AND PROCEDURES

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

Administration of concomitant medications must be reported along with dosage information, dates of administration, and reasons for use. For medications with a single active ingredient, generic names for concomitant medication 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. All treatments being taken in addition to the IP by the subjects on entry to the study or at any time during the study are regarded as concomitant treatments and must be documented on the appropriate section of the eCRF. All prior medications that were continuing at the time of study discontinuation in the prior study or any new medications that started between the prior study discontinuation and enrollment in RPC01-3204 need to be documented.

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

8.1.1 Corticosteroid Taper

If subjects are still receiving corticosteroids in the Open-label Extension Study, subjects should begin tapering corticosteroids once clinical response or clinical remission has been achieved.

[redacted]

8.1.2 Aminosalicylates or Purified Medicinal Probiotics

Subjects receiving 5-aminosalicylic acid (ASA) or purified medicinal probiotics should maintain a stable dose throughout the study unless reduction or discontinuation is clinically indicated.

8.1.3 COVID-19 Vaccination

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

Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in subjects receiving ozanimod is unknown. The individual 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 otherwise authorized (eg, Emergency Use Authorization [FDA] or equivalent) by national health authorities.

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

[redacted]

[redacted]

[redacted]

8.3 Required Concomitant Medications and Procedures

Not applicable.

9 STATISTICAL CONSIDERATIONS

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

9.1 Overview

This is a Phase 3, open-label, multicenter extension study to evaluate the safety and efficacy of ozanimod in subjects with moderately to severely active CD, defined as a CDAI score of ≥ 220 to ≤ 450. It is anticipated that approximately [redacted] subjects who participated in prior studies of ozanimod in CD will be eligible for treatment in this study

9.2 Study Population Definitions

All subjects who receive at least 1 dose of IP will comprise both the Intent-to-Treat (ITT) population and the Safety population. These populations will be used to summarize all safety and efficacy data, respectively.

9.3 Sample Size and Power Considerations

As this is an Open-label Extension Study for subjects who participated in a prior study of ozanimod for CD, there is no statistical basis for the sample size. It is anticipated that approximately [redacted] subjects who participated in prior studies of ozanimod in CD will be eligible for treatment in this study.

9.4 Background and Demographic Characteristics

Subject demographics and baseline characteristics from RPC01-3201, RPC01-3202, and RPC01-2201 will define subject demographics and baseline characteristics for RPC01-3204. Descriptive summaries will be presented for the safety and efficacy variables collected. 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.

Subject demographics and baseline characteristics will include 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 abdominal pain and stool frequency, prior anti-TNF use, and prior corticosteroid use.

Subject baseline for a given assessment is defined as the most recent non-missing measurement for that assessment immediately prior to administration of the first dose of IP (or ozanimod for safety analysis) for that subject across all of the following studies: RPC01-3201, RPC01-3202, RPC01-3203, RPC01-3204, and RPC01-2201. Additional details are provided in the SAP.

9.5 Subject Disposition

Subject disposition will include, at the minimum, the following:

- the number of subjects enrolled
- the number of subjects dosed
- subject status including completion of prior study
- the number of subjects completing the RPC01-3204 Study
- the number of subjects not completing the RPC01-3204 Study by reason for dropout

9.6 Efficacy Analysis

Due to the open-label nature of the study and the lack of a control group, all data will be summarized, and no hypothesis testing will be performed. Each efficacy endpoint will be summarized and [redacted] around the estimates may also be presented. All efficacy data will be listed.

For all proportion-based efficacy endpoints, subjects with missing efficacy data will be considered non-responders.

For continuous efficacy endpoints, subjects with missing data will have their last post-baseline value carried forward.

Observed-cases analyses will also be presented for all efficacy endpoints.

9.7 Safety Analysis

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

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

Adverse events with an onset date on or after the first dose of drug in this study, or with an onset prior to the first dose of IP that increase in severity on or after the first dose of IP, will be considered treatment emergent. Treatment-emergent AEs will be summarized for the Safety population by system organ class and preferred term and presented in descending order of frequency within each System Organ Class. Serious AEs and AEs leading to discontinuation will be summarized similarly. Adverse events will be summarized by patient years of exposure (PYE).

Associated laboratory parameters such as hepatic profile, 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 will be produced showing the frequency of shifts from baseline to the highest and to the lowest on-study value in and out of the normal range as well as by visit. Changes from Baseline to each visit for each laboratory parameter will also be summarized.

