Official Title: **Efficacy and Safety of Oral OPS-2071 in Subjects With Crohn's Disease Showing Symptoms of Active Inflammation Despite Ongoing Treatment**

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Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

OPS-2071

REVISED CLINICAL PROTOCOL

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Trial to Assess the Efficacy and Safety of Orally Administered OPS-2071 for 12 Weeks in Subjects With Crohn's Disease Showing Symptoms of Active Inflammation Despite Ongoing Treatment

Protocol No. 341-201-00004
IND No. 137377
EudraCT No. 2019-000176-41

CONFIDENTIAL – PROPRIETARY INFORMATION

Clinical Development Phase:	2
Sponsor:	Otsuka Pharmaceutical Development & Commercialization, Inc. 2440 Research Boulevard Rockville, Maryland 20850, United States
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Protocol 341-201-00004

Protocol Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: OPS-2071	Protocol No.: 341-201-00004 IND No.: 137377 EudraCT No.: 2019-000176-41
Protocol Title:	A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Trial to Assess the Efficacy and Safety of Orally Administered OPS-2071 for 12 Weeks in Subjects With Crohn's Disease Showing Symptoms of Active Inflammation Despite Ongoing Treatment
Clinical Phase/Trial Type:	Phase 2/Therapeutic use
Treatment Indication:	Crohn's disease
Objective(s):	**Primary:** To investigate the therapeutic effect of OPS-2071 (150, 300, or 600 mg twice a day [BID]) add-on therapy administered orally for 12 weeks in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment. **Secondary:** To determine the safety and tolerability of OPS-2071 (150, 300, or 600 mg BID) add-on therapy administered orally for 12 weeks in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment.
Trial Design:	This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept trial to assess the efficacy and safety of 3 doses of OPS-2071 (150, 300, or 600 mg BID) in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment. OPS-2071 will be added to ongoing treatment for Crohn's disease. Details of ongoing treatment are provided below in the inclusion and exclusion criteria.

	Screening will occur up to 28 days prior to randomization. At the start of the screening period, a fecal sample will be collected for stool microbiology testing (eg, for culture, *Clostridium difficile*, ova and parasites) and to exclude any type of infectious colitis, and to assess the fecal microbiota. During the screening period, subjects will be dispensed an electronic diary to complete to collect data for the baseline Crohn's Disease Activity Index (CDAI) assessment. After completion of the diary for 7 days, subjects will undergo bowel preparation for 3 days (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation) and then an ileocolonoscopy with biopsy will occur (within 7 to 10 days prior to Day 1). The ileocolonoscopy will be centrally read to assess inflammation in order to confirm trial eligibility. Optional cytomegalovirus testing can be done on the biopsy specimen, if clinically indicated. Eligible subjects will be randomized on Day 1 in a 1:1:1:1 ratio to 1 of 4 treatments: placebo BID, OPS-2071 150 mg BID, OPS-2071 300 mg BID, or OPS-2071 600 mg BID. The randomization will be stratified by CDAI score (CDAI 180 - 300 and CDAI > 300 - 450) and concomitant Crohn's disease medication status (subjects who are treated with anti-TNF-α monoclonal antibody, subjects who are treated with low-dose steroids, and subjects who are treated with other Crohn's disease medications). Blood samples for pharmacokinetic analysis will be collected throughout the 12-week treatment period according to the schedule of assessments. A 30-day (post-treatment) follow-up assessment will be performed for all subjects; the CDAI score will be calculated, inflammatory biomarkers and microbiota flora will be checked, and safety measures will be performed. Subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial are considered as treatment failures (nonresponders).
Subject Population:	Approximately 240 male and female subjects between the ages of 18 and 70 (inclusive), with Crohn's disease and showing symptoms of active inflammation despite ongoing treatment, will be randomized. Active mucosal inflammation will be confirmed by centrally read ileocolonoscopy.

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Inclusion/Exclusion Criteria:	**Key inclusion criteria:** • Diagnosis of Crohn's disease localized in the ileum and/or colon, with active mucosal inflammation and visible lesion(s), documented by centrally read ileocolonoscopy and a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥ 6 (≥ 4 for isolated ileal disease). • Subjects who do not have an optimal response (daily stool frequency > 3 and pain score > 1) to their current ongoing treatment of biologics (eg, first anti-tumor necrosis factor-alpha [TNF-α] monoclonal antibody), immunosuppressants, low-dose steroids, or 5-aminosalicylic acid (5-ASA) formulations. Note: The minimum duration of prior treatment required for a subject to be considered as having a nonoptimal response includes completing at least the recommended induction regimen for approved biologics and/or treatment at a therapeutic dose for a stable duration that would be anticipated to result in improvement (ie, 12 weeks for azathioprine, 4 weeks for methotrexate). • Subjects who are on stable Crohn's disease medications for at least 4 weeks. • Subjects with a CDAI score between 180 and 450 points, inclusive. **Key exclusion criteria:** • Use of prednisone or prednisolone > 30 mg/day or budesonide > 9 mg/day within 4 weeks prior to screening; or intravenous steroids within 4 weeks prior to screening. • Subjects with known or suspected (family history, unexplained syncope) long QT syndrome or QT interval corrected for heart rate by the Fridericia formula (QTcF) > 470 msec for females or > 450 msec for males at baseline. • Subjects with known existing aortic aneurysm, or who are at risk for an aortic aneurysm, such as subjects with peripheral atherosclerotic vascular diseases, uncontrolled hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly subjects (over the age of 70).

	• Subjects with inadequate organ function, as follows:
	  • Serum creatinine > 1.5 × the upper limit of normal (ULN)
	  • Aspartate aminotransferase or alanine aminotransferase levels > 1.5 × ULN
	  • Total bilirubin > 1.5 × ULN. Elevated unconjugated bilirubin related to Gilbert's syndrome is allowed.
	• Known hypersensitivity to quinolones or other significant adverse reaction to quinolones.
	• Subjects with a history of treatment failure with 2 or more biologics.
	Note: The rationale for excluding subjects who have failed 2 or more biologics is due to the fact that they may represent an especially difficult-to-treat population (ie, medically refractory) that may not benefit substantially from fluoroquinolones and/or will likely need additional, more invasive treatment (ie, surgical resection).
	• Subjects with risk factors for tendon rupture (ie, psoriasis, ankylosing spondylitis, competitive athletes, renal failure, diabetes mellitus) or who have a history of tendon rupture and/or ongoing tendinopathy.
	• Subjects with systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg.
	• Subjects taking quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, ibutilide, dronedarone, or propafenone.

Trial Site(s):	Approximately 100 trial sites in the United States, Canada, and Europe.

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Investigational Medicinal Product(s), Dose, Dosage regimen, Treatment period, Formulation, Mode of Administration:	Eligible subjects will be randomized on Day 1 to 1 of 4 treatments: placebo BID, OPS-2071 150 mg BID, OPS-2071 300 mg BID, or OPS-2071 600 mg BID. The investigational medicinal product (IMP) will be supplied as 150-mg and 300-mg OPS-2071 tablets, and matching placebo tablets. The IMP will be administered as oral tablets, BID (8 to 12 hours apart), starting on Day 1 for a total of 12 weeks. The timing of the first dose of IMP will be at the subject's or trial site's discretion. Each subject will take 6 tablets daily (to maintain blinding); 3 tablets for the morning dose and 3 tablets 8 to 12 hours later. The IMP will be administered with up to 240 mL (8 fluid ounces) of still water, at least 1 hour before or after a meal. Water intake will be restricted for 1 hour before and after the morning dose of IMP at Day 1 and Week 6 for the robust blood sampling.
Trial Assessments:	**Efficacy:** CDAI score, SES-CD, and the two-item patient reported outcome (PRO-2). **Pharmacokinetic:** Blood samples will be collected to determine the concentrations of OPS-2071 and its metabolite, M34101. **Pharmacodynamic (biomarkers):** A blood sample will be collected to assess C-reactive protein (CRP) and a fecal sample will be collected to assess fecal calprotectin (FCP). **Safety:** adverse event (AE) reporting, clinical laboratory tests, physical examinations (including height and weight), vital signs, and 12-lead electrocardiograms. **Screening/Other:** demography, medical and medication history, viral hepatitis and human immunodeficiency virus screen, urine pregnancy test, optional follicle-stimulating hormone (FSH) test, urine alcohol and drug screen, ileocolonoscopy with biopsy, fecal microbiota, daily subject diary, and blood sampling for future biospecimen research.
Criteria for Evaluation:	**Primary Endpoint:** The percentage of subjects who, at Week 12, achieve clinical remission (defined as a CDAI score < 150).

Secondary Efficacy Endpoints:

1) The percentage of subjects with endoscopic response, defined as a reduction of the SES-CD by at least 50%, at Week 12.
2) Change from baseline in the SES-CD score.
3) The percentage of subjects with PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1) at Week 12.
4) The percentage of subjects with clinical response, defined as at least a 25% decrease in the CDAI score, at Week 12.
5) The percentage of subjects who, at Week 12, achieve endoscopic remission (defined as a SES-CD score of 0 to 2; or a score of 0 to 4, with no individual subscore greater than 1).
6) The percentage of subjects with a decrease from baseline of ≥ 100 points in the CDAI score.

Secondary Safety Endpoint: The percentage of subjects by specific AEs, which will be recorded with the onset date, resolution or stabilization date, severity grade, and relatedness to IMP.

Exploratory Endpoints:

1) By-visit analysis of CDAI remission (defined as a CDAI score < 150).
2) By-visit analysis of PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1).
3) The percentage of subjects with a biological response in subjects with elevated levels of CRP, defined as a reduction in the level of CRP to within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.
4) The percentage of subjects with a biological response in subjects with elevated levels of FCP, defined as a reduction in the level of FCP to within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.
5) Characterization of the fecal microbiota profile and abundance based on taxonomic and functional annotation from next-generation sequencing, change from baseline, and association with phenotype, at Week 2, Week 12, and at the 30-day follow-up.

Statistical Methods:	**Sample Size:** For the primary endpoint of clinical remission (CDAI score < 150), assuming a 40% response rate in the OPS-2071 600 mg BID and 300 mg BID dose groups and a 20% response rate in the placebo group, 60 randomized subjects per treatment group would provide 80% power to detect a treatment difference between the OPS-2071 pooled dose groups (600 mg BID and 300 mg BID) and the placebo group in the primary endpoint, using a 2-sided alpha of 0.05. The total sample size of the trial is 240 randomized subjects with 1:1:1:1 randomization to OPS-2071 600 mg BID, 300 mg BID, or 150 mg BID, or placebo BID. The power of individual dose comparison with placebo under the same assumption is 67%. For the secondary endpoint of endoscopic response, assuming a 26.5% response rate in the OPS-2071 600 mg BID and 300 mg BID dose groups and a 10% response rate in the placebo group, 60 subjects per treatment group would provide 80% power for the comparison between the OPS-2071 pooled dose groups (600 mg BID and 300 mg BID) and the placebo group, and 65% power for the individual dose comparison with placebo, using a 2-sided alpha of 0.05. **Primary Endpoint Analysis:** Subjects with stable dosages in their baseline Crohn's disease medications will be randomized into treatment groups of OPS-2071 600 mg BID, 300 mg BID, or 150 mg BID, or placebo BID, stratified by CDAI score (CDAI 180 - 300 and CDAI > 300 - 450) and concomitant Crohn's disease medication status (subjects who are treated with anti-TNF-α monoclonal antibody, subjects who are treated with low-dose steroids, and subjects who are treated with other Crohn's disease medications) for 12-week treatments. Dosages of baseline Crohn's disease medications are expected to be maintained constant throughout the full duration of the trial. However, doses of baseline Crohn's disease medications can be decreased per the investigator's judgment. If a higher dosage of a baseline Crohn's disease medication or a new medication for Crohn's disease is to be administrated to a subject during the double-blind treatment period, the subject will be considered as a treatment failure (nonremission subject or nonresponder) in the analyses of the primary and secondary endpoints.

	Logistic regression with terms of treatment group, the randomization stratification factors, location of disease, country, age, sex, disease duration, smoking habit, and baseline CDAI, and baseline CDAI with CDAI stratification factor interaction will be applied to the primary endpoint. Remission and nonremission subjects (ie, treatment failures) are defined as follows: • Subjects who complete the trial and meet the primary endpoint definition at Week 12 without increasing dosages of baseline Crohn's disease medications or taking a new medication for Crohn's disease during the double-blind treatment period will be considered as remission subjects for the endpoint. • Subjects who increase dosages of baseline Crohn's disease medications or take a new medication for Crohn's disease during the double-blind treatment period, or subjects who withdraw from the trial during the double-blind period, in addition to the subjects who fail to meet the primary endpoint at Week 12, will be considered as nonremission subjects for the endpoint. The primary analysis of this trial is comparison of the pooled OPS-2071 600 mg BID and 300 mg BID treatment groups with placebo in the primary endpoint of clinical remission. If this analysis is significant at a 2-sided alpha level of 0.05, comparisons to OPS-2071 600 mg BID versus placebo and OPS-2071 300 mg BID versus placebo in the primary endpoint will be conducted with a 2-sided alpha level of 0.05 in each comparison. If the comparison of the pooled OPS-2071 dose groups versus placebo in the primary endpoint is significant at a 2-sided alpha level of 0.05, and a comparison, say, OPS-2071 600 mg BID versus placebo, is also significant at a 2-sided alpha level of 0.05, the null hypothesis of equal response of OPS-2071 600 mg BID and placebo in the primary endpoint will be considered rejected with an experiment-wise Type I error of 0.05.
	The comparison between OPS-2071 150 mg BID versus placebo in the primary endpoint is considered as a secondary analysis and is provided in Section 7.4.2.

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Trial Duration:	The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 22 months. Individual participation for subjects who complete the trial without early withdrawal will be up to 20 weeks, consisting of the following: screening period of up to 28 days, a 12-week treatment period, and a 30-day (post-treatment) follow-up assessment.

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{24h}	Area under the concentration-time curve from time zero to 24 hours
AUC_{∞}	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_t	Area under the concentration-time curve from time zero to the last quantifiable concentration
BCRP	Breast cancer resistance protein
BID	Twice a day
CDAI	Crohn's Disease Activity Index
C_{max}	Maximum (peak) plasma concentration of the drug
CMV	Cytomegalovirus
CRO	Clinical Research Organization
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FBR	Future biospecimen research
FCP	Fecal calprotectin
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board
IRE	Immediately reportable event
ITT	Intent-to-treat
LPS	Lipopolysaccharide
NOAEL	No observed adverse effect level
O&P	Ova and parasite
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
POC	Proof-of-concept

PQC	Product quality complaint
PRO-2	Two-item patient reported outcome
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate by the Fridericia formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SES-CD	Simple Endoscopic Score for Crohn's Disease
$t_{1/2}$	Apparent terminal phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum (peak) concentration
TNF-α	Tumor necrosis factor alpha
UK	United Kingdom
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

1 Introduction

OPS-2071 is a novel agent synthesized by Otsuka Pharmaceutical Company, Ltd (Otsuka) that is currently being developed for the treatment of Crohn's disease and was previously investigated for the treatment of enteric infections, including those caused by *Clostridium difficile*. Phase 1 and 2 clinical trials conducted to date support advancement to the current proof-of-concept (POC) trial.

The prevalence of Crohn's disease is approximately 26 to 199 cases per 100000 persons and the incidence of Crohn's disease is approximately 3.1 to 14.6 cases per 100000 person-years.[1,2] Crohn's disease is characterized by inflammation of the mucosa in the intestines. Lesions may occur in any part of the gastrointestinal tract, and cause abdominal pain, diarrhea, bloody stools, anemia, weight loss, and other symptoms. Crohn's disease is an immune-mediated condition with unknown etiology, with impacts of environmental, microbial, and genetic factors. Among other factors, disruption of the balance between the host immune system and the intestinal microbes in Crohn's disease patients may trigger an inflammatory response.[3] Current available treatment options have numerous unwanted side effects with suboptimal efficacy. Although steroids have acceptable efficacy, in combination with other treatments, they have unfavorable side effects.[4] Crohn's disease is a chronic disease, progressing through episodes of flare-ups of inflammation. The recurring inflammation damages the bowel mucosa and over time can result in serious complications such as bowel strictures, obstruction, and bacterial infection forming abscesses and/or fistulas that can bypass segments of the intestines resulting in malnutrition. As a result, at least 50% of patients require surgery in the first 10 years and approximately 70% to 80% of patients require surgery within their lifetime.[5] The high need for surgery indicates that the current available treatments fail to successfully address the pathology of Crohn's disease. Therefore, there are substantial unmet needs in this area.

