CLINICAL STUDY PROTOCOL

An Open-label, Multicenter Clinical Trial to Assess the Safety and Efficacy of Three Different Doses of OPS-2071 in Patients With Bacterial Enteritis
(Phase 2a Trial)

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(Phase 2a Trial)

Clinical Protocol

Protocol No.: 341-13-002

Confidential

Otsuka Pharmaceutical Co., Ltd.

2-9 Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan

Version 3.0: 15 Jul 2016

Statement of Confidentiality

The trial protocol is to be treated as confidential information and is to be made available only to persons involved in the trial. The content of the protocol is not to be disclosed to any third party without the prior written consent of Otsuka Pharmaceutical Co., Ltd., except in the case of its being explained to a candidate trial subject. Disclosure of the results of the trial to academic societies or journals, etc, in part or in whole, will require the prior written approval of Otsuka Pharmaceutical Co., Ltd.

Trial Protocol Synopsis

Name of Test Product	OPS-2071
Trial Title	An open-label, multicenter clinical trial to assess the safety and efficacy of three different doses of OPS-2071 in patients with bacterial enteritis
Trial Objectives	Primary objectives: • To assess the safety and efficacy of oral multiple doses of OPS-2071 in patients with bacterial enteritis associated with *Clostridium difficile* infection (CDI) or enteric infection (caused by *Salmonella, Campylobacter*, or pathogenic *Escherichia coli* [*E. coli*]) • To assess the pharmacokinetics of multiple doses of OPS-2071 in patients with bacterial enteritis associated with CDI or enteric infection Secondary objectives: • To assess the recurrence rate of CDI in patients with bacterial enteritis associated with CDI after multiple doses of OPS-2071 • To assess the time to resolution of diarrhea in patients with bacterial enteritis associated with CDI or enteric infection after multiple doses of OPS-2071 • To assess the improvement of clinical symptoms in patients with bacterial enteritis associated with CDI or enteric infection after multiple doses of OPS-2071 • To assess the sensitivity to OPS-2071 of the causative pathogen strain isolated from patients with bacterial enteritis associated with CDI or enteric infection
Phase of Development	Phase: 2a Type of trial: Dose-ranging trial
Trial Design	Multi-center, randomized, open-label trial
Target Disease	Bacterial enteritis
Target Number of Patients	A total of 60 patients with 20 patients (10 patients each in CDI and enteric infection groups) in each dosing group. Enroll 10 patients in each dosing group of the CDI group to assess microbiological outcome. For the enteric infection group, enroll at least five patients in each dosing group to

	assess microbiological outcome with the sum of *Salmonella, Campylobacter*, and pathogenic *E. coli*. If a sufficient number of patients are not available for microbiological assessment after enrollment of 10 patients in each group, enroll more patients.
Inclusion Criteria	Patients who meet all of the following criteria will be selected. 1. The patient is an Asian male or female of minimum legal age to provide consent (ie, 21 years for Singapore, 19 years for Korea, and 20 years for Japan at time of informed consent). 2. The patient provides written, informed consent before the clinical trial is initiated. 3. The patient has distinctive symptoms and findings of bacterial enteritis (regardless of inpatient or outpatient.) 4. The patient has bacterial enteritis with one or more of the following causative pathogens either proven or presumed: *Clostridium difficile* (*C. difficile*), *Salmonella*, *Campylobacter*, pathogenic *E. coli*, and other bacteria estimated to cause bacterial enteritis (except for typhoid bacillus, *Salmonella paratyphi A*, enterohemorrhagic *E. coli*, *Shigella*, and *Vibrio cholerae* [*V. cholerae*]) 5. The patient and his/her partner are willing to take contraceptive measures from initiation of investigational medicinal products (IMPs) to 4 weeks after administration of IMPs. <u>CDI group:</u> 6. The patient satisfies both the following: ✓ Liquid or unformed stools ≥ 3 times/day within 24 hours before the start of IMP administration ✓ A positive clinical laboratory result in one of the following methods to confirm CDI within 48 hours before the start of IMP administration: • Toxin A/B assay (positive for either or both

	toxins A and B) • Polymerase chain reaction (PCR) (detection of toxin genes) • Colonoscopy (findings of pseudomembranous colitis) <u>Enteric infection group:</u> 7. The patient satisfies all the following: ✓ Liquid or unformed stools ≥ 3 times/day within 24 hours before the start of IMP administration ✓ Any of the following clinical findings of enteric infection within 24 hours before the start of IMP administration • Either symptom of abdominal pain, nausea, or vomiting ✓ Negative toxin A/B assay or PCR within 48 hours before the start of IMP administration
Exclusion Criteria	Patients who fall under any of the following exclusion criteria will be excluded from participation in the trial. 1. Intractable vomiting, inability to take oral medication, patients with feeding tubes 2. The patient has severe or progressive underlying disease or complication, making it difficult to ensure safety in the study or proper efficacy assessment. 3. Complication of chronic bowel diseases such as Crohn's disease, ulcerative colitis, irritable bowel syndrome, or colorectal cancer 4. History of stem cell transplantation, organ transplantation, or bone marrow transplantation (within 6 months before the screening examination) 5. History of total colectomy 6. Suspected viral enteritis 7. History of allergic conditions caused by quinolone antibacterials