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

The change from baseline to each visit for each of the ECG parameters will be summarized. An outlier analysis of ECG results will be conducted.

9.8 Interim Analysis

Not applicable.

9.9 Other Topics

9.9.1 Population Pharmacokinetics and Pharmacokinetics-Pharmacodynamics Analyses

Population PK and PK/PD analyses will be performed using data from Phase 1 through 3 studies. Results will be reported in a separate independent report.

9.9.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be charged with monitoring safety and efficacy data from the study, as well as general aspects of study conduct. The committee will meet periodically during the study to review analyses 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.

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.

[redacted]

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, whether or not it is associated with an AE should be reported on the overdose 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 on an SAE Report Form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE Report Form and eCRF but should not be reported as an SAE itself.

10.1.1 Treatment of Overdose of Investigational Product

An overdose is any dose of IP given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly

reported to the CRO's Medical Monitor or other designated Drug Safety Center. Cases of overdose should be recorded in the overdose eCRF and AEs associated with the overdose should be reported on relevant AE/SAE sections in the eCRF.

10.1.2 Monitoring of Subjects with Adverse Events and Serious Adverse Events

Investigators must carefully monitor each subject for AEs. This includes clinical laboratory variables. Assessments must be made of the seriousness, severity, and relationship to the administration of the IP. After the initial AE/SAE report, the Investigator is required to follow up proactively 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 the end of Safety Follow-up [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 within [redacted] days of the last dose of treatment with the IP, whether or not considered related to the IP, must also be reported. Adverse events and SAEs will be recorded on the AE page of the eCRF and in the subject's source documents. Refer to Section 13 for instructions on how to report SAEs to Drug Safety.

10.2 Evaluation of Adverse Events

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

10.2.1 Seriousness

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

- results in death
- is life-threatening

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

[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

The decision to temporarily interrupt dosing as a result of an AE or SAE remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. Prior to interruption,

the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

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

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

10.2.6 Outcome

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

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

10.2.7 Adverse Events of Special Interest

Potential AEs that may be a consequence of S1P receptor modulation, AESIs, will be monitored during the study. [redacted] The sponsor may request additional medical information concerning the 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 in consultation with the Medical Monitor or designee, or at the request of the Sponsor. Approval from the Medical Monitor or designee must be obtained if retest is required to be repeated > 2 times and is not already pre-specified in the protocol.

[redacted]

11.1 Hematology

Red blood cell count, total and differential white blood cell (WBC) count (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), platelet count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

[redacted]

[redacted]

11.2 Chemistry

- Full chemistry panel at Day 1 visit: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, glucose, albumin, alkaline phosphatase, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (GGT), total bilirubin, conjugated bilirubin, total cholesterol, triglycerides, [redacted] and low-density lipoprotein, [redacted]
- All other visits: sodium, potassium, chloride, calcium, magnesium, phosphate, blood urea nitrogen, albumin, alkaline phosphatase, creatinine, ALT, AST, GGT, total bilirubin, conjugated bilirubin, [redacted]; Total cholesterol, triglycerides, [redacted] and low-density lipoprotein will also be included [redacted] and at ET/EoT. [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.

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 consent from the 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

[redacted]

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a FCBP regardless of disease state) occurring while the subject is on IP, or within [redacted] days of the subject's last dose of IP, are considered immediately reportable events. Investigational product is to be discontinued immediately, and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to 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 within [redacted] days of the last dose of treatment with the IP, whether or not considered related to the IP, must also be reported. Any SAE that is ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

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

The SAE contact information is as follows:

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

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

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

13.1 Safety Queries

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

13.2 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Sponsor's Drug Safety will determine the expectedness of events suspected of being related to ozanimod based on the 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 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), sponsor or its 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 investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

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

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

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

The Investigator must keep copies of all pertinent safety information on file including correspondence with the 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 IP(s):

- AE
- 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.
- AE: 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.

[redacted]

[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. [redacted]

[redacted].

- Withdrawal by subject: The subject may choose to discontinue IP at any time. Every effort should be made within the bounds of safety and subject choice to have each subject complete the End of Treatment Visit and [redacted] If a subject 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 (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/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

This is an Open-label Extension Study; however, to maintain the blind from the parent study from which a subject may be entering, certain procedures such as [redacted] and [redacted] for all subjects entering from a blinded parent study will be conducted as outlined in this protocol.