OPS-2071 belongs to the fluoroquinolone family of compounds and has shown anti-inflammatory and potent antibacterial activity in in vitro and in vivo assays. In animal studies, it has been shown to be relatively well tolerated and to have low bioavailability, resulting in low systemic exposure. OPS-2071 showed a curative effect against colitis in inflammatory bowel disease (IBD) models.[6] In in vitro studies, OPS-2071 inhibited tumor necrosis factor alpha (TNF-α) production in a dose-dependent manner and showed potent antibacterial activity against intestinal bacteria, *C difficile*.[7,8] Thus, OPS-2071 is being developed as a novel agent for the treatment of Crohn's

Disease. This POC trial will evaluate the efficacy and safety of OPS-2071 as an add-on therapy in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment.

Please refer to the Investigator's Brochure (IB) for more detailed information.[9] A brief summary of nonclinical and clinical data is included below.

1.1 Nonclinical Data

An overview of the nonclinical profile of OPS-2071 following oral administration is provided below.

The efficacy of OPS-2071 was evaluated in a mouse model (naive T-cell transfer model) of IBD. OPS-2071 at a dose of ≥ 5 mg/kg demonstrated both therapeutic and preventive effects on colon inflammation in the IBD model. Additionally, OPS-2071 was shown to inhibit the production of TNF-α in lipopolysaccharide (LPS)-stimulated TNF-α release in human whole blood in a dose-dependent manner and exhibited a marked potency when compared to ciprofloxacin, rifaximin, and 5-aminosalicylic acid (5-ASA) in the same assay.

Following single oral administration in mice, hamsters, rats, and monkeys, the plasma exposure of OPS-2071 increased with dose escalation. The oral bioavailability of OPS-2071 at 1 mg/kg was 2.9% in male rats and 5.0% in male monkeys.

Safety pharmacology studies have demonstrated an acceptable safety profile for OPS-2071 in rodent and nonrodent animal species. A single oral dose of OPS-2071 at up to 2000 mg/kg had no adverse effects on general signs and behavior in male rats in a modified Irwin's comprehensive observation assessment. In addition, OPS-2071 had no effect on the binding of muscimol [methylene-3H(N)] to GABA receptors in the rat cerebellum membrane, indicating that it lacks convulsant adverse effects. No effects on respiratory and cardiovascular parameters occurred in conscious dogs given single oral doses of OPS-2071 ≤ 2000 mg/kg. In vitro, OPS-2071 inhibited human ether-a-go-go related gene current expressed in Chinese hamster ovary-K1 cells, with a 30% inhibitory concentration of 1.32×10^{-4} mol/L. Repeat-dose oral toxicity studies were conducted for up to 26 weeks in rats and 13 weeks in monkeys. No significant toxicity signals were observed up to the highest dose tested (ie, 2000 mg/kg); hence, the no observed adverse effect level (NOAEL) was estimated to be 2000 mg/kg/day in both male and female rats and monkeys. At the NOAEL, the maximum (peak) plasma concentration of the drug (C_{max}) and area under the concentration-time curve from time zero to 24 hours (AUC_{24h})

of OPS-2071 in rats at Week 26 were, respectively, 127.7 ng/mL and 1449 ng·h/mL in males and 449.1 ng/mL and 5184 ng·h/mL in females. In monkeys at Week 13, the plasma C_{max} and AUC_{24h} of OPS-2071 at the NOAEL were, respectively, 346.1 ng/mL and 4940 ng·h/mL in males and 433.6 ng/mL and 5488 ng·h/mL in females.

Three in vitro and 2 in vivo (intraperitoneal administration) genotoxicity studies (compliant with good laboratory practice) were conducted with OPS-2071. In a bacterial reverse mutation test, OPS-2071 showed mutagenicity in one strain (TA102) of *Salmonella typhimurium*, but no mutagenicity was found in 4 other standard strains either with or without rat liver S9. In a mammalian cell chromosome aberration test, OPS-2071 showed clastogenicity in human peripheral blood lymphocytes. These effects have been reported with other quinolone antibiotics and are attributed to their inhibitory effect on the bacterial prokaryotic deoxyribonucleic acid (DNA) gyrase and topoisomerase IV, and the analogous mammalian enzyme topoisomerase II. OPS-2071 was not genotoxic in the forward mutation assay and the in vivo genotoxicity assays (bone marrow erythrocyte micronucleus test and the liver unscheduled DNA synthesis test).

Please refer to the IB for more detailed information.

1.2 Clinical Data

The safety and pharmacokinetics (PK) of OPS-2071 in healthy subjects have been assessed in 3 phase 1 trials in Singapore, Korea, and Japan, and in one phase 1 mass balance trial in the United Kingdom (UK). The Singapore trial (Trial 341-12-001) consisted of 3 parts: a single-dose part (Part 1, 30 to 1200 mg), a single-dose food effect part (Part 2, 600 mg), and a multiple-dose part (Part 3, 60 to 600 mg twice a day [BID]). The Korean trial (Trial 341-KOA-1301i) consisted of 2 parts: a single-dose part (Part 1, 30 to 1200 mg) and a multiple-dose part (Part 2, 60 to 600 mg BID). The Japanese trial (Trial 341-13-001) was a single-dose trial of 30 to 1200 mg. The UK trial (Trial 341-14-001) was a single-dose trial that assessed the absorption, metabolism, and excretion of 50 mg ^{14}C-OPS-2071 in healthy male Japanese subjects.

Following single-dose administration of OPS-2071 at 30, 60, 120, 240, 300, 600, 900, and 1200 mg in a fasting state in the Singapore, Korean, and Japanese trials, plasma concentrations of OPS-2071 increased rapidly. The median time to maximum (peak) concentration (t_{max}) was 1.0 to 4.0 hours postdose across the 30 to 1200 mg dose range. Following multiple-dose administration after a light meal, the median t_{max} was 2.0 to 3.5 hours in the Singapore trial. Following multiple-dose administration before a morning

meal and before an evening meal, the median t_{max} was 2.5 to 3.5 hours in the Korean trial.

OPS-2071 C_{max}, area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_t), and area under the concentration-time curve from time zero extrapolated to infinity (AUC_∞) values increased in a less than dose proportional manner across the 30 to 1200 mg dose range following single doses in the Singapore, Korean, and Japanese trials and across the 60 to 600 mg dose range following multiple-dose administration in the Singapore and Korean trials.

The mean apparent terminal phase half-life ($t_{1/2}$) of OPS-2071 was variable at 10 to 21 hours for the single-dose treatments across the 30 to 1200 mg dose range in the Singapore trial. The $t_{1/2}$ ranged from approximately 12 to 50 hours in the Korean and Japanese trials across the same dose range, without any clear trend. The mean apparent plasma clearance was also variable at approximately 50 to 1200 L/h across the same dose range in the 3 trials.

Following administration of OPS-2071 at a dose of 600 mg in a fed state, C_{max} was 2.2-fold higher and AUC_t and AUC_∞ were 2.0-fold higher compared to administration in a fasted state. OPS-2071 has a low-solubility profile across all pHs and is poorly absorbed after oral administration primarily due to its low solubility.

The mean percent of OPS-2071 excreted in urine was approximately 2.4% or less of the administered dose following single- and multiple-dose administration in the Singapore and Korean trials and single-dose administration in the Japanese trial.

Based on the results of a mass balance trial following a single dose of 50 mg ^{14}C-OPS-2071 (Trial 341-14-001), the mean overall total recovery of radioactivity in feces and urine combined was 84% of the administered dose. The principal route of elimination was in feces (approximately 78%), while urinary excretion was approximately 6%. The major analytes in urine were M34101 and OPS-2071, which accounted for average 4.6% and 0.9% of the total administered dose. The primary analyte in feces was OPS-2071, which accounted for an average of 72.3% of the total administered dose.

In the Singapore and Korean trials, there was no apparent trend in the growth of bacterial microflora in feces for the different doses of OPS-2071 and placebo over time.

One phase 2a trial (Trial 341-13-002) was conducted in Singapore, Korea, and Japan in subjects with bacterial enteritis associated with *C difficile* infection or enteric infection to assess 3 different doses (50, 100, and 200 mg) of OPS-2071. In the *C difficile* infection group, OPS-2071 was administered to 5 subjects at a dose of 100 mg BID for up to 10 days. The microbiology assessments and clinical assessments results showed improvement. None of the subjects who were judged as "clinical cure" at the end of treatment had a relapse at follow-up 2 (Day 38). No meaningful efficacy conclusions were made due to the low number of subjects. In the enteric infection group, 37 subjects received treatment with 50, 100, or 200 mg of OPS-2071 for up to 7 days. The efficacy analysis of 32 subjects concluded that 26 subjects had "clinical cure," 5 subjects had "clinical improvement," and 1 subject was evaluated as "clinical failure."

Please refer to the IB for more detailed information.

1.3 Known and Potential Risks and Benefits

There is a substantial unmet need for the treatment of Crohn's disease (see Section 1). OPS-2071 has anti-inflammatory and antibacterial activity in vitro and has demonstrated efficacy in animal models of Crohn's disease. Therefore, this compound may be effective for the treatment of patients with active Crohn's disease who require initiation of treatment or change in current therapy.

OPS-2071 is a fluoroquinolone. Common adverse effects of this drug class include nausea, diarrhea, headache, dizziness, and insomnia. Serious adverse effects that have been associated with systemic use of fluoroquinolones include tendinitis, tendon rupture, peripheral neuropathy, muscle pain, muscle weakness, joint pain, joint swelling, anxiety, depression, hallucinations, suicidal ideation, confusion, worsening of myasthenia gravis, skin rash, photosensitivity, palpitations, tachycardia, atrial fibrillation, hypoglycemic coma, and aortic aneurysm rupture.[10,11,12] Preclinical studies have shown limited bioavailability and systemic exposure of OPS-2071. Therefore, OPS-2071 is expected to primarily act locally and to have a lower likelihood of causing adverse reactions usually associated with systemic exposure to fluoroquinolones.

Clinical experience and nonclinical safety studies have demonstrated an acceptable safety profile for OPS-2071. The safety of OPS-2071 has been extensively studied in rodent and nonrodent animals. The nonclinical studies did not identify any potential risks after oral administration of OPS-2071 that would warrant monitoring. Following oral doses of OPS-2071 of up to 2000 mg/kg, no toxicologically relevant findings were observed in rats and monkeys treated for up to 26 or 13 weeks, respectively. Hence, the NOAEL was

estimated to be 2000 mg/kg/day in both male and female rats and monkeys. Safety information is also available from small groups of healthy subjects and subjects with bacterial enteritis associated with *C difficile* infection or enteric infection, as detailed below.

To date, OPS-2071 has been evaluated in humans in 4 completed phase 1 clinical trials and 1 completed phase 2a clinical trial. In the 5 completed trials conducted in Singapore, Korea, Japan, and the UK, there were no deaths and no subject was withdrawn due to an adverse event (AE) related to OPS-2071. In the phase 1 Singapore trial, 1 subject was withdrawn from the trial due to Grade 4 (Common Terminology Criteria for Adverse Events severity grading) serious adverse events (SAEs) of syncope and hemorrhage intracranial and a Grade 1 AE of atrial fibrillation, all of which resolved and were assessed by the investigator as unrelated to OPS-2071. In the phase 2a trial, 1 serious treatment-emergent adverse event (TEAE) of pyrexia of moderate severity was reported for 1 subject with enteric infection. The event resolved and was considered potentially related to the investigational medicinal product (IMP) by the investigator. There were no expected adverse drug reactions as there were no events that occurred in at least 2 subjects and were deemed serious.

In all 5 completed trials combined, the TEAEs that occurred in more than 1 subject in the OPS-2071 group (n = 136) after single-dose administration and at a higher incidence than the placebo group (n = 48) included the following: headache (5 subjects), abdominal pain, gastroenteritis, pharyngitis, blood creatine phosphokinase increased, and epistaxis (each in 2 subjects).

In all 5 completed trials combined, the TEAEs that occurred in more than 1 subject in the OPS-2071 group (n = 90) after multiple-dose administration and at a higher incidence than the placebo group (n = 16) included the following: headache (7 subjects), somnolence (3 subjects), eosinophilia, nausea, neck pain, and epistaxis (each in 2 subjects).

Other TEAEs that were observed included alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and blood bilirubin increased, all of which are considered a class effect of quinolones. However, the incidence rate in placebo-treated subjects was higher than in the OPS-2071 group. Across the completed trials, the increased AST events were not consistent; eg, the highest value was approximately 8 times the upper limit of normal (ULN), and that was observed at baseline and decreased to within the normal range in 1 week, while taking OPS-2071. No clear trend on ALT/AST elevation was observed across the completed trials.

Treatment-emergent AEs related to proarrhythmia and phototoxicity, which are also considered class effects of quinolones, were seen in 5 of 226 OPS-2071 subjects, comprising atrial fibrillation, ventricular extrasystoles, electrocardiogram (ECG) QT prolonged, rash, and rash erythematous (1 subject each).

In summary, OPS-2071 was generally well tolerated and the TEAEs reported included some of the known fluoroquinolone class effects but no subject was withdrawn due to an AE related to OPS-2071. The potential benefits of a new treatment option for Crohn's disease outweigh the potential risks and therefore warrants the start of a POC clinical trial with OPS-2071 for Crohn's disease.

Please refer to the IB for more detailed safety information from the completed individual clinical trials.

2 Trial Rationale and Objectives

2.1 Trial Rationale

OPS-2071 has anti-inflammatory and antibacterial activity and is anticipated to be effective in the treatment of Crohn's disease due to its unique mode of action. In vitro investigations of OPS-2071 showed a dual mechanism of action, including a potent, broad spectrum antibacterial effect and a strong anti-inflammatory effect that translated into significant attenuation of numerous cytokines, including TNF-α. In a naive T-cell transfer model in mice, OPS-2071 at doses ≥ 5 mg/kg prevented the development of colitis induced by activated T-cell transfer, as measured by the histopathological score and TNF-α levels in the intestinal mucosa of animals. Moreover, in an in vitro assay using human whole blood, OPS-2071 suppressed LPS-induced TNF-α production measured in supernatant.

In this phase 2 POC trial, the safety and efficacy of OPS-2071 will be evaluated as an add-on therapy in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment. Subjects with a Crohn's Disease Activity Index (CDAI) score between 180 and 450 points (inclusive) will be eligible for enrollment. The CDAI range of 180 to 450 was chosen to ensure that subjects with active Crohn's disease will be enrolled in this trial. Because there is no well tolerated and nontoxic treatment available for these patients, it is believed that this patient population will most likely benefit from the addition of OPS-2071 to their ongoing treatment for Crohn's disease.

2.2 Dosing Rationale

The dose selection and regimen in this trial are based on preclinical safety data (refer to Section 1.1) and on existing clinical data obtained in phase 1 trials.

Data from 3 phase 1 trials that were performed in healthy subjects have shown that single oral doses up to 1200 mg daily and multiple oral doses of 60 to 600 mg BID (for up to 7 days) were safe and well tolerated (Trials 341-12-001, 341-13-001, and 341-KOA-130li). Based on the results of the safety and tolerability trials in healthy subjects, 3 oral dose levels of 150, 300, and 600 mg BID (the highest safe dose in healthy subjects) were selected for this trial.

2.3 Trial Objectives

The primary objective of the trial is to investigate the therapeutic effect of OPS-2071 (150, 300, or 600 mg BID) add-on therapy administered orally for 12 weeks in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment.

The secondary objective of the trial is to determine the safety and tolerability of OPS-2071 (150, 300, or 600 mg BID) add-on therapy administered orally for 12 weeks in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment.

3 Trial Design

3.1 Type/Design of Trial

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, POC trial to assess the efficacy and safety of 3 doses of OPS-2071 (150, 300, or 600 mg BID) in subjects with Crohn's disease showing symptoms of active inflammation despite ongoing treatment. OPS-2071 will be added to ongoing treatment for Crohn's disease, with some restrictions, as noted in Section 3.4.