	8. The patient has a current diagnosis or history of convulsive disorders, such as convulsion and epilepsy. 9. The patient has a severe hepatic dysfunction (eg, AST [GOT] or ALT [GPT] ≥ 3 times of the upper limit of normal at the study center, etc) 10. The patient has a severe cardiac dysfunction (eg, cardiac arrest, ischemic disease) 11. The patient has cardiac arrhythmia or congenital or sporadic long QTc syndrome. Or the patient is treated with a drug reported to prolong QTc interval (eg, amiodarone, sotalol, disopyramide, quinidine, procainamide, terfenadine, astemizole, cisapride, pimozide) 12. The patient has a moderate or severe renal dysfunction (eg, serum creatinine level ≥ 2 mg/dL or necessity of renal dialysis, etc) 13. The patient was treated with UDP-glucuronosyltransferase 1A1 (UGT1A1) inhibitors (atazanavir) within 2 days before the start of IMP administration. 14. Women with confirmed or suspected pregnancy or breast-feeding women 15. The patient was treated with another IMPs within 3 months before the screening examination 16. Patients judged to be ineligible by the investigator for any other reasons <u>CDI group:</u> 17. The patient was treated with drugs and therapies to treat CDI within 24 hours before the start of IMP administration. 18. The patient with severe and complex CDI who has any of the following at the screening examination. • Complicated disease: ileus, mental status changes, organ dysfunction (kidney and respiratory organs), septic shock, peritonitis, toxic megacolon, marked

	dehydration • Admission to intensive care unit due to CDI <u>Enteric infection group:</u> 19. The patient was treated with other antibacterial agent by oral administration or injection within 7 days before the start of IMP administration. 20. Typhoid bacillus, *Salmonella paratyphi A*, enterohemorrhagic *E. coli, Shigella,* or *V. cholerae* was isolated/identified. 21. The patient has marked dehydration at the screening examination.
Discontinuation Criteria	1. If the patient wishes to withdraw 2. If it is found after the start of the trial that the patient did not meet all the inclusion criteria or fell under any of the exclusion criteria 3. If a drug or therapy from either item 1 or item 7 in the list of prohibited concomitant drugs and therapies is used or judged to be required 4. If an AE making continuation of trial participation difficult occurs 5. If the female patient is found to be pregnant 6. If symptoms of the primary disease exacerbate, and the investigator or subinvestigator judges that it is not appropriate to continue the trial participation 7. If it becomes impossible to comply with the protocol for any another reason or if the investigator or subinvestigator judges that it is necessary to discontinue the trial participation for any another reason
Investigational Medicinal Products, Dose and Regimen, and Treatment Period	<u>Investigational medicinal products:</u> OPS-2071 25 mg tablets, 50 mg tablets, 100 mg tablets <u>Dose and regimen:</u> Any of the daily three dosages of 50, 100, 200, or 400 mg of OPS-2071 is administered twice a day in the morning and

	evening to the CDI group for 10 days and to the enteric infection group for 7 days. Take IMP after meal where possible with at least 10 hours of interval between dosings. Ensure to have evening meal before dosing on the previous day of blood collection for PK and to have breakfast before dosing on the day to perform blood collection for PK. Whether or not the symptoms improve during the treatment period, use all IMPs prescribed for the predetermined period. Follow the algorithm shown below to decide on dosage. Start with the 100 mg group. The safety and efficacy during the treatment period will be assessed separately for the CDI group and the enteric infection group by the Data Review Committee (DRC). 1. If there are no safety concerns and IMP is considered effective in the 100 mg group: The next step is to randomize 10 patients each who were not in the 100 mg group to the 200 mg or 50 mg group. The two groups will be treated in parallel. Treatment will be started in the CDI and enteric infection groups, respectively. 2. If there are no safety concerns and IMP is considered not effective in the 100 mg group: The next step is to allocate 10 patients who were not in the 100 mg group to the 200 mg group. Treatment will be started in the CDI and enteric infection groups, respectively. The DRC assesses the safety of the 200 mg group during the treatment period. If the 200 mg has no safety concerns, 10 patients who were not in the 100 mg or 200 mg group will be allocated to the 400 mg group as the next step. Treatment will be started in the CDI and enteric infection groups, respectively.
Prohibited Concomitant Drugs and Therapies and Restricted Concomitant	<u>Prohibited concomitant drugs and therapies:</u> The use of following drugs and therapies will be prohibited

Drugs	during the period from the start day of IMP administration to the end day of the trial for items 1 and 7, from screening to the end day of the trial for the following items 2 through 6, and from the start day of IMP administration to the end day of IMP administration for item 8. 1) For enteric infection group only: antibiotic agents/synthetic antibacterial agents (oral, injection, suppository) 2) For enteric infection group only: non-steroidal anti-inflammatory/analgesic drugs (oral, injection, suppository)* 3) For enteric infection group only: corticosteroid preparation (oral, injection, suppository) 4) For enteric infection group only: immunosuppressant medications (oral, injection, suppository) 5) For enteric infection group only: biological preparation (TNF inhibitor) 6) Antidiarrheal drugs, drugs to inhibit bowel motility 7) Other drugs and therapies to treat CDI and enteric infection (eg, fecal microbiota transplantation) 8) UGT1A1 inhibitors (atazanavir) *: Use for purposes other than treating enteric infection is allowed. (Concomitant use is allowed for treating common cold during the trial period.) <u>Restricted concomitant drugs:</u> Among of drugs listed below, concomitant use of drugs listed in item 1) are prohibited in principle from the start day of the IMP administration until the day of examination at the end of treatment if the drugs are used for a purpose other than treatment of CDI. However, in cases that drugs are used to treat an underlying disease at the time of screening and cannot be discontinued even after the start day of the IMP administration due to the necessity for continuous drug treatment, such concomitant use is allowed. Drugs listed in items 2) through 5) are allowed to be administered concomitantly as long as the drugs are used at the time of screening and the dose regimen is not changed during the