16 REGULATORY CONSIDERATIONS

16.1 Good Clinical Practice

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

16.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. The sponsor's staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

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

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) for the study.

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

The information contained in the protocol and amendments (with the exception of the information provided by the sponsor on public registry websites) is considered sponsor confidential information. Only information that is previously disclosed by sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Study Agreement. Sponsor's protocol, amendment, and Investigator's Brochure information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from the sponsor. Information proposed for posting on the Investigator's or their institution's website must be submitted to the sponsor for review and approval, providing at least 5 business days for review.

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

16.3 Subject Information and Informed Consent

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

occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

16.4 Confidentiality

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

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

16.5 Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor's Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/IEC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/IEC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

16.6 Institutional Review Board/Independent Ethics Committee Review and Approval

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

IP can only be supplied to an Investigator by the sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by the 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/ 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 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/EC
- composition of the IRB/EC
- 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 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 sponsor prior to destruction of any records. If

the Investigator is unable to meet this obligation, the Investigator must ask sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

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

18 QUALITY CONTROL AND QUALITY ASSURANCE

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

18.1 Study Monitoring and Source Data Verification

The sponsor ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an 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, and 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 unless retention presents a risk to personnel. When reporting, provide as much product information as possible. Suspected IP quality issues will be investigated, and a response will be provided back to the investigational site.

18.3 Audits and Inspections

In addition to the routine monitoring procedures, a GCP Quality Assurance unit exists within 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 16.2, 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 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 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6-MP	6-mercaptopurine
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase (SGPT)
[redacted]	[redacted]
ASA	Aminosalicylic acid
AST	Aspartate aminotransferase (SGOT)
[redacted]	[redacted]
AZA	azathioprine
[redacted]	[redacted]
β-hCG	β-subunit of human chorionic gonadotropin
CBC	Complete blood count
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
[redacted]	[redacted]
DMC	Data Monitoring Committee
EC	Ethics Committees
EC50	Effective concentration-50
ECG	Electrocardiogram
eCRF	Case report form
EEA	European Economic Area
ELISA	Enzyme linked immunosorbent assay
EMA	European Medicines Agency
EoT	End of treatment
ET	Early termination

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
FCBP	Female of Childbearing Potential
FDA	Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practices
HR	Heart rate
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
IgM	Immunoglobulin M
ICF	Informed consent form
ICH	International Council on Harmonisation
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
[redacted]	[redacted]
[redacted]	[redacted]
LFT	Liver function test
MERS-CoV	Middle East respiratory syndrome coronavirus
MTX	Methotrexate
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PD	Pharmacodynamic
[redacted]	[redacted]

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
PFT	Pulmonary function test
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
PYE	Patient years of exposure
[redacted]	[redacted]
RMS	Relapsing multiple sclerosis
S1P	Sphingosine-1-phosphate
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
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
UC	Ulcerative colitis
[redacted]	[redacted]
WBC	White blood cell

APPENDIX B SARS-COV-2 GUIDELINES

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

If the subject receives a positive SARS-CoV-2 test result and is asymptomatic during the pre-baseline 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 participant at a higher risk of receiving investigational treatment

If the subject receives a positive SARS-CoV-2 test result and is symptomatic during the pre-baseline 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 participant at a higher risk of receiving investigational treatment

Each study visit will include an assessment for AEs including SARS-CoV-2 and other infections. In order to facilitate reporting of SARS-CoV-2 events that occur during the study, all AEs and SAEs related to SARS CoV-2 should be reported from the time of consent until the final study visit (Section 10.1).

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

Evaluation and management of SARS-CoV-2 infections arising during the course of the trial are left to the discretion and expertise of the Investigator. For subjects who are exhibiting symptoms consistent with COVID-19, the Sponsor advises the Investigator to consult the Medical Monitor.

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

the eCRF. A separate logline should be entered for each vaccine administered with the dose number following the vaccine name/trade name.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Removal of Adolescent Subjects**

The study design has been updated to reflect the development of a comprehensive pediatric program. Adolescents have been removed as potential subjects. The minimum age to enter the study has been adjusted to 18 years. No adolescent has been randomized into the study under any previous version of the protocol.