Screening will occur up to 28 days prior to randomization. At the start of the screening period, a fecal sample will be collected for stool microbiology testing (eg, for culture, *C difficile*, ova and parasites [O&P]) and to exclude any type of infectious colitis, and to assess the fecal microbiota. During the screening period, subjects will be dispensed an electronic diary to complete to collect data for the baseline CDAI assessment. After completion of the diary for 7 days, subjects will undergo bowel preparation for 3 days (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation)

and then an ileocolonoscopy with biopsy will occur (within 7 to 10 days prior to Day 1). The ileocolonoscopy will be centrally read to assess inflammation in order to confirm trial eligibility. Optional cytomegalovirus (CMV) testing can be done on the biopsy specimen, if clinically indicated.

Eligible subjects will be randomized on Day 1 in a 1:1:1:1 ratio to 1 of 4 treatments: placebo BID, OPS-2071 150 mg BID, OPS-2071 300 mg BID, or OPS-2071 600 mg BID. The randomization will be stratified by CDAI score (CDAI 180 - 300 and CDAI > 300 - 450) and concomitant Crohn's disease medication status (subjects who are treated with anti-TNF-α monoclonal antibody, subjects who are treated with low-dose steroids, and subjects who are treated with other Crohn's disease medications). The IMP will be administered twice a day, 8 to 12 hours apart, starting on Day 1 for a total of 12 weeks. Blood samples for PK analysis will be collected throughout the 12-week treatment period according to the schedule of assessments (Table 3.7-1). Efficacy will be assessed using the CDAI, Simple Endoscopic Score for Crohn's Disease (SES-CD), and the two-item patient reported outcome (PRO-2). A 30-day (post-treatment) follow-up assessment will be performed for all subjects; the CDAI score will be calculated, inflammatory biomarkers and microbiota flora will be checked, and safety measures will be performed. Subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial are considered as treatment failures (nonresponders). These subjects are encouraged to stay in the trial for continuous data collection.

A blood sample for future biospecimen research (FBR) will be taken from subjects who consent to the collection of this sample.

A schematic of the trial design is provided in Figure 3.1-1.

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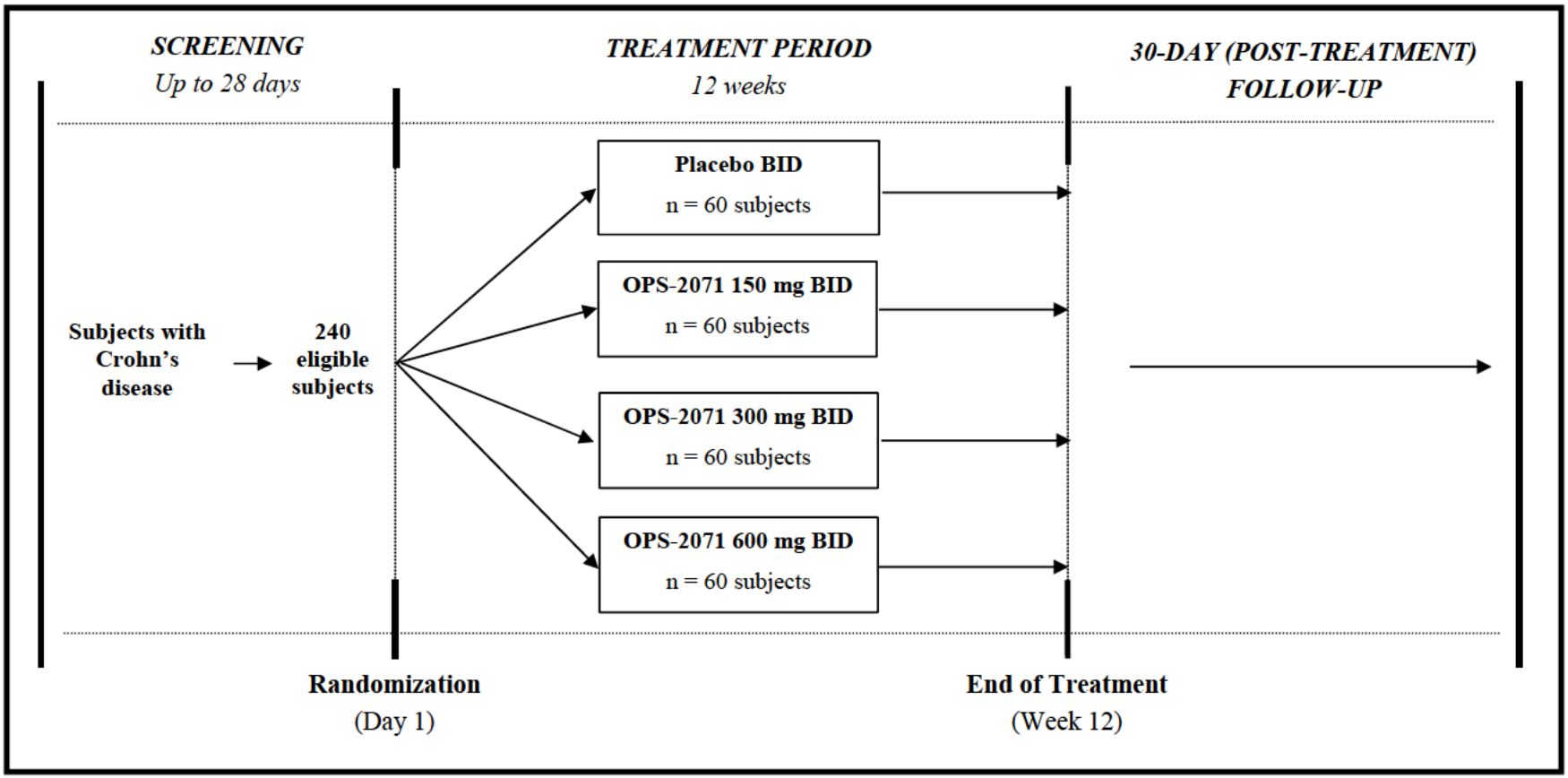

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

Eligible subjects will be randomized on Day 1 to 1 of 4 treatments: placebo BID, OPS-2071 150 mg BID, OPS-2071 300 mg BID, or OPS-2071 600 mg BID. The IMP will be supplied as 150-mg and 300-mg OPS-2071 tablets, and matching placebo tablets. The IMP will be administered as oral tablets, BID (8 to 12 hours apart), starting on Day 1 for a total of 12 weeks. The timing of the first dose of IMP will be at the subject's or trial site's discretion. Each subject will take 6 tablets daily (to maintain blinding); 3 tablets for the morning dose and 3 tablets 8 to 12 hours later. The IMP will be administered with up to 240 mL (8 fluid ounces) of still water, at least 1 hour before or after a meal. Water intake will be restricted for 1 hour before and after the morning dose of IMP at Day 1 and Week 6 for the robust blood sampling.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

Approximately 240 male and female subjects between the ages of 18 and 70 (inclusive), with Crohn's disease and showing symptoms of active inflammation despite ongoing treatment, will be randomized. Active mucosal inflammation will be confirmed by centrally read ileocolonoscopy. Discontinued or withdrawn subjects will not be replaced.

3.3.2 Subject Selection and Numbering

All subjects will be assigned a unique subject identification number (ie, screening number) upon signing the informed consent form (ICF). Subjects will be assigned a randomization number upon randomization on Day 1.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws), documented using an electronic informed consent system, and the consenting process will be recorded in the subject's medical record. The ICF will be approved by the same institutional review board (IRB)/independent ethics committee (IEC) that approves this protocol.

Each ICF will comply with the International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guideline[13] and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any site-specific ICF used in the trial before submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Prospective trial participants will be provided with controlled access to the electronic ICF application by trial site staff. When the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate, the participant will electronically sign in the electronic ICF application and an electronic date and timestamp will be applied to the signature. The subject will be given a printed, signed copy of the ICF. Any other parties required by the IRB/IEC (trial site staff, witnesses, or legally authorized representative) are also required to sign electronically and these signatures will be stored with the electronic ICF in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines. These signatures cannot be altered, removed, or copied.

At sites where the electronic ICF application is not used, paper consent forms will be signed after the trial site staff and the participant agree that the participant has enough information to make an informed decision to participate. Any other parties required to provide signatures will also sign the paper consent forms, and the forms will be stored in accordance with the ICH GCP Guideline and local regulatory requirements/guidelines.

Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on trial participation.

Separate from the main ICF, subjects may also provide optional informed consent for FBR; ie, the subject may participate in the main trial without agreeing to provide an FBR sample. If a subject withdraws the consent for FBR, the subject’s samples will be destroyed.

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3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria presented in Table 3.4.2-1.

Table 3.4.2-1 Inclusion Criteria	
1.	Male and female subjects between the ages of 18 and 70 years, inclusive.
2.	Diagnosis of Crohn's disease localized in the ileum and/or colon, with active mucosal inflammation and visible lesion(s), documented by centrally read ileocolonoscopy and a SES-CD ≥ 6 (≥ 4 for isolated ileal disease).
3.	Subjects who do not have an optimal response[a] (daily stool frequency > 3 and pain score > 1) to their current ongoing treatment of biologics (eg, first anti-TNF-α monoclonal antibody), immunosuppressants, low-dose steroids, or 5-ASA formulations.
4.	Subjects who are on stable Crohn's disease medications for at least 4 weeks.
5.	Subjects with a CDAI score between 180 and 450 points, inclusive.
6.	Subjects who are willing and able to follow the trial protocol and have signed informed consent.

[a]The minimum duration of prior treatment required for a subject to be considered as having a nonoptimal response includes completing at least the recommended induction regimen for approved biologics and/or treatment at a therapeutic dose for a stable duration that would be anticipated to result in improvement (ie, 12 weeks for azathioprine, 4 weeks for methotrexate). Prior treatment examples and their minimum durations can be found in Appendix 4 .

3.4.3 Exclusion Criteria

Subjects will be excluded if they meet any of the exclusion criteria in Table 3.4.3-1.

Table 3.4.3-1 Exclusion Criteria	
1.	Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
2.	Sexually active males or WOCBP who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of IMP. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, birth control implant, or birth control depot injection. A vaginal diaphragm, condom with spermicide, or sponge with spermicide may also be used as measures to prevent pregnancy, but must be used in combination with at least one of the previous methods.
3.	Subjects taking any nonsteroidal anti-inflammatory drugs that cannot be stopped or replaced.
4.	Use of prednisone or prednisolone > 30 mg/day or budesonide > 9 mg/day within 4 weeks prior to screening; or intravenous steroids within 4 weeks prior to screening.
5.	Subjects taking antithrombotic drugs.
6.	Subjects with symptomatic bowel stenosis, fistula, or stoma; or with more than 2 bowel resections.
7.	Subjects with short bowel syndrome.
8.	Subjects with known existing aortic aneurysm, or who are at risk for an aortic aneurysm, such as subjects with peripheral atherosclerotic vascular diseases, uncontrolled hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly subjects (over the age of 70).
9.	Subjects with known or suspected (family history, unexplained syncope) long QT syndrome or QTcF > 470 msec for females or > 450 msec for males at baseline.

Table 3.4.3-1 Exclusion Criteria	
10.	Subjects with inadequate organ function, as follows: • Serum creatinine > 1.5 × ULN • AST or ALT levels > 1.5 × ULN • Total bilirubin > 1.5 × ULN. Elevated unconjugated bilirubin related to Gilbert's syndrome is allowed.
11.	Use of antibiotics (eg, metronidazole, rifaximin, tinidazole, ciprofloxacin, clarithromycin) within 15 days prior to screening or for greater than 2 months within the past year. A short course (maximum of 5 days) of antibiotics will be permitted during the trial, as needed, for indications other than Crohn's disease.
12.	Known hypersensitivity to quinolones or other significant adverse reaction to quinolones.
13.	Conditions or circumstances that could prevent completion of the trial according to the judgment of the investigator, including an uncontrolled comorbidity, heart condition, or dysfunction of any other organ; peripheral neuropathy; known arrhythmias, atrial fibrillation, or paroxysmal tachycardia; history of myasthenia gravis; history of drug or alcohol abuse, mental illness, or noncompliance with treatments or visits; or known immune-deficiency.[a]
14.	HIV infection, viral hepatitis, prior organ transplant, or malignant disease that is not in remission for at least 3 years, with the exception of basal cell carcinoma.
15.	Subjects who have used any investigational drug within 2 months prior to screening.
16.	Blood donation in the last 2 months.
17.	Use of inhibitors of UGT1A1 and UGT1A9 (eg, Silybin, diclofenac, mycophenolic acid, efavirenz, regorafenib) and BCRP (eg, Estrone, 17β-estradiol, flavonoids, herb extracts, gefitinib, imatinib, tamoxifen, novobiocin, nelfinavir, ritonavir, dipyridamole, fumitremorgin C, Ko143, cyclosporine, curcumin, eltrombopag, omeprazole, ivermectin).
18.	Subjects with a history of treatment failure with 2 or more biologics.[b]
19.	Subjects with risk factors for tendon rupture (ie, psoriasis, ankylosing spondylitis, competitive athletes, renal failure, diabetes mellitus) or who have a history of tendon rupture and/or ongoing tendinopathy.
20.	Subjects with systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg.
21.	Subjects taking quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, ibutilide, dronedarone, or propafenone.

BCRP = breast cancer resistance protein; HIV = human immunodeficiency virus; QTcF = QT interval corrected for heart rate by the Fridericia formula; WOCBP = women of childbearing potential.

[a]Subjects that test positive for marijuana or for confirmed prescription medications (eg, opioid analgesics) may be permitted to be enrolled if they have no evidence of a substance use disorder. Allowance for subjects testing positive for marijuana or confirmed prescription medications at screening requires explicit approval from the medical monitor.

[b]The rationale for excluding subjects who have failed 2 or more biologics is due to the fact that they may represent an especially difficult-to-treat population (ie, medically refractory) that may not benefit substantially from fluoroquinolones and/or will likely need additional, more invasive treatment (ie, surgical resection).

Subjects must agree to restrictions as described in Section 4.

Subjects excluded for drug or alcohol abuse are not eligible to be rescreened for participation in the trial. However, subjects excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. Subjects are permitted to be

rescreened 3 times. In the event that the subject is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.5 Endpoints

3.5.1 Primary Endpoint

The primary endpoint is the percentage of subjects who, at Week 12, achieve clinical remission (defined as a CDAI score < 150).

3.5.2 Secondary Endpoints

3.5.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1) The percentage of subjects with endoscopic response, defined as a reduction of the SES-CD by at least 50%, at Week 12.
2) Change from baseline in the SES-CD score.
3) The percentage of subjects with PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1) at Week 12.
4) The percentage of subjects with clinical response, defined as at least a 25% decrease in the CDAI score, at Week 12.
5) The percentage of subjects who, at Week 12, achieve endoscopic remission (defined as a SES-CD score of 0 to 2; or a score of 0 to 4, with no individual subscore greater than 1).
6) The percentage of subjects with a decrease from baseline of ≥ 100 points in the CDAI score.

3.5.2.2 Secondary Safety Endpoint

The secondary safety endpoint is the percentage of subjects by specific AEs, which will be recorded with the onset date, resolution or stabilization date, severity grade, and relatedness to IMP.

3.5.3 Exploratory Endpoints

The exploratory endpoints are as follows:

1) By-visit analysis of CDAI remission (defined as a CDAI score < 150).
2) By-visit analysis of PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1).
3) The percentage of subjects with a biological response in subjects with elevated levels of C-reactive protein (CRP), defined as a reduction in the level of CRP to

within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.

4) The percentage of subjects with a biological response in subjects with elevated levels of fecal calprotectin (FCP), defined as a reduction in the level of FCP to within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.
5) Characterization of the fecal microbiota profile and abundance based on taxonomic and functional annotation from next-generation sequencing, change from baseline, and association with phenotype, at Week 2, Week 12, and at the 30-day follow-up.