	period from screening until the day of examination at the end of treatment. Drugs listed in item 6) are allowed to be administered concomitantly under the following conditions: the drugs are used at the time of screening, and the dose regimen is not changed in the period from screening to the end day of trial for CDI groups, or the period from screening to the end day of IMP administration for enteric infection group. If the foods described in item 6) are taken, instruct the patient not to change the daily amount of consumption during the period from screening until the end day of the trial. 1) For CDI group only: antibiotic agents/synthetic antibacterial agents (oral, injection, suppository) 2) For CDI group only: non-steroidal anti-inflammatory/analgesic drugs (oral, injection, suppository)* 3) For CDI group only: corticosteroid preparation (oral, injection, suppository) 4) For CDI group only: immunosuppressant medications (oral, injection, suppository) 5) or CDI group only: biological preparation (TNF inhibitor) 6) Probiotics *: Use for purposes other than treating CDI is allowed. (Concomitant use is allowed for treating common cold during the trial period.)
Endpoints	<u>Safety endpoints:</u> • Adverse events, clinical laboratory tests, vital signs (body temperature, blood pressure, and pulse rate), 12-lead electrocardiogram (ECG) <u>Efficacy endpoints:</u> • Microbiological outcome (microbiological outcome, toxin A/B assay) • Clinical response • Recurrence of CDI (CDI group only) • Time to resolution of diarrhea • Improvement of clinical symptoms

	• Drug sensitivity of isolated strain Pharmacokinetics endpoints: • Plasma pharmacokinetics: plasma concentration, pharmacokinetic parameters (maximum [peak] plasma concentration of the drug [C_{max}], time to maximum [peak] plasma concentration [t_{max}], C_{max} normalized by dose [C_{max}/D]) of OPS-2071

Criteria for Evaluation

Microbiological outcome:

Microbiological outcome will be judged according to the following assessment criteria for the bacterial strain isolated as the causative pathogen based on the data from the microbiological examination. For infection due to multiple causative pathogens, microbiological outcome will be assessed for each individual pathogen.

Time of Observation			Assessment of Microbiological Outcome
Baseline	**Day 4**	**End of Treatment**	
+	–	–	Excellent
+	+	–	Good
–			
+	Not applicable		
+	+	+	Poor
–			
+	–		
+	Not applicable		
Others			Unknown/ indeterminate

+: culture positive; – : culture negative
Not applicable: Bacterial culture test was not performed. The causative pathogen was not isolated or identified.

Assessment of Microbiological Outcome	**Definition**
Excellent	Pathogen is absent from bacterial culture obtained at Day 4 and at the end of treatment.
Good	Pathogen is still present in bacterial culture obtained at Day 4, and absent from bacterial culture at the end of treatment.
Poor	Pathogen is still present in bacterial culture obtained at the end of treatment
Unknown/ indeterminate	Applicable to none of the above, but falls under the cases below for example. • Cultures are not available because of withdrawal from the study or other reasons. • Culture was obtained after the use of prohibited concomitant drugs/therapies. • Any other circumstance, which makes it impossible to define the microbiological response.

Clinical response:

Assess clinical response at the time of observation (Day 4

and end of treatment) according to the following assessment criteria.

Clinical Response Assessment	Definition
Clinical cure	Meeting all the following criteria within 24 hours before observation • No liquid or unformed stool • No abdominal symptoms and no other symptoms (fever, nausea, vomiting) • No need of medication or therapy to treat CDI or enteric infection
Clinical improvement	Fulfilling at least one of the following criteria within 24 hours before observation • Liquid or unformed stools ≤ 2 times/day • No abdominal symptoms and no other symptoms (fever, nausea, vomiting) • No need of medication or therapy to treat CDI or enteric infection
Clinical failure	Fulfilling none of the above-mentioned clinical improvement criteria. Patients who received medication or therapy to treat CDI or enteric infection prior to the time of observation are to be assessed as "clinical failure".

Recurrence of CDI (CDI group only):

For patients who achieved "clinical cure" at the end of treatment, assess the recurrence of CDI at follow-up 2 (FU2) or withdrawal according to the following assessment criteria.