Revised sections: Protocol Summary; **Section 1.1,** Disease Background; **Section 2.2,** Study Endpoints; **Section 4.2**, Inclusion Criteria; [redacted]; **Section 6,** Procedures; [redacted] **Section 9.4**, Background and Demographic Characteristics; **Section 12.1**, Female Subjects of Childbearing Potential; **Section 14.2**, Study Discontinuation; **Section 16.3**, Subject Information and Informed Consent; and **Section 20,** References

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

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

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

- **Addition of SARS-CoV-2 Guidance**

Due to the global SARS-CoV-2 pandemic, new considerations and requirements have been included to address the following:

[redacted]

- Adverse event reporting of COVID-19 cases, including an assessment for AEs at each study visit, and reporting requirements for testing-related and treatment-related procedures.
- Guidance for the management of a positive SARS-CoV-2 test result prior to enrollment, including the assessment of symptoms, the presence of sequelae, and the effect on eligibility.
- Drug Interruption due to COVID-19, including the decision to interrupt remaining the physician's decision, and including the request to contact the Medical Monitor to discuss treatment re-initiation.
- Vaccine considerations and reporting, including the requirement that it must be a non-live, replication incompetent vaccine.

[redacted]

Revised sections: Protocol Summary; **Section 1.2.4**, Benefit Risk Assessment; [redacted] **Section 6**, Procedures; **Section 6.1.2**, Pre-Baseline Assessments/Day 1 Visit; **Section 8.1.3**, COVID-19 Vaccination; **Section 10.1**, Monitoring, Recording, and Reporting of Adverse Events; and **Appendix B**, SARS-CoV-2 Guidelines.

- **Modification of First Dose Monitoring Requirements**

To ensure complete cardiac evaluation for subjects identified as at risk, the [redacted] and [redacted] have been enhanced as follows:

- Added study exclusion criterion for subjects with resting [redacted].
- Additional ECGs have been inserted at Hour 2 and Hour 4 postdose.
- [redacted]
- [redacted]

Revised sections: **Section 4.3.3**, Exclusions Related to Laboratory Results and Other Assessments; [redacted] and **Section 6.4.3**, Electrocardiogram

- **Pulmonary Function Tests for all Subjects**

To ensure adequate characterization of ozanimod's safety profile and to facilitate a robust dataset of pulmonary function in patients with CD, baseline and subsequent pulmonary function tests (PFTs) are being re-introduced in all subjects.

Revised sections: [redacted] **Section 6.4.4**, Pulmonary Function Test

[redacted]

[redacted]

- **Product Quality Complaint Notification Update**

Updated the guidelines on when and how to report a Product Quality Complaint to the current procedure.

Revised sections: **Section 18.2**, Product Quality Complaint

- **Minor editorial changes were made to enhance clarity of the protocol, as well as an update to sponsor address, abbreviations, and references.**

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Sample Size Adjustment**

The sample size was adjusted to [redacted] to account for the removal of the 0.46 mg treatment arm in 3203. This is sufficient for statistical considerations using the estimated treatment difference between ozanimod and placebo for the primary and first key secondary endpoints.

Revised sections: Protocol Summary; **Section 3.1**, Study Design; **Section 4.1**, Number of Subjects; **Section 9.1**, Overview; and **Section 9.3**, Sample Size and Power Considerations .

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

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

Revised sections: **Section 1.2.2,** Summary of Clinical Studies in Inflammatory Bowel Disease

- **Inclusion of [redacted] as Adverse Events of Special Interest and Study Discontinuation Criteria**

Adverse events of special interest will include monitoring criteria for [redacted] and confirmed diagnosis will require discontinuation from the study. This guidance is aligned with the company core data sheet and the prescribing information for ozanimod.

Revised section: **Section 10.2.7**, Adverse Events of Special Interest and **Section 14.2,** Study Discontinuation

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

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

Revised sections: [redacted]; **Section 6.4.4**, Pulmonary Function Test; and [redacted]

- [redacted]

The [redacted] and [redacted] has been revised to align with the prescribing information for ozanimod (Zeposia).

Revised sections: [redacted]; [redacted] and **Section 6.4.3**, Electrocardiogram

[redacted]

- **CDAI Calculation**

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

Revised section: Section 6.3.1 Crohn's Disease Activity Index

- **Instructions for Missed Doses**

Additional instructions for missed doses were included in accordance with the prescribing information for ozanimod.

Revised section: **Section 7.2.1**, Instructions for Missed Doses

- **Update to Liver Function Testing and Discontinuation Criteria**

[redacted] This guidance is aligned with the Food and Drug Administration (FDA) guidance on liver injury evaluation and balances the call for immediate action with the technical limitations around central laboratory processing.