3.6 Measures to Minimize/Avoid Bias

This is a double-blind trial; therefore, neither the investigator nor the subject will have knowledge of the treatment assignment (eg, OPS-2071 150 mg BID, OPS-2071 300 mg BID, OPS-2071 600 mg BID, or placebo BID). Treatment assignments will be based on a computer-generated randomization code provided an Otsuka Independent Statistician Department. Sponsor personnel, including those involved in monitoring, data management, and data analysis, will not have access to the treatment code during the trial. Access to the treatment codes will be restricted to personnel charged with reporting SAEs to regulatory agencies. The randomization will be stratified by CDAI score (CDAI 180 - 300 and CDAI > 300 - 450) and concomitant Crohn's disease medication status (subjects who are treated with anti-TNF-α monoclonal antibody, subjects who are treated with low-dose steroids, and subjects who are treated with other Crohn's disease medications), and designed to allocate subjects in a 1:1:1:1 ratio.

3.7 Trial Procedures

The duration of this trial from first subject enrolled to last subject completed is estimated to be approximately 22 months. Individual participation for subjects who complete the trial without early withdrawal will be up to 20 weeks, consisting of the following: screening period of up to 28 days, a 12-week treatment period, and a 30-day (post-treatment) follow-up assessment.

Trial assessment time points are summarized in Table 3.7-1.

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Table 3.7-1 Schedule of Assessments

Assessment	Screening[a]	Treatment Period							End of Treatment[b]	30-day (Post-treatment) Follow-up (± 2 days)
	Day −28 to Day −1	Day 1	Day 8 (± 2 days)	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 2 days)	Week 8 (± 2 days)	Week 10 (± 2 days)	Week 12 (+ 2 days)	
Informed consent	X									
Eligibility criteria	X	X								
Demographics	X									
Medical history	X									
Height	X									
Weight	X			X	X	X	X	X	X	X
Viral hepatitis and HIV screen	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
ECGs at sparse blood sampling sites	X[c]	X[c]	X[c]	X[c]		X[c]			X[c]	X[c]
ECGs at robust blood sampling sites	X[c]	X[d]	X[c]	X[c]		X[d]			X[c]	X[c]
Sparse blood sampling		X[e]		X[e]		X[e]			X[e]	
Robust blood sampling		X[f]		X[e]		X[f]			X[e]	
Urine pregnancy test[g]	X	X				X			X	
FSH (optional)	X									
Clinical laboratory tests (hematology, serum chemistry, and urinalysis)	X	X[h]	X	X	X[i]	X	X[i]	X[i]	X	X[j]

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Table 3.7-1 Schedule of Assessments

Assessment	Screening[a]	Treatment Period							End of Treatment[b]	30-day (Post-treatment) Follow-up (± 2 days)
	Day −28 to Day −1	Day 1	Day 8 (± 2 days)	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 2 days)	Week 8 (± 2 days)	Week 10 (± 2 days)	Week 12 (+ 2 days)	
Urine alcohol and drug screen[k]	X									
Physical examination[l]	X			X		X			X	X
CDAI	X[m]			X	X	X	X	X	X[n]	X
SES-CD	X								X[o]	
Stool microbiology testing (eg, for culture, *C difficile*, O&P)	X									
Fecal biomarker: FCP		X				X			X[p]	X
Fecal microbiota	X[q]			X					X[p]	X
Ileocolonoscopy with biopsy	X								X[r]	
CMV (optional)	X								X	
Randomization		X								
Dispense IMP		X	X	X	X	X	X	X		
Administer IMP		X	X	X	X	X	X	X	X[s]	
CRP		X[t]				X[u]			X[u]	X[u]
FBR sample collection		X[t]								
Diary[v]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

Table 3.7-1 Schedule of Assessments

Assessment	Screening[a]	Treatment Period							End of Treatment[b]	30-day (Post-treatment) Follow-up (± 2 days)
	Day −28 to Day −1	Day 1	Day 8 (± 2 days)	Week 2 (± 2 days)	Week 4 (± 2 days)	Week 6 (± 2 days)	Week 8 (± 2 days)	Week 10 (± 2 days)	Week 12 (+ 2 days)	
Adverse events	X	X	X	X	X	X	X	X	X	X

FSH = follicle-stimulating hormone.

[a]At the start of the screening period, a fecal sample will be collected for stool microbiology testing (eg, for culture, *C difficile*, O&P) and to exclude any type of infectious colitis, and to assess the fecal microbiota. During the screening period, subjects will be dispensed an electronic diary to complete to collect data for the baseline CDAI assessment. After completion of the diary for 7 days, subjects will undergo bowel preparation for 3 days (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation) and then an ileocolonoscopy with biopsy will occur (within 7 to 10 days prior to Day 1). The ileocolonoscopy will be centrally read to assess inflammation in order to confirm trial eligibility.

[b]The End of Treatment visit will include all assessments listed for Week 12, except for the ileocolonoscopy with biopsy and SES-CD score.

[c]At the sparse blood sampling trial sites, standard safety ECGs will be conducted during the screening period; predose on Day 1; 1 to 4 hours postdose on Day 1, Day 8, Week 2, Week 6, and Week 12/End of Treatment; and at the 30-day post-treatment follow-up. At the robust blood sampling trial sites, standard safety ECGs will be conducted during the screening period; 1 to 4 hours postdose on Day 8, Week 2, and Week 12/End of Treatment; and at the 30-day post-treatment follow-up.

[d]At the robust blood sampling trial sites, triplicate ECGs will be recorded on Day 1 and Week 6 at predose (prior to the morning dose) and at 2, 4, and 8 hours after the morning dose. The 3 ECG replicates will be extracted from a 5 minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine position). There will be at least 1 minute between each ECG. Blood samples for PK analysis should be taken immediately following the triplicate ECG assessments.

[e]At the sparse blood sampling trial sites, blood samples for PK analysis will be collected on Day 1 at predose and on Day 1, Week 2, Week 6, and Week 12/End of Treatment 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests. At the robust blood sampling trial sites, additional blood samples for PK analysis will be collected at Week 2 and Week 12/End of Treatment 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests.

[f]At the robust blood sampling trial sites, blood samples for PK analysis will be collected on Day 1 and Week 6 at predose and at 2, 4, and 8 hours after the morning dose. Blood samples for PK analysis should be taken immediately following the triplicate ECG assessments. Once robust blood sampling has been completed, these trial sites will continue to complete sparse blood sampling.

[g]If the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test.

[h]Only serum chemistries are required at Day 1; however, if there was a significant change (as determined by the investigator) in any of the subject's concomitant medications since the screening visit, hematology and urinalysis are also required.

[i]Only hematology is required at Weeks 4, 8, and 10.

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[j]Only serum chemistry and hematology are required at the 30-day post-treatment follow-up.

[k]Subjects that test positive for marijuana or for confirmed prescription medications (eg, opioid analgesics) may be permitted to be enrolled if they have no evidence of a substance use disorder. Allowance for subjects testing positive for marijuana or confirmed prescription medications at screening requires explicit approval from the medical monitor.

[l]A full physical examination will be conducted at screening and a directed/targeted physical examination will be conducted at the subsequent visits. For purposes of this trial, the directed/targeted physical examination will include an abdominal examination.

[m]The CDAI score at screening will be calculated using the formula in eSource for eligibility.

[n]Assess the first 3 elements of the CDAI prior to the bowel preparation: number of liquid or soft stools each day for 7 days; abdominal pain (graded from 0 - 3 on severity) each day for 7 days; and general well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days.

[o]Determine the SES-CD after the Week 12 ileocolonoscopy has been completed.

[p]Collect a fecal sample for the FCP and microbiota assessment approximately 5 days prior to the Week 12 (eg, Day 79) visit date, prior to the bowel preparation and ileocolonoscopy; this is to ensure that subjects are taking IMP when these assessments are completed.

[q]Collect a fecal sample for the microbiota assessment prior to the bowel preparation and ileocolonoscopy.

[r]The 3-day bowel preparation (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation) should be approximately 4 days prior to the Week 12 (eg, Day 80 through Day 82) visit date; this is to ensure that subjects are taking IMP when this assessment is completed. An ileocolonoscopy with biopsy will be conducted up to approximately 1 day prior to the Week 12 (eg, Day 83) visit date. The ileocolonoscopy will be centrally read. The bowel preparation and ileocolonoscopy with biopsy will not be performed at the End of Treatment visit.

[s]At Week 12, only the morning dose of IMP will be administered.

[t]The blood samples for the FBR and CRP assessments will be collected prior to the first dose on Day 1.

[u]If CRP is not elevated on Day 1, there is no need for any further CRP assessments.

[v]A daily diary will be completed by subjects throughout the trial (see Section 3.7.2.4).

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3.7.1 Schedule of Assessments

3.7.1.1 Screening (Day −28 to Day −1)

Screening will occur up to 28 days prior to randomization and will include the following assessments to determine subject eligibility:

- Review trial procedures and information regarding the nature of the trial and obtain informed consent prior to any trial-related procedures
- Review inclusion and exclusion criteria, including documenting birth control methods
- Collect demographic information
- Document medical history, including smoking status
- Perform a viral hepatitis and human immunodeficiency virus (HIV) screen
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a urine pregnancy test for women of childbearing potential (WOCBP) (if the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test)
- Collect a blood sample for follicle-stimulating hormone (FSH) testing (optional; perimenopausal and postmenopausal female subjects only)
- Perform a 12-lead standard safety ECG
- Collect blood samples for hematology and serum chemistry, and a urine sample for urinalysis (including a urine alcohol and drug screen)
- Perform a physical examination (including height and body weight)
- Collect a fecal sample for stool microbiology testing (eg, for culture, *C difficile*, O&P) and to exclude any type of infectious colitis, and the microbiota assessment, prior to the bowel preparation and ileocolonoscopy
- Dispense an electronic diary to subjects; subjects will be instructed to complete a daily diary (see Section 3.7.2.4)
- Determine the CDAI score after completion of the 7-day daily diary
- After confirming a qualifying CDAI score, the following will occur:
  - Bowel preparation for 3 days (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation), then
  - An ileocolonoscopy with biopsy will be conducted (within 7 to 10 days prior to Day 1). The ileocolonoscopy will be centrally read to assess inflammation in order to confirm trial eligibility.
- Determine the SES-CD with results from the ileocolonoscopy
- Optional CMV testing can be done on the biopsy specimen, if clinically indicated
- Review and record any concomitant medications

3.7.1.2 Day 1

The following assessments will be performed prior to the first dose of IMP on Day 1:

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Verify inclusion and exclusion criteria, including birth control methods
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a urine pregnancy test for WOCBP (if the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test)
- Perform a 12-lead ECG
  - At the sparse blood sampling trial sites, standard safety ECGs will be conducted predose on Day 1
  - At the robust blood sampling trial sites, triplicate ECGs will be recorded on Day 1 at predose (prior to the morning dose)
- Collect blood samples for PK analysis at sparse blood sampling trial sites
- Collect blood samples for PK analysis immediately following the triplicate ECGs at robust blood sampling trial sites
- Collect a blood sample for serum chemistry at Day 1; however, if there was a significant change (as determined by the investigator) in any of the subject's concomitant medications since the screening visit, then also collect a blood sample for hematology and urinalysis
- Collect a blood sample for the CRP assessment
- Collect a fecal sample for the FCP assessment
- Collect a blood sample for FBR (for consenting subjects only)
- Review and record any concomitant medications
- Assess and record any AEs

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized using the trial's interactive web/voice response system and will take the first dose of IMP on Day 1 (the date and time of dose administration must be recorded in eSource).

The following assessments will occur on Day 1 after the first dose of IMP:

- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate) (1 to 4 hours after the morning dose)
- Perform a 12-lead ECG
  - At the sparse blood sampling trial sites, standard safety ECGs will be conducted 1 to 4 hours postdose on Day 1
  - At the robust blood sampling trial sites, triplicate ECGs will be recorded on Day 1 at 2, 4, and 8 hours after the morning dose
- Collect blood samples for PK analysis
  - Sparse blood sampling trial sites: 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests
  - Robust blood sampling trial sites: 2, 4, and 8 hours after the morning dose immediately following the triplicate ECGs
- Review and record any concomitant medications
- Assess and record any AEs
- Subjects will be dispensed IMP and will take the second dose 8 to 12 hours after the first dose

3.7.1.3 Day 8 (± 2 days)

The following assessments will occur on Day 8:

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a 12-lead standard safety ECG
- Collect blood samples for hematology and serum chemistry, and a urine sample for urinalysis
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

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3.7.1.4 Week 2 (± 2 days)

The following assessments will occur at Week 2 (around Day 14):

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Record the date and time of dose administration in eSource
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a 12-lead standard safety ECG
- Collect blood samples for PK analysis 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests
- Collect blood samples for hematology and serum chemistry, and a urine sample for urinalysis
- Perform a physical examination (including body weight)
- Determine the CDAI score
- Collect a fecal sample for the microbiota assessment
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

3.7.1.5 Week 4 (± 2 days)

The following assessments will occur at Week 4 (around Day 28):

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Collect a blood sample for hematology
- Measure body weight
- Determine the CDAI score
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

3.7.1.6 Week 6 (± 2 days)

The following assessments will occur at Week 6 (around Day 42); (assessments for subjects who have consented to robust blood sampling must occur prior to the first dose of IMP at Week 6):

- Record the date and time of the last preceding dose in eSource (for robust predose blood sampling only)
- Subjects will complete a daily diary (see Section 3.7.2.4). The daily diary will be checked to ensure proper completion by the subject.
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Record the date and time of dose administration in eSource
- Perform a urine pregnancy test for WOCBP (if the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test)
- Perform a 12-lead ECG
  - At the sparse blood sampling trial sites, standard safety ECGs will be conducted
  - At the robust blood sampling trial sites, triplicate ECGs will be recorded at predose (prior to the morning dose) and at 2, 4, and 8 hours after the morning dose
- Collect blood samples for PK analysis
  - Sparse blood sampling trial sites: 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests
  - Robust blood sampling trial sites: predose and 2, 4, and 8 hours after the morning dose, immediately following the triplicate ECGs
- Collect blood samples for hematology and serum chemistry, and a urine sample for urinalysis
- Collect a blood sample for the CRP assessment (not needed if CRP is not elevated on Day 1)
- Perform a physical examination (including body weight)
- Determine the CDAI score
- Collect a fecal sample for the FCP assessment
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

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3.7.1.7 Week 8 (± 2 days)

The following assessments will occur at Week 8 (around Day 56):

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Collect a blood sample for hematology
- Measure body weight
- Determine the CDAI score
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

3.7.1.8 Week 10 (± 2 days)

The following assessments will occur at Week 10 (around Day 70):

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Collect a blood sample for hematology
- Measure body weight
- Determine the CDAI score
- Review and record any concomitant medications
- Assess and record any AEs

After the above assessments have been completed, subjects will be dispensed IMP.

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3.7.1.9 Week 12 (+ 2 days)/End of Treatment

The following assessments will occur at Week 12 (around Day 84)/End of Treatment:

- Subjects will complete a daily diary (see Section 3.7.2.4)
- Record the date and time of dose administration in eSource
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a urine pregnancy test for WOCBP (if the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test)
- Perform a 12-lead standard safety ECG
- Collect blood samples for PK analysis 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests
- Collect blood samples for hematology and serum chemistry, and a urine sample for urinalysis
- Collect a blood sample for the CRP assessment (not needed if CRP is not elevated on Day 1)
- Perform a physical examination (including body weight)
- Determine the CDAI score (for the Week 12 visit, follow the specific assessment as outlined below)
- Collect a fecal sample for the FCP and microbiota assessment (for the Week 12 visit, follow the specific assessment as outlined below)
- All unused IMP will be collected, and final IMP accountability will be performed
- Review and record any concomitant medications
- Assess and record any AEs

The subject must be taking IMP when the following assessments are completed. In order to ensure this occurs, the following schedule must be followed for Week 12 only:

- Collect a fecal sample for the FCP and microbiota assessment approximately 5 days prior to the Week 12 (eg, Day 79) visit date, prior to the bowel preparation and ileocolonoscopy
- Assess the first 3 elements of the CDAI prior to the bowel preparation:
  - Number of liquid or soft stools each day for 7 days
  - Abdominal pain (graded from 0 - 3 on severity) each day for 7 days
  - General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days
- The 3-day bowel preparation (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation) should be approximately 4 days prior to the Week 12 (eg, Day 80 through Day 82) visit date

- An ileocolonoscopy with biopsy will be conducted up to approximately 1 day prior to the Week 12 (eg, Day 83) visit date. The ileocolonoscopy will be centrally read.
- Determine the SES-CD after the Week 12 ileocolonoscopy has been completed
- Optional CMV testing can be done on the biopsy specimen, if clinically indicated

3.7.1.10 30-day Post-treatment Follow-up (± 2 days)

The following assessments will occur at the 30-day post-treatment follow-up:

- Subjects will complete their diary (see Section 3.7.2.4)
- Take vital signs (blood pressure, heart rate, body temperature, and respiratory rate)
- Perform a 12-lead standard safety ECG
- Collect blood samples for hematology and serum chemistry
- Collect a blood sample for the CRP assessment (not needed if CRP is not elevated on Day 1)
- Perform a physical examination (including body weight)
- Determine the CDAI score
- Collect a fecal sample for the FCP and microbiota assessment
- Review and record any concomitant medications
- Assess and record any AEs

3.7.2 Efficacy Assessments

Efficacy will be assessed during the trial using the CDAI, SES-CD, and PRO-2. Patient-reported components of the CDAI and PRO-2 will be collected via a daily diary that will be completed by subjects throughout the trial.