Assessment of Recurrence of CDI	Definition
Sustained cure	No recurrence
Recurrence	Meeting all the following criteria • New episode of diarrhea is occurred in the period from the end of treatment to FU2 or withdrawal (liquid or unformed stools ≥ 3 times/day within 24 hours) • Medication or therapy is required to treat CDI in the period from the end of treatment to FU2 or withdrawal • A positive toxin A/B assay at FU2 or withdrawal (positive for either or both toxins)

	Time to resolution of diarrhea: The time from the start of dosing until the first formed stool (except in cases where liquid or unformed stools recurs) will be evaluated as time to resolution of diarrhea.
Scheduled Duration of the Trial	01 Jul 2015 through 31 Mar 2017

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List of Abbreviations and Definition of Terms

List of Abbreviations

Abbreviation	Expansion
AAD	Antibiotic-associated diarrhea
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZM	Azithromycin
BMI	Body mass index
CDAD	*Clostridium difficile*-associated diarrhea
CDI	*Clostridium difficile* infection
CPFX	Ciprofloxacin
CPPS	Clinical per protocol set
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
EDC	Electronic data capture
FAS	Full analysis set
FDX	Fidaxomicin
FU	Follow-up
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response Services
IUD	Intrauterine device
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MIC_{90}	Minimum inhibitory concentration required to inhibit the growth of 90% of bacterial strains tested
MPC	Mutant prevention concentration
MPPS	Microbiological per protocol set
MTZ	Metronidazole
PMDA	Pharmaceuticals and Medical Devises Agency
PCR	Polymerase chain reaction
PK	Pharmacokinetics

Abbreviation	Expansion
PKS	Pharmacokinetics set
PP	Per protocol
QTc	Corrected QT interval
QT_cB	QT interval corrected using the Bazette's formula
QTcF	QT interval as corrected by Fridericia's formula
RFX	Rifaximin
SAE	Serious adverse event
SS	Safety set
TEAE	Treatment-emergent adverse event
UGT	Uridine diphosphate glucuronosyltransferase
URTI	Upper respiratory tract infection
VCM	Vancomycin
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

Definitions of Terms

Term	Definition
Screen failure	A screen failure is a patient from whom written informed consent was obtained, but to whom the investigational medicinal product was not assigned.
Trial start date for individual patient	The day of obtaining the patient's written informed consent
Trial completion date for individual patient	CDI group: The completion day of follow-up 2 (FU2) or withdrawal examination for individual patients Enteric infection group: The completion day of follow-up 1 (FU1) or withdrawal examination for individual patients
Trial withdrawal date for individual patient	The day when withdrawal is considered necessary by the investigator or subinvestigator for individual patient or the day of withdrawal examination
Trial period for individual patient	Period from the day of obtaining the patient's informed consent to the day of trial completion. It does not include the follow-up period after the trial completion date for individual patient.

List of Pharmacokinetic Parameters

Abbreviation and Term (Unit)		Expansion or Definition
AUC_{0-t}	µg·h/L	Area under the concentration-time curve calculated to the last observable concentration at time t
$AUC_{0-\infty}$	µg·h/L	Area under the concentration-time curve from time zero to infinity
C_{max}	µg/L	Maximum (peak) plasma concentration of the drug
C_{max}/D	µg/L/mg	C_{max} normalized by dose
$fe_{f,xh}$	%	Fraction of the drug excreted into the feces to x hours
$fe_{u,xh}$	%	Fraction of the systemically available drug excreted into the urine to x hours
t_{max}	h	Time to maximum (peak) plasma concentration

1 Introduction

1.1 Background of Trial Plan

According to the World Health Organization (WHO) report, diarrheal disease is in the top-10 list of leading causes of death in the world, with 1.5 million people dying from diarrheal disease in 2012. [1] Diarrhea is the major symptom of enteric infections caused by bacteria such as *Salmonella*, *Campylobacter*, *Vibrio*, *Shigella*, and *Escherichia coli* (*E. coli*). In addition, a number of antibiotic-resistant pathogens have been reported in recent years,[2] and quinolone-resistant *Campylobacter* in particular has become widespread.[3,4]

All of the commercially available antibiotics have the potential to cause diarrhea during treatment of infectious diseases.[5] Use of antibiotics sometimes disrupts intestinal flora, followed by microbial substitution, which leads to an increase in pathogenic bacteria and eventually induces diarrhea (antibiotic-associated diarrhea: AAD). Since *Clostridium difficile* (*C. difficile)* is resistant to most of the currently available antibiotics, and AAD caused by *C. difficile* is specifically known as *C. difficile* infection (CDI).[6] Use of existing quinolone drugs has been known to increase the risk of CDI,[7] and the number of CDI cases has been increasing in recent years.[8] Metronidazole (MTZ) and vancomycin (VCM) are the preferred first-line therapeutic agents for CDI; however, treatment failure with the use of MTZ and recurrence with the use of VCM in 15% to 30% of cases have been reported.[9] An additional concern regarding the use of VCM is the emergence of VCM-resistant enterococci (VRE).[8]

In order to solve these problems, Otsuka Pharmaceutical Co. Ltd. discovered OPS-2071, which shows a broad spectrum of activity against intestinal infectious bacteria, including *C. difficile* and *Campylobacter*, and is expected to cause few adverse effects because of its low systemic absorption following oral administration.[10] OPS-2071 is a new chemical entity with a quinolone structure for enteric infections, including CDI.