In addition, confirmation is not required to discontinue a subject based on the liver function test criteria outlined in Section 14.2.

Revised sections: **Section 11.2**, Chemistry and **Section 14**, Discontinuations

[redacted]

Revised sections: Protocol Summary; **Section 2.2.4,** Overview of Key Safety Assessments; [redacted] and **Section 9.7**: Safety Analysis

[redacted]

[redacted]

Revised sections: Protocol Summary; [redacted]

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

This document summarizes the changes that were made between Protocol RPC01-3204 Version 4 (dated 10 June 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:

- Revisions to reflect the addition of adolescent subjects
- Changed to Safety Follow-up from [redacted] to [redacted] Safety Follow-up Visit to ensure adequate collection of adverse events that could be associated with investigational product. The timing of the visit is based on the estimated time needed to clear the major active metabolites of RPC1063 in the vast majority of patients (ie, 5 half-lives of CC112273 and CC1084037 and accounting for variation of half-life duration in a human population).
- Extended the requirements for contraception in females after treatment discontinuation from the [redacted] Safety Follow-up Visit to the [redacted] Safety Follow-up Visit.
- Addition of withdrawal/dependence questionnaires
- Minor editorial changes to enhance clarity of the protocol, and update study personnel names

This document summarizes the changes that were made between Protocol RPC01-3204 Version 3 (dated 18 June 2018) and Version 2 (dated 19 December 2017).

1. OVERVIEW OF KEY CHANGES

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

- [redacted] because in vitro data show that the major active metabolite CC112273 is formed by and inhibits MAO-B. The potential for clinical interaction with MAO inhibitors has not been studied.
- Added [redacted] inhibitors to the list of medications that are prohibited during the trial until the [redacted] Safety Follow-up Visit. In a Phase 1 drug-drug interaction study, a strong inhibitor of [redacted], had no effect on ozanimod exposure, while it approximately doubled the exposure of its active metabolites, RP101988 and RP101075. While the major active metabolite CC112273 is not a substrate of drug transporters, it is unknown if the increase in RP101075 (via RP101988) may also lead to a similar increase in CC112273, which is formed directly from RP101075.
- [redacted]
- [redacted] was added to the list of medications that cannot or should not be used during the trial or after investigational product discontinuation because in vitro data show that the major active metabolite CC112273 is further metabolized by [redacted]. The potential for clinical interactions with [redacted] has not been studied and therefore co-administration is not recommended.
- [redacted].
- The protocol was updated to add new protocol template language regarding handling of product quality complaints for any drug product manufactured by or on behalf of Celgene Corporation.

The following bulleted list identifies global changes to the protocol:

- Language has been changed to indicate that subjects from Study RPC01-1201 are now eligible to participate in this study if they meet the eligibility criteria.
- Language has been changed to indicate the scientific and medical rationale for the length of study and study duration for subjects.
- A [redacted] Safety Follow-up Visit was added throughout the document and to the [redacted] to ensure adequate collection of adverse events that could be associated with investigational product. The timing of the visit is based on the estimated time needed to clear the major active metabolite of ozanimod (RPC1063, which is 5 half-lives of CC112273).
- The term “patient” was changed to “subject” throughout the document in order to maintain consistency throughout the protocol.

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

This document summarizes the changes that were made between Protocol RPC01-3204 Version 1.0 (dated 26 September 2017) and Version 2.0 (dated 19 December 2017).

1. OVERVIEW OF KEY CHANGES

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

- The CDEIS is being introduced as a key efficacy endpoint because it is an established endoscopic measure.

[redacted]

- The section on the evaluation of adverse events was modified since the investigator will not determine whether an adverse event is an adverse event of special interest (AESI). This change was made to better align with the planned designation of AESIs by the sponsor and to align with the Medical Monitoring plan.
- The criteria for discontinuation, including subjects with liver function test abnormalities and subjects with clinically significant [redacted], was updated to provide further guidance to investigators on monitoring the study.
- Text on a Data Safety Monitoring Board (DSMB) was added to align with our current plan for DSMB review.

The following bulleted list identifies global changes to the protocol:

- Abbreviations lists in footnotes and Appendix A: Table of Abbreviations were updated.
- The list of references has been updated based on changes in this amendment.
- Edits were made throughout the document for the purposes of clarity and protocol consistency.
- Minor typographical corrections have been made.