3.7.2.1 Crohn's Disease Activity Index

The CDAI (Appendix 2) is a composite measurement of disease activity of Crohn's, and is a marker of severity of the subject's condition.[14] The CDAI will be used to assess the primary endpoint of this trial. Some components of the CDAI will be reported by the investigator (physical examination for the presence of an abdominal mass and extraintestinal complications, laboratory results for hematocrit levels, and weight) while other components of the CDAI will be determined with data collected in a subject diary (number of liquid or soft stools, number of antidiarrheal medications, abdominal pain score, and general well-being). The CDAI score at screening will be calculated using the formula in eSource for eligibility. Further details will be provided in a study manual.

3.7.2.2 Simple Endoscopic Score for Crohn's Disease (SES-CD)

The SES-CD (Appendix 3) is a total score that indicates endoscopic disease activity status based on endoscopy results regarding the size of ulcers, surface ulceration, affected surface size, and presence of luminal narrowing.[15] A decrease of 50% of the SES-CD score is prognostically significant. The SES-CD, supported by histology readings, will be used to assess the secondary efficacy endpoints in this trial. Further details will be provided in a study manual.

3.7.2.3 Two-item Patient Reported Outcome (PRO-2)

The PRO-2 is a symptom control measure based on 2 patient-reported components (stool frequency and abdominal pain) of the CDAI. Further details will be provided in a study manual.

3.7.2.4 Subject Diary

An electronic daily diary will be completed by subjects throughout the trial to record data for the following:

- Patient-reported components of the CDAI score and PRO-2 (stool frequency and number of liquid or soft stools, number of antidiarrheal medications taken, abdominal pain score, and general well-being)
- Presence of visible blood in the stool
- Assessments related to stool sample collection (eg, alcohol intake, list of food and drinks)

Subjects will begin completing the daily diary after signing the consent and will continue completing the daily diary until the 30-day post-treatment follow-up visit.

During the screening period, subjects will be dispensed an electronic diary to complete to collect data for the baseline CDAI assessment. After completion of the diary for 7 days, subjects will undergo bowel preparation for 3 days and then an ileocolonoscopy with biopsy will occur (within 7 to 10 days prior to Day 1). Stool frequency during the week of bowel preparation and ileocolonoscopy will not be used; the daily diary will be restarted on Day 1 (after randomization).

3.7.2.5 Investigator Assessments

The investigator will record the following assessments throughout the trial at the appropriate time points:

- Investigator-reported components of the CDAI score (physical examination for assessment of an abdominal mass and extraintestinal complications, laboratory results for hematocrit levels, and weight)
- Endoscopic results for the SES-CD score (ulcers, surface involved by disease, surface involved by ulcerations, and narrowings)

The CDAI score will be calculated using both subject- and investigator-reported data.

3.7.3 Safety Assessments

3.7.3.1 Adverse Events

Refer to Section 5, Reporting of Adverse Events.

3.7.3.2 Clinical Laboratory Assessments

A central laboratory designated by the sponsor will be used for all laboratory testing required during the trial. Clinical laboratory assessments will be performed at the time points specified in Table 3.7-1. The clinical laboratory assessments for this trial are listed in Table 3.7.3.2-1.

Table 3.7.3.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Hematocrit	Alkaline phosphatase
Hemoglobin	ALT
International normalized ratio	AST
Mean corpuscular hemoglobin	Bicarbonate (or carbon dioxide)
Mean corpuscular hemoglobin concentration	Bilirubin, total
Mean corpuscular volume	Blood urea nitrogen
Partial thromboplastin time	Calcium
Platelets	Chloride
Prothrombin time	Creatinine
RBC count	Gamma glutamyl transferase
WBC count with differential	Glucose
	Potassium
Urinalysis:	Protein, total
Appearance	Sodium
Color	
Blood	Additional Tests:
Glucose	Urine pregnancy for WOCBP
Microscopic analysis, WBC/RBC counts per high powered field	(a positive urine pregnancy test must be confirmed with a serum pregnancy test)
pH	FSH (optional; perimenopausal and postmenopausal female subjects only)
Protein	CMV (optional CMV testing can be done on the biopsy specimen, if clinically indicated)
Specific gravity	CRP
	FCP
	HIV
	Viral hepatitis B and C serology
	Stool microbiology testing (eg, for culture, *C difficile*, O&P)
	Urine alcohol and drug screen

RBC = red blood cell; WBC = white blood cell.

The total volume of blood to be collected during the trial will be documented in the ICF.

A urine pregnancy test will be conducted in WOCBP prior to trial intervention (at screening and again on Day 1 [baseline]); results must be available prior to the administration of the IMP. If the urine pregnancy test result is positive, the investigator must follow-up with a confirmatory serum pregnancy test. Additional pregnancy tests may be conducted based on local regulatory requirements, as needed.

Only serum chemistries are required at Day 1; however, if there was a significant change (as determined by the investigator) in any of the subject's concomitant medications since the screening visit, hematology and urinalysis are also required. Only hematology is required at Weeks 4, 8, and 10; and only serum chemistry and hematology are required at the 30-day post-treatment follow-up.

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3.7.3.3 Physical Examination and Vital Signs

A full physical examination will be conducted at screening and a directed/targeted physical examination will be conducted at the subsequent visits as noted in Table 3.7-1. The full physical examination will include an evaluation of the following body systems: head and neck; ears, eyes, nose, and throat; thorax; abdomen; genitourinary; extremities; neurological; and skin and mucosae. There is no need for a genitourinary exam if the subject has confirmation from a gynecologist or urologist of a gender- and age-appropriate exam conducted within 1 year. For purposes of this trial, the directed/targeted physical examination will include an abdominal examination.

Whenever possible, the same individual should perform all physical examinations for any individual subject throughout the course of the trial (for consistency of assessment). For trial sites in the United States, individuals performing the physical examination must be permitted to do so by local regulations, must be listed on the Food and Drug Administration (FDA) Form 1572 as principal investigator or subinvestigator, and must be listed on the trial site delegation of authority form as performing this function.

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be measured at the time points specified in Table 3.7-1. Blood pressure and heart rate measurements will be made in the supine and sitting positions after the subject has been in each position for at least 5 minutes. Vital signs should be measured before blood samples for PK analysis are collected, when applicable.

3.7.3.4 Electrocardiogram Assessments

The 12-lead ECGs will be performed in the supine position.

At the sparse blood sampling sites, standard safety ECGs will be conducted during the screening period; predose on Day 1; 1 to 4 hours postdose on Day 1, Day 8, Week 2, Week 6, and Week 12/End of Treatment; and at the 30-day post-treatment follow-up.

At the robust blood sampling sites, triplicate ECGs will be recorded on Day 1 and Week 6 at predose (prior to the morning dose) and at 2, 4, and 8 hours after the morning dose. The 3 ECG replicates will be extracted from a 5-minute “ECG window” (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine position). There will be at least 1 minute between each ECG. Baseline will be the average of the 3 ECG measurements conducted in triplicate at predose on Day 1. Blood samples for PK analysis should be taken immediately following the triplicate ECG assessments. Additional standard safety ECGs will be conducted during the screening period; 1 to

4 hours postdose on Day 8, Week 2, and Week 12/End of Treatment; and at the 30-day post-treatment follow-up visit.

Subjects should be monitored for potentially clinically significant ECG results. Any abnormalities considered by the investigator to be clinically significant are to be recorded as AEs on the AE screen in eSource.

The ECGs should be performed before blood sample collection, when applicable. A central ECG service will be utilized for reading all ECGs. Additional ECGs may be conducted based on local regulatory requirements, as needed.

3.7.3.5 Other Safety Assessments

3.7.3.5.1 Ileocolonoscopy With Biopsy

After completion of a daily diary for 7 days during the screening period, subjects will undergo bowel preparation for 3 days (consisting of 2 days of dietary modifications and 1 day of cleansing bowel preparation) and then an ileocolonoscopy with biopsy will be performed. The ileocolonoscopy should be performed within 7 to 10 days prior to Day 1. An ileocolonoscopy with biopsy will be performed again at Week 12/End of Treatment, after another 3 days of bowel preparation. The 3-day bowel preparation should be approximately 4 days prior to the Week 12 (eg, Day 80 through Day 82) visit date; this is to ensure that subjects are still taking IMP for these assessments. An ileocolonoscopy with biopsy will be conducted up to approximately 1 day prior to the Week 12 (eg, Day 83) visit date.

The readings of these ileocolonoscopies will be conducted by a central reading facility. Detailed language on the collection of the ileocolonoscopy data will be provided in a study manual. Detailed language on the readings of the ileocolonoscopies will be provided in an ileocolonoscopy charter.

3.7.4 Prior and Concomitant Medications

The investigator will record all medications and therapies taken by the subject from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which subjects are evaluated for primary and/or secondary objectives) in the electronic source records (eSource). The investigator will record all medications and therapies taken by the subject for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact) in eSource.

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3.7.5 Pharmacokinetic/Pharmacodynamic Assessments

3.7.5.1 Pharmacokinetic Assessments

3.7.5.1.1 Pharmacokinetic Blood Samples

Blood samples (4 mL, NaF/KOx) will be collected and processed into plasma to determine the concentrations of OPS-2071 and its metabolite, M34101, at the time points outlined below. The concentrations of additional metabolites that are not identified in the protocol may also be determined if needed.

Two different PK blood sampling schemes, an extensive (robust) and a sparse sampling scheme, will be utilized at different trial sites. Forty subjects from selected trial sites will be required for robust blood sampling.

At the sparse blood sampling trial sites, blood samples for PK analysis will be collected on Day 1 at predose and on Day 1, Week 2, Week 6, and Week 12/End of Treatment 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests.

A total of 40 subjects at the robust blood sampling trial sites will receive OPS-2071 or placebo according to the randomization plan. At the robust blood sampling trial sites, blood samples for PK analysis will be collected from 40 subjects immediately following the triplicate ECG assessments, on Day 1 and Week 6 at predose and at 2, 4, and 8 hours after the morning dose. Additional blood samples for PK analysis will be collected at the robust blood sampling trial sites at Week 2 and Week 12/End of Treatment 1 to 4 hours after the morning dose at the same time as the collection of blood samples for clinical laboratory tests. Robust blood sampling will be completed once there are 40 subjects that have completed the trial on-treatment. Once robust blood sampling has been completed, these trial sites will continue to complete sparse blood sampling.

Processing, storage, and shipping instructions for blood samples for PK analysis are provided in Appendix 1.

3.7.5.1.2 Pharmacokinetic Urine Samples

No urine samples will be collected for PK analysis.

3.7.5.2 Pharmacodynamic Assessments

A blood sample will be collected and processed into plasma to assess CRP. If CRP is not elevated on Day 1, there is no need for any further CRP assessments. In addition, a fecal sample will be collected to assess FCP.

No formal pharmacodynamic (PD) assessments are planned.

3.7.6 Fecal Microbiota

Fecal samples will be collected at the time points defined in Table 3.7-1 for the stool microbiology testing, FCP, and microbiota assessment. During screening, the fecal sample should be collected prior to the bowel preparation and ileocolonoscopy. Collection and processing instructions will be provided separately.

Fecal samples for the microbiota assessment will be analyzed and changes relative to baseline in the abundance and taxonomical profile will be evaluated. Questions that are applicable to the fecal microbiota assessment will be included in the questionnaire that is part of each subject's diary. Data from the microbiota assessment will be reported separately.

3.7.7 Future Biospecimen Research Sample Collection

A whole blood sample (up to 10 mL) for FBR will be collected only from subjects who consent to this sample collection.

Research performed on this sample may include genetic analyses (eg, DNA, gene expression profiling [ribonucleic acid], proteomics, metabolomics, and/or the measurement of other analytes). Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

NOTE: If subjects consent to the optional blood sample collection for FBR, then the second aliquot of blood samples for PK analysis collected from these subjects may be stored and used for this research.

Processing, storage, and shipping instructions for blood samples for FBR are provided in Appendix 1.

3.7.8 End of Treatment/End of Trial

If a subject discontinues IMP before Week 12, the last date that the subject received IMP will be recorded as the End of Treatment. See Section 3.8 for more information on the End of Treatment rules for this trial.

The end of trial date is defined as the last date of contact from the 30-day post-treatment follow-up visit screen in eSource for the last subject completing or withdrawing from the trial.

3.7.9 Independent Data Monitoring Committee

For this trial, an Independent Data Monitoring Committee (IDMC; also known as a Data Safety Monitoring Board) will be established. The role of the IDMC and the various criteria adhered to will be delineated in detail in a separate IDMC charter document, but in general, this group will meet on a regular basis to ensure the safe and ethical treatment of trial subjects, the scientific integrity of the trial, and that the trial is conducted within the bounds of ethical medical practice. The IDMC may make recommendations to the sponsor to amend or terminate the trial based on grounds of safety, futility, or greater than expected efficacy as defined by the accepted statistical practices and procedures to be detailed in their charter.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, IRBs/IEC, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB/IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and GCP. The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site.

3.8.3 Individual Subject Discontinuation

3.8.3.1 Treatment Interruption

All attempts should be made to avoid treatment interruption during the trial. For subjects who have an interruption of treatment, the investigator or designee will contact the sponsor at the earliest possible time by telephone. The sponsor should be notified when there is a planned or inadvertent treatment interruption of 4 days or more in a 7-day period. The investigator and sponsor will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the trial site monitor. The treatment interruption will be recorded in eSource and also recorded as a protocol deviation (Section 3.13).

3.8.3.2 Treatment Discontinuation and/or Trial Discontinuation

After randomization, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. Subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial will be considered as treatment failures (nonresponders) in the efficacy analysis. However, based on investigator's judgement, these subjects may continue their IMP treatment, or discontinue their IMP treatment, but are encouraged to stay in the trial for scheduled study assessments. Each investigator should comprehensively review the circumstances for each subject and refer to Section 3.8.3.5 for additional information. A subject who discontinues treatment will be recorded as an IMP discontinuation in eSource and have an End of Treatment visit. Subjects who discontinue from the trial will have an End of Treatment visit, which should be scheduled as soon as possible after the subject's last dose of IMP, and a 30-day post-treatment follow-up visit to collect the assessments defined in the schedule of assessments (Table 3.7-1).

Subjects who discontinue IMP, but remain on their stable baseline Crohn's medication, will complete an End of Treatment visit and are allowed to stay in the trial and have efficacy evaluations at Week 12.

If a subject discontinues from the trial prematurely, the reason must be fully evaluated and recorded appropriately in source documents and in eSource. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal.

All subjects have the right to withdraw at any point during treatment without prejudice. The investigator can discontinue a subject's participation in the trial at any time if medically necessary. Subjects whose consents are completely withdrawn will be discontinued from the trial and the reason will be recorded in eSource. These subjects will complete the End of Treatment visit.

Subjects who are discontinued from the trial will not be replaced.