1.2 Study Results and Trial Rationale

1.2.1 Nonclinical Study Results

1.2.1.1 Efficacy Pharmacology

1) Efficacy Pharmacology

In vitro studies showed OPS-2071 to have broad and potent antibacterial activity against clinically isolated bacteria that caused enteric infections. The antibacterial activity of OPS-2071 was equivalent or superior to that of existing drugs. Moreover, OPS-2071 showed potent activity against *C. difficile* [minimum inhibitory concentration required to

inhibit the growth of 90% of bacterial strains tested (MIC_{90}): 0.5 μg/mL] and *Campylobacter jejuni* (*C. jejuni*) (MIC_{90}: 0.25 μg/mL), both of which are known to be resistant to existing quinolone drugs. The antibacterial activity of OPS-2071 against *C. difficile* was comparable to that of rifaximin (RFX) and fidaxomicin (FDX) and superior to that of other antibiotics, including VCM. The antibacterial activity of OPS-2071 against *C. jejuni* was comparable to that of azithromycin (AZM) and superior to that of other antibiotics.

No spontaneous resistance to OPS-2071 was observed. The frequency of spontaneous resistance to OPS-2071 was lower than that for RFX and FDX, which are under development or have already been approved as therapeutic agents for *C. difficile* infection. The mutant prevention concentrations (MPC: concentration that shows no emergence of resistant bacteria) of OPS-2071 were similar to or lower than those of existing quinolones and VCM, and considerably lower than those of RFX and FDX. The risk of emergence of bacteria resistant to OPS-2071 is therefore presumed to be similar to or lower than for existing quinolones and VCM and considerably lower than for RFX and FDX.

The therapeutic efficacy of OPS-2071 was examined using two animal models, a mouse typhoid model and a hamster *C. difficile*-associated diarrhea (CDAD) model, and potency was observed to be well correlated with that observed in vitro. The efficacy of OPS-2071 was similar to that of ciprofloxacin (CPFX) in the mouse typhoid model and superior to that of VCM, FDX, and metronidazole (MTZ) in the hamster CDAD model. These results indicate that OPS-2071 has the potential to be a potent antibiotic for the treatment of a variety of infectious intestinal diseases, including typhoid fever and CDI.

2) Safety Pharmacology

OPS-2071 at single oral doses of up to 2000 mg/kg showed no effects on general signs and behavior in rats or on respiratory and cardiovascular parameters in conscious dogs. OPS-2071 inhibited human ether-a-go-go related gene current in Chinese hamster ovary cells at 100 μmol/L with a 30% inhibitory concentration of 132 μmol/L. OPS-2071 did not induce prolongation of QT interval, corrected QT interval (QTc), monophasic action potential duration at 90% repolarization, effective refractory period, or terminal repolarization period even at an intravenous dose of 3 mg/kg in anesthetized dogs, suggesting a low potential for proarrhythmic effects. OPS-2071 showed no inhibitory effects on γ-aminobutyric acid receptor binding in either the absence or presence of flurbiprofen or biphenylacetate, nonsteroidal anti-inflammatory analgetics, suggesting a low potential for convulsion.

3) Nonclinical Absorption, Distribution, Metabolism, and Excretion

Absorption

Following single oral administration in mice, hamsters, rats and monkeys, the plasma exposure of OPS-2071 increased with dose increase. The oral bioavailability of OPS-2071 at 1 mg/kg was 2.9% in male rats and 5.0% in male monkeys. No apparent sex differences were observed in the plasma concentration profile of OPS-2071 in rats. Plasma exposure of OPS-2071 was lower for oral administration in a fed state than for a fasted state in rats. In monkeys, absorption of OPS-2071 was delayed following administration in a fed state versus a fasted state. OPS-2071 showed higher membrane permeability in vitro than in metoprolol, a high permeability marker.

Distribution:

Following oral administration of ^{14}C-OPS-2071 at 3 mg/kg to male and female rats, concentrations of radioactivity in the stomach, small intestine, large intestine, kidney, and liver were considerably higher than that in the plasma at 1 hour postdose (time to maximum concentration [t_{max}] was 1 hour in all of these tissues except the large intestine). Radioactivity was hardly detected in the central nervous system. Following oral administration of ^{14}C-OPS-2071 at 3 mg/kg to male pigmented rats, OPS-2071 and its metabolites were scarcely bound to melanin. The in vitro protein binding of ^{14}C-OPS-2071 was lower than 79.3% in human, mouse, hamster, rat, rabbit, dog, and monkey serum.

Metabolism

Following repeated oral administration of OPS-2071 at 2000 mg/kg/day, a glucuronide of OPS-2071 was detected in rat and monkey plasma, and a hydrate of OPS-2071 was detected in monkey plasma. In reaction with human uridine diphosphate (UDP) glucuronosyltransferase (UGT)-expressing microsomes, a glucuronide of OPS-2071 was predominantly produced by UDP-glucuronosyltransferase 1A1 (UGT1A1)-mediated reaction and slightly produced by UGT1A9-mediated reaction. OPS-2071 had no inhibitory effect on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 at up to 100 μmol/L. OPS-2071 at up to 5 μmol/L caused no induction of CYP1A2, CYP2B6, and CYP3A4.