3.8.3.3 Documenting Reasons for Treatment Discontinuation

A subject may discontinue IMP for a number of reasons, including those listed below:

- Reasons related to AE:
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the subject at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
  - SAE
  - Other potentially IMP-related safety concerns or AEs
- Death
- Reasons unrelated to medical condition (provide detail and review AE history with subject)
- Withdrawal of informed consent (complete written withdrawal of consent form)
- Lost to follow-up
- Pregnancy (see Section 5.5)
- Termination of all or part of the trial by the sponsor

Adverse events that are stopping rules to be reported directly to the medical monitor include the following:

1) A confirmed prolongation of QTcF with an absolute value > 500 msec or any QTcF interval prolonged 60 msec or greater compared to baseline
2) Hemoglobin count of < 8.0 g/dL
3) Platelet count of 100000 µL or less
4) Discontinuation of treatment should be considered for liver function test abnormalities if:

   a) ALT or AST > 8 × ULN

   b) ALT or AST > 5 × ULN for more than 2 weeks

   c) ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio > 1.5

d) ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

5) New onset *C difficile* or enteric infection
6) Any IMP-related clinically significant event that jeopardizes the safety or health of the subject
7) Any IMP-related clinically significant event, uncontrolled by optimal medical care
8) Any toxicity related to IMP administration, requiring the delay of administration of IMP > 5 days

If the subject discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Refer to Section 3.8.3.2 for requirements in the event of IMP discontinuation.

3.8.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial, but only for future participation. The investigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up (these methods of follow-up will also be noted in the trial ICF):

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by an in-home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and staff).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and therefore should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 3.8.3.2). A subject may, however, indicate that further trial participation is creating a burden on their work or social schedule. Therefore, the investigator should follow the procedures outlined in Section 3.8.3.3 to determine if the subject can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above degrees of follow-up are considered to have completely withdrawn their consent to participate in the trial.

Subjects who withdraw from the trial will not be replaced.

3.8.3.5 Continued Trial Participation After IMP Discontinuation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be given instructions to meet and discuss with the subject their options of continuing in the trial. The investigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent. Subjects who discontinue IMP are allowed to stay in the trial and have efficacy evaluations at Week 12. Subjects who achieve clinical remission during the trial should be encouraged to stay in the trial, have their efficacy evaluation at Week 12, and see if they can achieve endoscopic remission in addition to clinical remission.

3.9 Screen Failures

A screen failure subject is one from whom informed consent is obtained and is documented (ie, subject signs an ICF), but who is not randomized or assigned to trial treatment. Subjects who sign an ICF but who are not started on treatment are permitted to be rescreened. Subjects excluded for drug or alcohol abuse are not eligible to be rescreened for participation in the trial. However, subjects excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. Subjects are permitted to be rescreened 3 times. In the event that the subject is rescreened, a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

3.10 Definition of Completed Subjects

The treatment period is defined as the time period during which subjects are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the subject actually consumed all doses of the IMP. Subjects who are evaluated at the last scheduled visit during the treatment period will be defined as trial completers. Subjects who complete the Week 12 visit on IMP will be considered as on-treatment completers. Subjects who discontinue IMP but complete the Week 12 visit will be considered as off-treatment completers.

3.11 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted on or before the 30-day post-treatment follow-up, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up" as the reason for discontinuation. Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

3.12 Subject Compliance

The date and time of the first dose of IMP administration will be recorded. The date and time of the dose administered on the days of blood sampling for PK analysis will also be recorded. Information regarding any missed or inappropriately administered doses will also be documented in eSource. Subjects with > 20% missed doses will be considered noncompliant. If subjects do not comply with the protocol, it is at the discretion of the investigator and sponsor to terminate their participation in the trial.

3.13 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor at the earliest possible time by telephone. The investigator and sponsor will discuss the details of the deviation and agree upon the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor, and reviewed by the site monitor.

4 Restrictions

4.1 Prohibited Medications

In vitro studies have shown that OPS-2071 is a substrate of breast cancer resistance protein (BCRP) transporters, UGT1A1 mainly and UGT1A9 partially. Hence, it is recommended to avoid concomitant use of BCRP inhibitors (eg, Estrone, 17β-estradiol, flavonoids, herb extracts, gefitinib, imatinib, tamoxifen, novobiocin, nelfinavir, ritonavir, dipyridamole, fumitremorgin C, Ko143, cyclosporine, curcumin, eltrombopag, omeprazole, ivermectin) and UGT1A1 or UGT1A9 inhibitors (eg, Silybin, diclofenac, mycophenolic acid, efavirenz, regorafenib).

The following medications are prohibited:

- Use of prednisone or prednisolone > 30 mg/day or budesonide > 9 mg/day, or intravenous steroids, within 4 weeks prior to screening. Low-dose steroids may be tapered down during the trial, based on inflammatory biomarkers and the investigator's judgment.
- Antibiotics (eg, metronidazole, rifaximin, tinidazole, ciprofloxacin, clarithromycin) within 15 days prior to screening or for greater than 2 months within the past year. A short course (maximum of 5 days) of antibiotics will be permitted during the trial, as needed, for indications other than Crohn's disease.
- Nonsteroidal anti-inflammatory drugs
- Antithrombotic drugs:
  - Anticoagulants: heparin or warfarin (also called Coumadin), rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Lixiana, Savaysa), betrixaban (Bevyxxa), bivalirudin, argatroban, and desirudin
  - Antiplatelet drugs: clopidogrel (Plavix) and aspirin (aspirin use of ≤ 325 mg daily are permitted)

- Quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, ibutilide, dronedarone, or propafenone

Subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial will be considered as treatment failures (nonresponders) in the efficacy analysis. These subjects are encouraged to stay in the trial for continuous data collection (Section 3.8.3.2).

4.2 Other Restrictions

Subjects should be recommended to limit the amount of caffeine to no more than 250 mg of caffeine products such as coffee, tea, soda, energy drinks, chocolate, or chocolate milk per day.

The use of over-the-counter probiotic supplements, including over-the-counter Lactobacillus products, is not permitted.

5 Reporting of Adverse Events

5.1 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. Adverse events will be recorded from the time the ICF is signed. Any significant changes from screening should be documented as an AE.

An adverse reaction is any untoward and unintended response to an IMP related to any dose administered. A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of investigational new drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongs hospitalization.
    - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
    - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious adverse events are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 5.4).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form to the sponsor. Pregnancy will only be documented on the AE screen in eSource if there is an abnormality or complication.

Adverse events that are stopping rules to be reported directly to the medical monitor are listed in Section 3.8.3.3.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is an abnormal (ie, clinically significant) change from baseline for that individual subject. This

determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant by the investigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in eSource. The intensity of an adverse experience is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related*: There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.

Not Related: There is no temporal or causal relationship between the IMP and the AE.

*Investigators should carefully consider consequences of the bowel preparation when assigning causality of AEs (eg, diarrhea).

5.2 Eliciting and Reporting Adverse Events

The investigator will periodically assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and in eSource. Serious AE collection is to begin after a subject has signed the ICF.

Use medical terminology in AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms. Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition. A reported AE that undergoes a change in severity, seriousness, or toxicity should be reported as a new AE in eSource.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 5.3. Special attention should be paid to recording hospitalization and concomitant medications.

5.3 Immediately Reportable Events

The investigator must immediately report after either the investigator or site personnel become aware of any SAE, AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy, by telephone, fax, or e-mail to the sponsor using the contact information on the cover page of this protocol. An IRE form must be completed and sent by e-mail, fax, or overnight courier to the sponsor. (Please note that the IRE form is NOT the AE screen in eSource.)

Subjects experiencing SAEs should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor.

5.4 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE in eSource.

5.5 Pregnancy

Women of childbearing potential are defined as female subjects for whom menstruation has started and who are not documented as sterile (ie, have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 months).

For WOCBP and for men who are sexually active, there must be a documented agreement that the subject and/or their partner will take effective measures to prevent pregnancy during the course of the trial and for 30 days after the last dose of IMP. Unless the subject is sterile (ie, women who have had a bilateral oophorectomy and/or hysterectomy or who have been postmenopausal for at least 12 consecutive months; or men who have had a bilateral orchiectomy) or remains abstinent, 2 of the following precautions must be used: vasectomy, tubal ligation, intrauterine device, birth control pills, birth control depot injection, or birth control implant. A vaginal diaphragm, condom with spermicide, or sponge with spermicide may also be used as measures to prevent pregnancy, but must be used in combination with at least one of the previous methods.

Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented at each trial visit.

Before enrolling WOCBP in this clinical trial, investigators must review the below guidelines about trial participation with all WOCBP. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Guidelines for the follow-up of a reported pregnancy

Before trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF stating that the above-mentioned risk factors and the consequences were discussed with her.

A urine pregnancy test for human chorionic gonadotropin will be performed at screening and again on Day 1 (baseline) for all WOCBP. If a urine test is performed and is positive, the investigator will follow up with a confirmatory serum test.

During the trial, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of the serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial.

The investigator must immediately notify the sponsor of any pregnancy associated with IMP exposure during the trial and for 30 days after the last dose of IMP, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate

pregnancy follow-up procedures should be considered, if indicated. In addition, the investigator must report to the sponsor, on appropriate Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth. Local regulatory requirements must be followed for follow-up and reporting on pregnancy cases and/or infants.

5.6 Procedure for Breaking the Blind

The investigator is encouraged to contact the sponsor/Clinical Research Organization (CRO) medical advisor to discuss their rationale for unblinding. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP will not be dependent upon the investigator receiving approval from the sponsor/CRO medical advisor (ie, the investigator will be able to obtain the code break information independent of the sponsor/CRO medical advisor). The investigator must contact the sponsor/CRO medical advisor by telephone or e-mail with an explanation of the need for opening the treatment assignment code within 24 hours of opening the code. If the blind is broken, the sponsor must be notified immediately (see the cover page of this protocol for contact information). Documentation of breaking the blind should be recorded in the subject's medical record with the date and time the blind was broken and the names of the personnel involved. Once the blind is broken for a subject, that subject may not reinitiate treatment with the IMP.

5.7 Follow-up of Adverse Events

5.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE screen in eSource with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in eSource. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history and occupation).

5.7.2 Follow-up of Serious Adverse Events and Immediately Reportable Events

This trial requires that subjects be actively monitored for SAEs and IREs up to 30 days after the last dose of IMP is administered.

Serious AEs and nonserious IREs that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE screen in eSource. If updated information (eg, resolved status) on SAE or IRE status becomes available after a subject's last scheduled contact (up to the last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE screen in eSource, according to the appropriate reporting procedures. The investigator will follow SAEs until the events are resolved, stabilized, or the subject is lost to follow-up or has died. Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the subject's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has been resolved or stabilized, or the subject is lost to follow-up or has died.

5.7.3 Follow-up and Reporting of Serious Adverse Events and Immediately Reportable Events Occurring after Last Scheduled Contact

Any new SAEs or IREs reported to the investigator that occur **after the last scheduled contact**, and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor. This may include SAEs or IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. The investigator should follow SAEs or IREs identified after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

6 Pharmacokinetic/Pharmacodynamic Analysis

6.1 Pharmacokinetic Methods

OPS-2071 and M34101 concentrations measured from blood samples collected at trial sites with a robust blood sampling schedule will be analyzed by noncompartmental methods and summarized using descriptive statistics. If additional metabolites are measured, the concentrations and noncompartmental analysis will also be summarized using the same technique.

6.2 Pharmacodynamic Methods

No PD analysis will be performed.

6.3 Pharmacokinetic/Pharmacodynamic Methods

No formal PK/PD analysis is planned.

6.4 Fecal Microbiota Methods

Fecal samples for the microbiota assessment will be analyzed by next-generation sequencing for whole genome and/or 16S ribosomal DNA. Taxonomical abundance and functional representation, where applicable, will be determined. Detailed instructions for fecal microbiota sampling will be provided separately.

6.5 Future Biospecimen Research Methods

No prespecified FBR analysis is planned. Any future analysis will be reported separately.

7 Statistical Analysis

7.1 Sample Size

For the primary endpoint of clinical remission (CDAI score < 150), assuming a 40% response rate in the OPS-2071 600 mg BID and 300 mg BID dose groups and a 20% response rate in the placebo group, 60 randomized subjects per treatment group would provide 80% power to detect a treatment difference between the OPS-2071 pooled dose groups (600 mg BID and 300 mg BID) and the placebo group in the primary endpoint, using a 2-sided alpha of 0.05. The total sample size of the trial is 240 randomized subjects with 1:1:1:1 randomization to OPS-2071 600 mg BID, 300 mg BID, or 150 mg BID, or placebo BID. The power of individual dose comparison with placebo under the same assumption is 67%.

For the secondary endpoint of endoscopic response, assuming a 26.5% response rate in the OPS-2071 600 mg BID and 300 mg BID dose groups and a 10% response rate in the placebo group, 60 subjects per treatment group would provide 80% power for the comparison between the OPS-2071 pooled dose groups (600 mg BID and 300 mg BID) and the placebo group, and 65% power for the individual dose comparison with placebo, using a 2-sided alpha of 0.05.

7.2 Datasets for Analysis

The following samples are defined for this trial:

- Randomized: consists of all subjects who are randomized into this trial.
- Safety: consists of all subjects who are administered at least one dose of IMP.

- Efficacy: consists of all subjects who are in the Randomized Sample, take at least one dose of IMP, and have a baseline and at least one postbaseline evaluation of the CDAI score.

In general, baseline of an efficacy endpoint is defined as the last observation of the endpoint before the subject takes the first dose of IMP.

The core dataset for all efficacy analyses is based on the intent-to-treat (ITT) population, which will consist of all randomized subjects who take at least one dose of IMP. The Full Analysis Set, which is identical to the Efficacy Sample, will also be used in the efficacy analyses. As described below, in order to handle missing data and restrictions imposed by different types of analyses (eg, change from baseline analysis), other datasets derived from the ITT population will be used for the efficacy analyses.

7.3 Handling of Missing Data

7.3.1 Estimand and Strategies for Addressing Intercurrent Events

The estimand defining the treatment effect of interest in the protocol uses a mixture of composite strategy and treatment policy strategy specified in the ICH E9 addendum.[16] Subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial are considered as treatment failures (nonresponders) in the ITT analysis of the primary and secondary endpoints, though they are encouraged to stay in the trial to be followed continuously. Their efficacy evaluations after the change of baseline Crohn's disease medications will not be included in the efficacy analysis but will be provided in the listings. In addition, subjects who withdraw early from the trial are also considered as treatment failures (nonresponders) in the ITT analysis of all of the primary and secondary endpoints. Subjects who discontinue IMP during the trial with no baseline Crohn's disease medication dosage increases and/or new therapy for Crohn's disease through Week 12 are also encouraged to stay in the trial and take primary and secondary endpoint evaluations at Week 12 for efficacy analyses. Hence, missing data at Week 12 due to subjects' early withdrawal and change of baseline Crohn's disease medications is handled by an ITT analysis with all subjects treated as treatment failures (nonresponders).

For CDAI-related endpoints, if a subject has a Week 12 evaluation but a component of the score is missing, the value of the component in the most recent previous visit will be used for the calculation of the score and the endpoint if no more than 2 components of the CDAI score are missing. For a CDAI assessment, if more than 2 components of the score

are missing, the CDAI score will be set to missing. This approach is conservative since subjects randomized to OPS-2071 treatment groups are expected to have their Crohn's disease symptoms improved over time. No component is allowed to be missing in a PRO-related endpoint. The abdominal pain and stool frequency scores of PRO-2 are averaged over a 7-day period from the subject's diary.

7.4 Primary and Secondary Endpoint Analyses

This is a POC trial of OPS-2071 added to ongoing treatment in subjects with Crohn's disease showing symptoms of active inflammation. Subjects with stable dosages in their baseline Crohn's disease medications will be randomized into treatment groups of OPS-2071 600 mg BID, 300 mg BID, or 150 mg BID, or placebo BID, stratified by CDAI score (CDAI 180 - 300 and CDAI > 300 - 450) and concomitant Crohn's disease medication status (subjects who are treated with anti-TNF-α monoclonal antibody, subjects who are treated with low-dose steroids, and subjects who are treated with other Crohn's disease medications) for 12-week treatments. Dosages of baseline Crohn's disease medications are expected to be maintained constant throughout the full duration of the trial; however, doses of baseline Crohn's disease medications can be decreased per the investigator's judgment. If a higher dosage of a baseline Crohn's disease medication or a new medication for Crohn's disease is to be administrated to a subject during the double-blind treatment period, the subject will be considered as a treatment failure (nonremission subject or nonresponder) in the analyses of the primary and secondary endpoints.

7.4.1 Primary Endpoint Analysis

The primary endpoint of the trial is the percentage of subjects who, at Week 12, achieve clinical remission (CDAI score < 150).