Excretion

Following single oral administration of OPS-2071 at 2 mg/kg to hamsters, OPS-2071 in the cecal contents reached a C_{max} of 42.95 μg/g at 4 hours postdose and then decreased with a terminal-phase elimination half-life ($t_{1/2,z}$) of 8.3 hours, and the cumulative fecal excretion of OPS-2071 within 72 hours postdose accounted for 67.0% of the administered dose. Following oral administration of ^{14}C-OPS-2071 at 3 mg/kg, the urinary and fecal excretion of radioactivity within 168 hours postdose accounted for 1.416% to 2.297% and 95.35% to 96.14% of the administered dose in rats and 21.51% and 80.59% in monkeys, respectively.

4) Toxicology

In 4-week repeated-dose oral toxicity studies in rats and monkeys, no deaths or severe clinical signs were observed in either males or females at doses of up to 2000 mg/kg/day. In genotoxicity studies, OPS-2071 showed mutagenicity in vitro in a bacterial reverse mutation test in one strain (TA102) of *Salmonella Typhimurium*. However, no mutagenicity was found in four other standard strains. In a mammalian cell chromosome aberration test, OPS-2071 showed clastogenicity at 15 μg/mL and higher, but no genotoxicity was seen in an erythrocyte micronucleus test or in a liver unscheduled DNA synthesis test in male rats intraperitoneally administered OPS-2071 at up to 2000 mg/kg; thereby, the genotoxic potential seen in vitro is considered to have no relevance in clinical use. In reproductive and developmental toxicity studies, the no observed adverse effect level (NOAEL) with fertility and early embryonic development in male and female rats was considered to be 2000 mg/kg/day. In an embryo-fetal development study in rats, NOAEL was considered to be lower than 200 mg/kg/day for general toxicity in dams and 2000 mg/kg/day for reproduction in dams and for embryo-fetal development. In an embryo-fetal development study in mice, NOAEL was considered to be 2000 mg/kg/day. In an in vitro phototoxicity testing, OPS-2071 was considered to show phototoxic potential. However, no phototoxicity was noted in an in vivo skin phototoxicity study using mice intraperitoneally administered OPS-2071 at doses of up to 2000 mg/kg.

1.2.2 Effects in Humans

The safety and pharmacokinetics of OPS-2071 in healthy volunteers have been assessed in three phase 1 trials in Singapore, Korea, and Japan. The Singapore trial (Trial 341-12-001) addressed a single dose, multiple doses, and the effect of food. The Korean trial (Trial 341-KOA-1301i) addressed a single and multiple doses. The Japanese trial addressed a single dose (Trial 341-13-001). Multiple dosing was conducted by twice daily administration for 7 days.

1) Pharmacokinetics:

Following single administrations of OPS-2071 at doses of 30, 60, 120, 240, 300, 600, 900, and 1200 mg in a fasting state, median t_{max} was 1.0 to 4.0 hours postdose. Following multiple dose administration at doses of 60, 120, 300, and 600 mg after a light meal, median t_{max} was 2.0 to 3.5 hours in the Singapore trial, and following multiple dose administration before meals, median t_{max} was 2.5 to 3.5 hours in the Korean trial. OPS-2071 C_{max}, AUC from time zero to the last quantifiable concentration (AUC_{0-t}) and AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$) values increased dose-dependently but in a less than dose proportional manner following single- and multiple-dose administration. 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 in the Singapore trial and approximately at 12 to 50 hours in the Korean and Japanese trials across the same dose range.

Following administration of OPS-2071 at a single dose of 600 mg after consumption of a meal, C_{max} was 2.21, AUC_{0-t} and $AUC_{0-\infty}$ were 2.04-fold higher compared with the values following administration in a fasted state. In multiple dosing of OPS-2071, steady-state conditions were achieved by Day 2 of administration of OPS-2071.

The mean percent of OPS-2071 excreted in urine ($fe_{u,72h}$) was approximately 2.4% or less of the administered dose following single and multiple dose administration. The mean amount excreted in the feces as a percentage of dose administered ($fe_{f,72h}$) ranged from approximately 30.0% to 55.0% of the administered dose following single dose administration.

2) Pharmacodynamics:

In the Singapore and Korean trials, OPS-2071 at doses of 60, 120, 300, and 600 mg was repeatedly administered for assessing the effect on intestinal bacterial flora. Some intestinal bacteria decreased because of the repeated administration of OPS-2071. However, regardless of the dose of OPS-2071, the intestinal bacterial flora returned to the baseline status by the time of follow-up after the end of treatment. There was no apparent effect on intestinal bacterial flora.

3) Safety:

In the three trials, no subject was withdrawn due to an adverse event (AE) related to OPS-2071. In the Singapore trial, one subject was withdrawn from the trial due to three AEs of syncope, hemorrhage intracranial, and atrial fibrillation, all of which were unrelated to OPS-2071 (syncope and hemorrhage intracranial were also serious adverse events [SAEs]). In the Korean and Japanese trials, no subjects experienced any SAEs.

Singapore trial (Trial 341-12-001)

Following a single administration of OPS-2071 or placebo in a fasting state, five of 20 subjects (25%) experienced seven treatment-emergent adverse events (TEAEs) (OPS-2071: seven events in five subjects). There were two TEAEs of Grade 4 severity [Common Terminology Criteria for Adverse Events (CTCAE) severity grading], reported for one subject (30 mg); these were events of syncope and hemorrhage intracranial, assessed by the investigator as not related to the investigational medicinal product (IMP), but considered to be SAEs necessitating withdrawal. Subjects also experienced upper respiratory tract infections (URTIs; 2/20 [10%]), cough (1/20 [5%]), rhinorrhea (1/20 [5%]) and atrial fibrillation (1/20 [5%]).

Following administration of OPS-2071 at 600 mg in both fed and fasted states, one subject (1/12 [8.33%]) experienced two TEAEs, which were mild gastroenteritis and URTI.

Following multiple administration of OPS-2071 in a fed state, nine subjects (9/32 [28.13%]) experienced 15 TEAEs. Treatment-related TEAEs were five events of alanine aminotransferase (ALT) increased (5/32 [15.63%]), and one event (1/32 [3.13%]) each of ventricular extrasystoles, aspartate aminotransferase (AST) increased, electrocardiogram QT prolonged (described in the CRF as "QTcB > 450 ms"; however, central measurements revealed that QTcB and QTcF were < 450 ms), gamma-glutamyltransferase increased and headache.

Korean trial (Trial 341-KOA-1301i)

Following a single administration of OPS-2071 or placebo in a fasting state, 10 of 64 subjects (15.6%) experienced 14 TEAEs (OPS-2071: 12 events in eight subjects; placebo: two events in two subjects). TEAEs reported were two events (2/64 [3.1%]) each of URTI and epistaxis, and one event (1/64 [1.6%]) each of vision blurred, abdominal pain, abdominal pain upper, diarrhoea, oral pustule, dizziness, headache, pleuritic pain, rhinorrhoea, and dry skin.

Following multiple administration of OPS-2071 or placebo before morning meal and before evening meal, 10 of 32 subjects (31.3%) experienced 22 TEAEs (OPS-2071: 18 events in seven subjects; placebo: four events in three subjects). TEAEs reported were three events (3/32 [9.4%]) of diarrhoea, two events (2/32 [6.3%]) each of headache and somnolence, and one event (1/32 [3.1%]) each of dry eye, visual acuity reduced, abdominal distension, abdominal pain, abdominal pain upper, nausea, sensation of foreign body, epistaxis, oropharyngeal pain, pharyngeal haemorrhage, pleuritic pain, dry skin, pruritus, rash, and rash erythematous.

Japanese trial (Trial 341-13-001)

After single oral administration of OPS-2071 or placebo in a fasting state, a total of 25 TEAEs were reported for 22 (34.38%) of the 64 subjects (OPS-2071: 18 events in 16 subjects; placebo: seven events in six subjects). The highest incidence of TEAEs occurred in the System Organ Class of gastrointestinal disorders (13 events in 11 of the 64 subjects [17.19%], comprising 11 events of diarrhoea (10/64 [15.63%]) and two events of abdominal pain (1/64 [1.56%]). The other TEAEs comprised three events of headache (3/64 [4.69%]), two events (2/64 [3.13%]) each of pharyngitis and blood creatine phosphokinase increased, two events (1/64 [1.56%]) of ALT increased, and one event (1/64 [1.56%]) each of subcutaneous hematoma, AST increased, blood bilirubin increased, back pain, and proteinuria.

1.2.3 Trial Rationale

OPS-2071 is a novel anti-enteric infection agent with a quinolone structure that has been shown to have potent antibacterial activity against various bacteria known to cause general enteric infections, including CDI. This study is designed as a multi-center, open-label phase 2a trial to assess the safety and efficacy (microbiological outcome and clinical response) of three different doses of OPS-2071 in patients with bacterial enteritis.

For the trial population of this study, patients with bacterial enteritis will be divided into two groups, a CDI group for patients with bacterial enteritis associated with *C. difficile* infection and an enteric infection group for patients with bacterial enteritis for which the causative pathogen is *Salmonella, Campylobacter*, and pathogenic *E. coli*. The safety and efficacy will be assessed in each group. Since this is the first trial in patients, in order to ensure patient safety, *Salmonella*, *Campylobacter*, and pathogenic *E. coli*, which are relatively less likely to cause severe infection, have been selected as the causative pathogens for enteric infection. However, among these three types of bacteria, typhoidal *Salmonella*, enterohemorrhagic *E. coli* (EHEC), and *Vibrio cholerae* (*V. cholerae*) are excluded because they are more likely to cause severe infection. *Shigella* is also excluded for the same reason.

The dosage of OPS-2071 in this trial is estimated based on the results of non-clinical pharmacological test. In hamster CDAD model, the therapeutic effect of OPS-2071, VCM, and FDX was confirmed. The result demonstrated that OPS-2071 showed significant therapeutic effect at 0.04 to 1 mg/kg and VCM and FDX showed significant therapeutic effect at 1 to 5 mg/kg. Thus, OPS-2071 showed therapeutic effect equal to or greater than that of VCM or FDX at 1/25 to 1/5 lower concentrations. It is estimated that the clinical dose of OPS-2071 is 16 to 100 mg, and that dose range OPS-2071 is expected

to show therapeutic effect equal to or greater than VCM at 500 mg (clinical dose) and FDX at 400 mg (clinical dose). Within the range of 16 to 100 mg/day, a dose of 100 mg/day is expected to show the most satisfactory effectiveness and at present 100 mg is considered likely to be the recommended human dose, and therefore the starting dose is set at 100 mg/day. Concerning the treatment period, 10 days is selected for the CDI group in reference to American College of Gastroenterology (ACG) 2013 guideline,[11] and information of FDX, VCM, and MTZ. In the enteric infection group, the trial adopts a 7-day treatment period, regardless of the causative pathogen or the efficacy during the trial for an exploratory assessment on how OPS-2071 affects clinical response and microbiological outcome.