Logistic regression with terms of treatment group, the randomization stratification factors, location of disease, country, age, sex, disease duration, smoking habit, and baseline CDAI, and baseline CDAI with CDAI stratification factor interactions will be applied to the primary endpoint. The efficacy sample will be used in the efficacy analysis. Remission and nonremission subjects (ie, treatment failures) are defined as follows:

- Subjects who complete the trial and meet the primary endpoint definition at Week 12 without increasing dosages of baseline Crohn's disease medications or taking a new medication for Crohn's disease during the double-blind treatment period will be considered as remission subjects for the endpoint.
- Subjects who increase dosages of baseline Crohn's disease medications or take a new medication for Crohn's disease during the double-blind treatment period, or subjects who withdraw from the trial during the double-blind period, in addition to the subjects who fail to meet the primary endpoint at Week 12, will be considered as nonremission subjects for the endpoint.

The primary analysis of this trial is comparison of the pooled OPS-2071 600 mg BID and 300 mg BID treatment groups with placebo in the primary endpoint of clinical remission. If this analysis is significant at a 2-sided alpha level of 0.05, comparisons to OPS-2071 600 mg BID versus placebo and OPS-2071 300 mg BID versus placebo in the primary endpoint will be conducted with a 2-sided alpha level of 0.05 in each comparison. If the comparison of the pooled OPS-2071 dose groups versus placebo in the primary endpoint is significant at a 2-sided alpha level of 0.05, and a comparison, say, OPS-2071 600 mg BID versus placebo, is also significant at a 2-sided alpha level of 0.05, the null hypothesis of equal response of OPS-2071 600 mg BID and placebo in the primary endpoint will be considered rejected with an experiment-wise Type I error of 0.05.

The comparison between OPS-2071 150 mg BID versus placebo in the primary endpoint is considered as a secondary analysis and is provided in Section 7.4.2.

7.4.1.1 Sensitivity of the Primary Endpoint

A sensitivity analysis of the primary endpoint of clinical remission of missing data will be provided for subjects who withdraw from the trial before the Week 12 visit, or subjects who increase dosages of baseline Crohn's disease medications or take a new medication for Crohn's disease during the double-blind treatment period. A pattern-mixture model approach will be utilized to model the distribution of the observed responses and the distribution of the missing responses using a placebo-based multiple imputation. Imputation of missing CDAI scores will be produced using a regression approach[17] and the imputed CDAI remission status will be determined by checking if the

imputed CDAI score is less than 150. Details of this sensitivity analysis will be provided in the statistical analysis plan (SAP).

7.4.2 Secondary Endpoint Analysis

If both null hypotheses of OPS-2071 600 mg BID and 300 mg BID versus placebo in the primary endpoint of clinical remission are rejected with an experiment-wise Type I error of 0.05 by the test procedure provided in Section 7.4.1, a formal test of the secondary efficacy endpoint of endoscopic response (defined as a reduction of the SES-CD by at least 50%) for comparisons of OPS-2071 600 mg BID versus placebo and 300 mg BID versus placebo will be conducted, using a similar procedure used for the primary endpoint of clinical remission except replacing baseline CDAI with baseline SES-CD score.

If both null hypotheses of OPS-2071 600 mg BID versus placebo and 300 mg BID versus placebo in the secondary efficacy endpoint are rejected with an experiment wise Type I error of 0.05, the formal comparison of OPS-2071 150 mg BID versus placebo in the primary efficacy endpoint will be conducted, using the same model provided in the previous section for the primary analysis. Again, if the null hypothesis of the primary efficacy endpoint of OPS-2071 150 mg BID is rejected with experiment wise Type I error of 0.05, the formal comparison of OPS-2071 150 mg BID versus placebo in the secondary efficacy endpoint will be conducted, using the same model provided in the previous paragraph for the analysis of the secondary efficacy endpoint. Formal analyses of other secondary efficacy endpoints will start if the null hypothesis of OPS-2071 150 mg BID in the secondary efficacy endpoint of endoscopic response is rejected with experiment wise Type I error of 0.05.

Sensitivity analysis of missing data will be provided in the SAP for this secondary efficacy endpoint.

The other secondary efficacy endpoints of this trial are listed below by the order of the gatekeeping test procedure and tested after the rejection of all the null hypotheses in the primary and the first secondary efficacy endpoints. Formal test of the secondary efficacy endpoint #2 will start with a comparison of pooled OPS-2071 600 mg BID and 300 mg BID versus placebo. If it is significant, comparisons of 600 mg BID versus placebo and 300 mg BID versus placebo will be performed. If both comparisons are significant, formal comparison of OPS-2071 150 mg BID versus placebo will be conducted for the secondary efficacy endpoint #2. If this comparison is again significant, analysis of the secondary efficacy endpoint #3 will start using the same procedure, up to the secondary efficacy endpoint #6. Overall, this analytical procedure along with the gatekeeping protects the experiment-wise Type I error in the primary and secondary analyses.

2) Change from baseline in the SES-CD score.
3) The percentage of subjects with PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1) at Week 12.
4) The percentage of subjects with clinical response, defined as at least a 25% decrease in the CDAI score, at Week 12.
5) The percentage of subjects who, at Week 12, achieve endoscopic remission (defined as a SES-CD score of 0 to 2; or a score of 0 to 4, with no individual subscore greater than 1).
6) The percentage of subjects with a decrease from baseline of ≥ 100 points in the CDAI score.

Analysis of secondary endpoint #2 will be conducted using a procedure similar to the analyses of the secondary endpoint of endoscopic response, except the logistic regression will be replaced by an analysis of covariance (ANCOVA). The model used in the analysis of the primary endpoint will be applied to the analysis of secondary endpoints #3, #4, and #6, while the model used in the analysis of the secondary endpoint of endoscopic response will be applied to the analysis of secondary endpoint #5.

For the PRO-2 score used to derive PRO-2 remission, the abdominal pain score is reported as the daily worst abdominal pain (0 to 3) score and the stool frequency score is recorded as the number of loose or watery bowel movements (Bristol stool form scale 6 or 7) per day; both scores are averaged over a 7-day period.

A sensitivity analysis of secondary endpoint #3 (PRO-2 remission) of missing data will also be provided similar to the sensitivity analysis of the primary endpoint of CDAI clinical remission. Imputation of missing PRO-2 scores will be produced by applying a regression approach[17] to the abdominal pain and stool frequency scores, averaged over a

7-day period. The PRO-2 remission status will be determined by checking if the imputed stool frequency score is ≤ 3 and the imputed abdominal pain score is ≤ 1. Details of this sensitivity analysis will be provided in the SAP.

7.4.3 Exploratory Endpoint Analysis

The CDAI score and PRO-2 score will be evaluated at baseline and at Weeks 2, 4, 6, 8, 10, and 12 in this trial, so that the by-visit analysis of CDAI remission and PRO-2 remission (exploratory endpoints #1 and #2) at Weeks 2, 4, 6, 8, and 10, in addition to Week 12, will be provided and analyzed using a similar method with Week 12 replaced by Weeks 2, 4, 6, 8 or 10. Since the by-visit analysis of an endpoint is considered as supplemental to the analysis of the endpoint at Week 12, no adjustment in alpha is necessary.

Additional exploratory endpoints are as follows:

3) The percentage of subjects with a biological response in subjects with elevated levels of CRP, defined as a reduction in the level of CRP to within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.
4) The percentage of subjects with a biological response in subjects with elevated levels of FCP, defined as a reduction in the level of FCP to within the normal range or by at least 15%, at Week 6, Week 12, and at the 30-day follow-up.
5) Characterization of the fecal microbiota profile and abundance based on taxonomic and functional annotation from next-generation sequencing, change from baseline, and association with phenotype, at Week 2, Week 12, and at the 30-day follow-up.

Details of the statistical analyses will be provided in the SAP.

7.4.4 Interim Analysis

No interim analysis is planned for this trial.

7.5 Analysis of Demographic and Baseline Characteristics

Demographics, disease severity, baseline characteristics, and medical history at (predose) baseline will be summarized by descriptive statistics; eg, proportion, mean, median, standard deviation, and minimum and maximum values. These summary statistics will be reviewed to identify any potential lack of balance between the treatment groups.

7.6 Safety Analysis

7.6.1 Adverse Events

All AEs will be coded by system organ class and the Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

The TEAEs from the start of IMP to the first day of bowel preparation for ileocolonoscopy will be included in the TEAE summaries for all subjects who have bowel preparation for ileocolonoscopy at Week 12. The TEAEs that occur during the ileocolonoscopy preparation and procedure will be summarized separately.

7.6.2 Clinical Laboratory Data

Summary statistics for changes from baseline in the central clinical laboratory measurements will be provided for the safety sample. Potentially clinically significant results in laboratory tests identified using prospectively defined criteria, including criteria for liver enzyme elevations, will also be summarized for the safety sample. By-subject listings will be provided for data of local laboratory tests.

In addition, laboratory measurements that signal the potential for Hy's Law will be reported. An incidence table and a listing will be provided for subjects who meet one or combinations of the following criteria, without initial findings of cholestasis (alkaline phosphatase activity > 2 times the ULN):

- ALT or AST ≥ 3 times the ULN
- Bilirubin ≥ 2 times the ULN

7.6.3 Physical Examination and Vital Signs Data

By-subject listings will be provided for physical examinations. Summary statistics for changes from baseline in vital signs and potentially clinically significant results in vital signs will be summarized for the safety sample.

7.6.4 Electrocardiogram Data

The mean change from baseline and the incidence of clinically significant changes will be calculated for ECG parameters.

For the analysis of QT and the corrected QT interval (QTc), data from 3 consecutive complexes (representing 3 consecutive heart beats) will be measured to determine average values. The following QT corrections will be used for reporting purposes in the clinical study report:

1) QTcF is the length of the QT interval corrected for heart rate by the Fridericia formula: $QTcF=QT/(RR)^{0.33}$
2) QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN=QT/(RR)^{0.37}$

A regression analysis will be used to derive the slope and its 90% confidence interval of the change in QTc, adjusted from the placebo effect (ΔΔQTc), against the drug concentration by robust blood sampling visit.

8 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the OPS-2071 IB.[9]

8.1 Packaging and Labeling

The IMP will be provided to the investigators and the persons designated by the investigator(s) or institution(s) by the sponsor or designated agent. The IMP will be supplied as packages. Each package of IMP used in the dosing period will be labeled to clearly disclose the subject ID, compound ID, trial number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements.

8.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP should be stored according to conditions specified in the IMP label.

The clinical site staff will maintain a temperature log in the IMP storage area recording the temperature at least once each working day.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP (including investigational, active control, or placebo) received, dispensed, administered, and returned.

8.4 Returns and Destruction

Upon completion or termination of the trial, all IMP will be destroyed by the clinical trial site. The IMP may only be destroyed by the trial site(s) if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP accountability must be completed and verified by the assigned trial monitor prior to destruction. The trial site(s) may utilize qualified third party vendors for IMP destruction.

8.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or verbal communication by a healthcare professional, consumer, subject, medical representative, Competent Authority, regulatory agency, partner, affiliate or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Blister defects (eg, missing, empty blisters)
- Bottle defects (eg, under/over-fill, no safety seal)
- Vial defects
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

8.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor, or sponsor's designee, through and including reconciliation and up to destruction, including subject dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by e-mail or telephone within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Online - Send information required for reporting purposes (listed below) to [redacted]
- Phone [redacted]

Identification of a PQC by the subject should be reported to the site investigator, who should then follow one of the reporting mechanisms above.

8.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, subject, investigator, site, etc.)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures (if available)
- Availability for return

8.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If complaint sample is available for return, return it in the product retrieval package, which will be provided by the sponsor.

It must be documented in the site accountability record that a complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

8.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

9.2 Data Collection

During each subject's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed;
- The signature (or initials) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Source documents and source data will be captured electronically in this trial, and will meet the same fundamental elements of data quality (eg, attributable, legible, contemporaneous, original, and accurate) as paper records. These data will be collected

into a system that is fully validated. Changes to the data will be captured by an automatic audit trail.

The trial site will be given a tablet to directly record subject data and clinical observations on electronic forms. Designated trial site staff will not be given access to the system until they have been appropriately trained. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol-required assessments performed as a part of these visits, medical history, AEs, and concomitant medications. Because this trial is using an electronic source record as the original point of data capture, there is no additional data entry step for the trial site for data collected directly into the application – rather, the electronic source record directly populates the trial database.

Some data may be captured via paper and then entered into the eSource system. These and any other data treated in this manner will be source data verified by the trial clinical research associate, and the location of the source data (ie, eSource, paper, or a local electronic system) will be documented before the trial start. Any changes to information in paper source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Another exception will be clinical laboratory or central ECG data, where the official source documentation will be considered the report issued by the analyzing laboratory.

Remote monitoring of the original electronic source records will take place; however, on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess trial site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

At the end of the trial, the investigator must certify that the data entered into the eSource application are complete and accurate. After database lock, the investigator will receive an electronic copy of the subject data.

9.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with Section 8 of the ICH GCP Guideline E6 and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the ICH E6 GCP: Consolidated Guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and clinical site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and comparison of eSource with source documents. The investigator agrees to participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations (for trial sites in the United States), ICH GCP Guideline (E6), international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB/IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific and medical appropriateness of the trial. Further, in preparing and using screens in eSource, the investigator, subinvestigator and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject number and subject identification code will be used to identify each subject.

Financial aspects, subject insurance and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

12 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject numbers in eSource. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

14 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

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Appendix 1 Handling and Shipment of Bioanalytical Samples

Blood Samples for PK Analysis

After blood sample collection, mix the collection tube thoroughly by gently inverting the collection tube at least 8 to 10 times, or as recommended by the tube manufacturer. Place the collection tube in an ice/water bath. Within 45 minutes of collection, process the collection tube in a refrigerated centrifuge set at 3000 rpm for 15 minutes at 4°C (± 3°C). After centrifugation, remove the tube from the centrifuge and place again on ice until the plasma is removed. The centrifugal force should be kept at a constant setting throughout the trial.

After centrifugation, the plasma will be transferred to 2 separate tubes. When transferring plasma, it is important to avoid transferring any of the buffy coat into the plasma tube. Transfer an approximately equal volume of separated plasma into 2 separate barcode-labeled tubes, ensuring the labels state Aliquot 1 and Aliquot 2 or alternate wording that differentiates that the samples are different aliquots. Within 90 minutes of collection, store plasma samples in a freezer set to maintain a temperature of −70°C (± 10°C). If the trial site does not have access to a −70°C freezer, samples may be stored on dry ice until shipment if the shipment can be arranged within 3 days of collection.

Fecal Samples for Microbiota Assessment

Handling and shipment details for the fecal samples for the microbiota assessment will be provided separately.

Blood Samples for FBR

The trial sites are expected to follow the instructions for collection, processing, storage, and shipment of blood samples as specified.

Refrigerate the whole blood samples in an upright position at 4°C for at least 1 day but no longer than 4 days. Then, the samples should be stored upright at −70°C. If refrigerating is not possible, samples can be frozen directly from ambient but should only be done if necessary since it will produce lower yields.

The samples for FBR will be stored in the biorepository for potential analysis for up to 20 years from acquisition. The specimens will be stored under strict supervision in a limited access facility that operates to ensure the integrity of the specimens.

NOTE: If subjects consent to the optional blood sample collection for FBR, then the second aliquot of blood samples for PK analysis collected from these subjects may be stored and used for this research.

Sample Shipment

After collection and processing, each frozen specimen must be sealed in a vial and labeled with a waterproof pen, if applicable. Labels should be secured to each storage tube. Labels must be capable of being stored at −70°C and withstand multiple freeze/thaws. Labels should contain at least the following information: protocol number; subject number; time point of sample collection (eg, 8 hours postdose); aliquot number, and matrix. All tubes must be labeled such that all information on the tube can be verified, ie legible.

The samples for PK analysis will be shipped frozen to the bioanalytical laboratory or central laboratory. **It is important that the Aliquot 1 sample is shipped first.** Other samples will be shipped to the designated laboratory.

The specimens must be neatly packed and shipped with enough dry ice to completely fill the box. Avoid air spaces that allow evaporation of the dry ice. All frozen samples will be shipped Monday through Thursday, or on the following Monday for samples collected on Friday through Sunday, unless otherwise instructed by the sponsor.

All shipments will be accompanied by an electronic manifest and notification of shipment must be made by email on the day of shipment to the applicable laboratory or biorepository.

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Appendix 2 Crohn's Disease Activity Index (CDAI)

Clinical or Laboratory Variable	Weighting Factor
Sum of the number of liquid or soft stools assessed each day over 7 days	x 2
Sum of abdominal pain grade (graded from 0 - 3 on severity) assessed each day over 7 days	x 5
Sum of general well-being, subjectively assessed from 0 (well) to 4 (terrible) each day over 7 days	x 7
Presence of complications*	x 20
Taking Lomotil or opiates for diarrhea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Absolute hematocrit deviation of 47 – percentage value for men	x 6
Absolute hematocrit deviation of 42 – percentage value for women	x 6
Percentage deviation from standard weight	x 1

*One point each is added for each set of complications:

- the presence of joint pains (arthralgia) or frank arthritis
- inflammation of the iris or uveitis
- presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- anal fissures, fistulae or abscesses
- other fistulae
- fever during the previous week.

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Appendix 3 Simple Endoscopic Score for Crohn's Disease (SES-CD)

Score	**Meaning**
0 - 2	Remission
3 - 6	Mild endoscopic activity
7 - 15	Moderate endoscopic activity
> 15	Severe endoscopic activity

	SES-CD Values			
Variable	**0**	**1**	**2**	**3**
Size of ulcers	None	Aphthous ulcers (diameter 0.1 to 0.5 cm)	Large ulcers (diameter 0.5 to 2 cm)	Very large ulcers (diameter > 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

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Appendix 4 Minimum Duration of Prior Treatments for Crohn's Disease

Prior Treatment[a]	**Minimum duration of prior treatment required to be considered as having a nonoptimal response**
Corticosteroids (eg Budesonide and Prednisone)	8 weeks
Aminosalicylates (eg Sulfasalazine and 5-ASA derivatives)	8 weeks
Thiopurines (eg 6-mercaptopurine and Azathioprine)	12 weeks
Methotrexate	12 weeks
Tumor necrosis factor-alpha inhibitors	8 weeks
Ustekinamab	8 weeks
Vedolizumab	8 weeks

[a]List is not inclusive of all prior treatment options and investigator judgement is required.

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Appendix 5 Protocol Amendment(s)/Administrative Change(s)

Amendment Number: 1

Issue Date: 12 Apr 2019

PURPOSE:

The purpose of this protocol amendment is to modify the secondary and exploratory endpoints, as well as the schedule of assessments, and to remove the monthly telephone follow-up (and corresponding exploratory endpoint). In addition, exclusion criteria and stopping criteria were added, and inclusion criterion #3 and exclusion criteria #4, #12, #13, #14, and #19 were modified. Finally, other minor revisions were made and are listed below.

BACKGROUND:

Endoscopic remission is likely to be rare at 12 weeks; hence, this endpoint was placed amongst the general secondary endpoints. Since an endoscopic response by 12 weeks is possible, an endpoint was added to capture that data (by recording the change from baseline in SES-CD score). An endpoint was also added for a decrease from baseline of ≥ 100 points in the CDAI score because this is a common endpoint in Crohn's trial. The monthly telephone follow-up (and corresponding exploratory endpoint) was removed because this will have limited utility and may be confounded by many factors. Inclusion/exclusion criteria and stopping criteria were added and modified based on requests from the FDA. The other protocol revisions were made for clarity.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Moved the key secondary efficacy endpoint to the list of general secondary efficacy endpoints.
- Moved the third secondary endpoint of endoscopic response so that it is the first secondary endpoint.
- Added a secondary endpoint of "change from baseline in SES-CD score".
- Added a secondary endpoint of "the percentage of subjects with a decrease from baseline of ≥ 100 points in the CDAI score".
- Added "the percentage of subjects with" to the applicable secondary efficacy endpoints.

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- Added "the percentage of subjects by specific" to the secondary safety endpoint of AEs.
- Changed the first exploratory endpoint to "by-visit analysis of CDAI remission (defined as a CDAI score < 150)".
- Changed the second exploratory endpoint to "by-visit analysis of PRO-2 remission (defined as stool frequency ≤ 3 times per day and abdominal pain ≤ 1)".
- Added "the percentage of subjects with" to exploratory endpoints #3 and #4.
- Removed the monthly telephone follow-up, and as a result, changed the trial duration for each subject from 68 to 20 weeks.
- Removed the exploratory endpoint of "time to relapse for subjects who achieve clinical remission at the end of the trial".
- Added a note to inclusion criterion #3 that the minimum duration of prior treatment required for a subject to be considered as having a nonoptimal response includes completing at least the recommended induction regimen for approved biologics and/or treatment at a therapeutic dose for a stable duration that would be anticipated to result in improvement (ie, 12 weeks for azathioprine, 4 weeks for methotrexate).
- Modified exclusion criterion #4 to remove that low-dose steroids may be tapered down during the trial, since this will occur post-enrollment and is covered in Section 4.1.
- Modified exclusion criterion #12 by adding the use of antibiotics for greater than 2 months within the past year.
- Modified exclusion criterion #13 by adding "or other significant adverse reaction to quinolones".
- Modified exclusion criterion #14 by removing "subjects at risk for tendon rupture (or who have tendonitis)", because this is now covered in the newly added exclusion criterion below.
- Added a note to exclusion criterion #19 that the rationale for excluding subjects who have failed 2 or more biologics is due to the fact that they may represent an especially difficult-to-treat population (ie, medically refractory) that may not benefit substantially from fluoroquinolones and/or will likely need additional, more invasive treatment (ie, surgical resection).
- Added the following exclusion criteria:
  - Subjects with risk factors for tendon rupture (ie, psoriasis, ankylosing spondylitis, competitive athletes, renal failure, diabetes mellitus) or who have a history of tendon rupture and/or ongoing tendinopathy.
  - Subjects with systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg.
  - Subjects taking quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, ibutilide, dronedarone, or propafenone.

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- Added the following stopping criteria:
  1) A confirmed prolongation of QTcF with an absolute value > 500 msec or any QTcF interval prolonged 60 msec or greater compared to baseline
  2) Hemoglobin count of < 8.0 g/dL
  3) Platelet count of 50000 µL or less
  4) Discontinuation of treatment should be considered for liver function test abnormalities if:

     a) ALT or AST > 8 × ULN

     b) ALT or AST > 5 × ULN for more than 2 weeks

     c) ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or international normalized ratio > 1.5

     d) ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
  5) New onset *C difficile* or enteric infection
- Removed the following stopping criteria because these are covered in detail in the newly added stopping criteria above:
  - Any clinically significant electrophysiological change in ECG parameters; arrhythmias, etc.
  - Any clinically significant change in hematological parameters
- Added that discontinued or withdrawn subjects will not be replaced.
- Renamed the stool culture to "stool microbiology testing" and moved it from the clinical laboratory tests to a separate row in the schedule of assessments (Table 3.7-1), and clarified that the stool microbiology testing will be for culture, *C difficile*, and O&P.
- Added a footnote to the schedule of assessments (Table 3.7-1) to clarify that the fecal sample for the microbiota assessment at screening should be collected prior to the bowel preparation and ileocolonoscopy.
- Added a row for "Dispense IMP" and clarified that only the morning dose of IMP will be administered at Week 12, in the schedule of assessments (Table 3.7-1).
- Clarified that the End of Treatment visit will include all assessments listed for Week 12, except for the ileocolonoscopy with biopsy and SES-CD score, in the schedule of assessments (Table 3.7-1).
- Changed the assessment time points from "↔" to an "X" for the diary, concomitant medications, and AEs in the schedule of assessments (Table 3.7-1).
- Added an optional FSH test at screening (for perimenopausal and postmenopausal female subjects only).
- Added a urine alcohol and drug screen at screening.

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- Added that an optional CMV test can be done on the biopsy specimen, if clinically indicated, at screening and at Week 12.
- Clarified that only hematology is required at Weeks 4, 8, and 10, and only serum chemistry and hematology are required at the 30-day post-treatment follow-up.
- Clarified that a full physical examination will be conducted at screening and a directed/targeted physical examination will be conducted at the subsequent visits. Also noted that for the purposes of this trial, the directed/targeted physical examination will include an abdominal exam.
- Clarified that the ileocolonoscopy with biopsy will occur within 7 to 10 days prior to Day 1 (not baseline).
- Clarified that 240 subjects will be randomized (not enrolled).
- Clarified that at trial sites where the electronic ICF application is not used, paper consent forms may be used instead.
- Clarified that it is at the investigator's discretion what constitutes a significant change in any of the subject's concomitant medications in determining if liver function tests are required.
- Clarified that the CDAI score at screening will be calculated using the formula in eSource for eligibility.
- Revised the stratification from "severity of disease" to "CDAI score".
- In Section 3.7.2.4, modified the list of data that will be recorded in the daily diary and added that subjects will continue completing the daily diary until the 30-day post-treatment follow-up visit.
- Added stool microbiology testing (eg, for culture, *C difficile*, O&P), platelets, FSH, CMV, and a urine alcohol and drug screen, and removed triglycerides and uric acid, in the list of clinical laboratory assessments (Table 3.7.3.2-1).
- In Section 3.7.3.3, clarified that only blood pressure and heart rate measurements will be made in both the supine and sitting positions (temperature and heart rate will be recorded only once).
- In Section 3.7.5.1.1, changed the anticoagulant from K_2EDTA to sodium heparin for the PK blood samples.
- In Section 4.2, clarified the restrictions for caffeine and over-the-counter probiotic supplements.
- In Section 7.3.1, removed how average scores will be derived from the diary (these details will be provided in the SAP).
- Modified the secondary and exploratory endpoint analysis text in Sections 7.4.2 and 7.4.3, respectively, for consistency with the changes to the secondary and exploratory endpoints.

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ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

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Amendment Number: 2

Issue Date: 09 Dec 2019

PURPOSE:

The purpose of this protocol amendment is to provide clarification of effective measures to prevent pregnancy, clarification for water intake with dosing of IMP, clarification for the collection tube used for the PK blood samples, and update of required serum chemistry tests.

Revisions to the protocol per SAP changes include subjects who increase dosages of baseline Crohn's disease medications or take a new therapy for Crohn's disease during the trial should be considered as treatment failures, but are encouraged to stay in the trial.

Additional revisions were made in Appendix 2 around the Crohn's Disease Activity Index to clarify the clinical and laboratory variables and the addition of Appendix 4, Minimum Duration of Prior Treatments for Crohn's Disease. Finally, other minor revisions and clarifications were made and are listed below.

BACKGROUND:

Protocol Amendment 2 revisions are in response to HA questions from BfArM, German CEC, and AIFA. These revisions will not impact subject safety, the scope of the investigation, or the scientific quality of the trial. Other protocol revisions were made to provide clarity and corrections.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Nonresponders added in addition to treatment failures for nonremission subjects for clarity in Section 3.1 Type/Design of the Trial.
- Randomization stratification factors added to Section 3.1 Type/Design of Trial.
- Water restriction details added in Section 3.2 Trial Treatments to clarify restriction is around the morning dose of IMP at Days 1 and Week 6 due to blood sampling.
- Blood thinners revised to antithrombotic drugs in Section 3.4.3 Exclusion Criteria and Section 4.1 Prohibited Medications. Additional details around antithrombotic drugs included in Section 4.1.
- Footnote added on Table 3.4.2-1: that prior treatment examples and their minimum duration can be found in Appendix 4.

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- Footnote added for Tables 3.4.3-1 Exclusion Criteria and 3.7.1-1 Schedule of Assessments, to identify that subjects that test positive for marijuana or for confirmed prescription medications (eg, opioid analgesics) may be permitted to be enrolled if they have no evidence of a substance use disorder.
- In Sections 3.4.3 Exclusion Criteria and 5.5 Pregnancy; vaginal diaphragm, condom with spermicide, or sponge with spermicide revised to be used in addition to the primary precautionary methods listed. In Section 3.7.5.1.1, changed the anticoagulant from sodium heparin to NaF/KOx for the PK blood samples.
- Otsuka Biometrics Department revised to Otsuka Independent Statistician Department in Section 3.6 Measure to Minimize/Avoid Bias.
- Section 3.7.1.2 Day 1, Section 3.7.3.2 Clinical Laboratory Assessments, and footnote for Table 3.7-1 Schedule of Assessments revised to identify that serum chemistries are only required at Day 1 unless there was a significant change in concomitant medications since screening, then hematology and urinalysis are also required.
- Cholesterol and lactic dehydrogenase were removed from required tests under serum chemistry in Table 3.7.3.2-1, Clinical Laboratory Assessments.
- Section 3.7.8 End of Treatment/End of Trial wording around discontinuation corrected from Month 12 to Week 12.
- Section 3.8.3.2 revised to clarify subjects who are treatment failures but that may continue IMP.
- Section 3.8.3.3 stopping criteria for platelet count limit of 50000 µL adjusted to 100000 µL.
- In Section 5.5 Pregnancy, the term double-barrier method was removed from protocol.
- Revised Sections 3.1 Type/Design of Trial, 7.4 Primary and Secondary Endpoints, and 7.3.1 Estimand and Strategies for Addressing Intercurrent Events so that subjects can increase or add new Crohn's medication while in the study and are encouraged to remain on IMP.
- Sections 7.4.1 Primary Endpoint Analysis and 7.4.2 Secondary Endpoint Analysis were revised to reflect the revisions in comparison of OPS-2071 150 mg BID versus placebo to occur if both 600 mg BID versus placebo and 300 mg BID versus placebo in the secondary efficacy endpoint are rejected.
- Statement around mean change from baseline for endpoints #3, #4, and #5 removed from Section 7.4.3 Exploratory Endpoint Analysis.
- Variable around "Number of liquid or soft stools each day for 7 days" was revised to read "Sum of the number of liquid or soft stools accessed each day over 7 days" in the Crohn's Disease Activity Index in Appendix 2.
- Variable around "Abdominal pain (graded from 0 - 3 on severity) each day for 7 days" was revised to read "Average of abdominal pain grade (graded from 0 - 3

on severity) accessed each day over 7 days" in the Crohn's Disease Activity Index in Appendix 2.

- Minor wording revised for semantics Appendix 2.
- Crohn's Disease Activity Index in Appendix 2 laboratory variable "Hematocrit of < 0.47 in men and < 0.42 in women" was divided into two separate variables identifying absolute hematocrit of 47 and 42 for men and women, respectfully.
- Appendix 4 added to identify the minimum duration of prior Crohn's disease treatment required to be considered as having a non optimal response.

ADDITIONAL RISK TO THE SUBJECT:

There is no additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

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Amendment Number: 3

Issue Date: 22 Jan 2020

PURPOSE:

The purpose of this protocol amendment is to modify exclusion criterion #6 and #8 and to remove exclusion criterion #7 to provide clarity and align treatment with standard of care. A minor revision to delete a duplicate entry in Appendix 4 was also made as listed below.

BACKGROUND:

Protocol Amendment 3 revisions were made to provide clarity. These revisions are unlikely to impact subject safety, the scope of the investigation, or the scientific quality of the trial.

MODIFICATIONS TO PROTOCOL:

General Revisions:

- Modified exclusion criterion #6 by removing "> 5 mm" to clarify that subjects are excluded if they have symptomatic bowel stenosis and by updating "with 2 or more" to "with more than 2" to clarify which subjects with bowel resections are to be excluded.
- Removed exclusion criterion #7 "Subjects with a history of upper gastrointestinal involvement of Crohn's disease or perianal Crohn's disease" as these are not infrequent historical manifestations of Crohn's disease.
- Modified exclusion criterion #8 by removing "with prior surgery that removed the ileocecal valve or resections that led to" to clarify that subjects are excluded if they have short bowel syndrome.
- Removed the last prior treatment listed in Appendix 4, "Corticosteroids (eg, Budesonide and Prednisone)," as it is a duplicate of the first prior treatment listed in the Appendix.
- Updated the title of Appendix 4 and added Appendix 5 in the List of Appendices.

ADDITIONAL RISK TO THE SUBJECT:

There is unlikely any additional risk to the subjects.

A complete redline version of this amendment showing all changes from the previous version will be produced and will be available upon final approval of this amendment.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPS-2071, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where OPS-2071 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC- approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

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