In the trial design, 100 mg/day, considered to be the clinically recommended dose, is set for the starting dose. If there are no safety concerns and efficacy is confirmed in the 100 mg group, safety and efficacy will be assessed in the 200 mg group. By further confirming the safety and efficacy of OPS-2071 in the 50 mg group, the low dose cohort, at the same time, exploratory information on the recommended dose will be obtained. If efficacy at 100 mg/day is not confirmed and there are no safety concerns, the safety and efficacy of OPS-2071 will be assessed at 200 mg/day and then at 400 mg/day in a sequential ascending manner. Thus, the trial has a dose increase/decrease design. A Data Review Committee (DRC) will be established as a third-party organization for assessing the safety and efficacy of each dose escalation based on a consistent perspective of specialists.

The target number of enrollment is 10 patients in each dosage of the CDI group, and 10 patients in each dosage of the enteric infection group. To obtain information on microbiological outcome required for planning trial design on and after the next phase, each dosage secures at least 10 patients in the CDI group to assess the microbiological outcome and at least five patients in the enteric infection group to assess microbiological outcome with the sum of *Salmonella, Campylobacter*, and pathogenic *E. coli*. If a sufficient number of patients are not available for microbiological assessment after enrollment of 10 patients in each group, enroll more patients.

This trial is performed as a global trial in Japan, Korea, and Singapore. A phase 1 study was performed in Asian healthy male adults in Japan, Korea, and Singapore. The single-dose study demonstrated tolerability up to 1200 mg. In the 7-day multiple dose study (twice daily after meal), it was confirmed that there were no safety concerns up to 1200 mg/day as with the single dose. Individual variability was relatively high in all these countries, and distinctive difference among the studies was not noted in the exposure. There appears no remarkable difference in the safety and pharmacokinetics of Asian

subjects among three countries. Further, we consider there is no remarkable difference in the distribution of pathogens, risk factors of the development of symptoms, and patient background among three countries.

Preceding the planning of a phase 2a trial, a consultation before the beginning of the phase 2a trial was held with Pharmaceuticals and Medical Devices Agency (PMDA) on 11 Jun 2014. The face-to-face advice/post-termination consultation was subsequently performed on 10 Dec 2014.

Based on the above, we have judged that performing this trial as a global trial in patients with bacterial enteritis is scientifically and ethically appropriate.

Please refer to the investigational brochure for the detail of data described in this study protocol and other study results.

2 Trial Objectives

The objectives of this trial are:

Primary objectives:

- To assess the safety and efficacy of oral multiple doses of OPS-2071 in patients with bacterial enteritis associated with CDI or enteric infection (caused by *Salmonella, Campylobacter*, or pathogenic *E. coli*)
- To assess the pharmacokinetics of multiple doses of OPS-2071 in patients with bacterial enteritis associated with CDI or enteric infection.

Secondary objectives:

- To assess the recurrence rate of CDI in patients with bacterial enteritis associated with CDI after multiple doses of OPS-2071.
- To assess the time to resolution of diarrhea in patients with bacterial enteritis associated with CDI or enteric infection after multiple doses of OPS-2071.
- To assess the improvement of clinical symptoms in patients with bacterial enteritis associated with CDI or enteric infection after multiple doses of OPS-2071.
- To assess the sensitivity to OPS-2071 of the causative pathogen strain isolated from patients with bacterial enteritis associated with CDI or enteric infection.

3 Trial Plan

3.1 Trial Design

This is a multi-center, open-label trial to assess the safety and efficacy (microbiological outcome and clinical response) of three different doses of OPS-2071 in patients with bacterial enteritis.

Patients with bacterial enteritis will be divided into two groups, a CDI group for patients with bacterial enteritis associated with *C. difficile* infection and an enteric infection group for patients with bacterial enteritis for which the causative pathogen is *Salmonella, Campylobacter*, or pathogenic *E. coli*.

Outline of the trial design is shown in Figure 3.1-1.

The target number of enrollment is 10 patients in each dosage of the CDI group, and 10 patients in each dosage of enteric infection group. Enroll 10 patients in each dosing group of the CDI group to assess microbiological outcome. For the enteric infection group, enroll at least five patients in each dosing group to assess microbiological outcome with the sum of *Salmonella, Campylobacter*, and pathogenic *E. coli*. If a sufficient number of patients are not available for microbiological assessment after enrollment of 10 patients in each group, enroll more patients.

Of daily dosages of 50, 100, 200, or 400 mg of OPS-2071, three dosages of 100, 50, and 200 mg, or 100, 200, and 400 mg are administered. The DRC will assess the appropriateness of dose escalation.

Any of the daily three dosages of 50, 100, 200, or 400 mg of OPS-2071 is administered twice a day in the morning and evening to the CDI group for 10 days and to the enteric infection group for 7 days. Whether or not the symptoms improve during the treatment period, use all IMPs prescribed for the predetermined period.

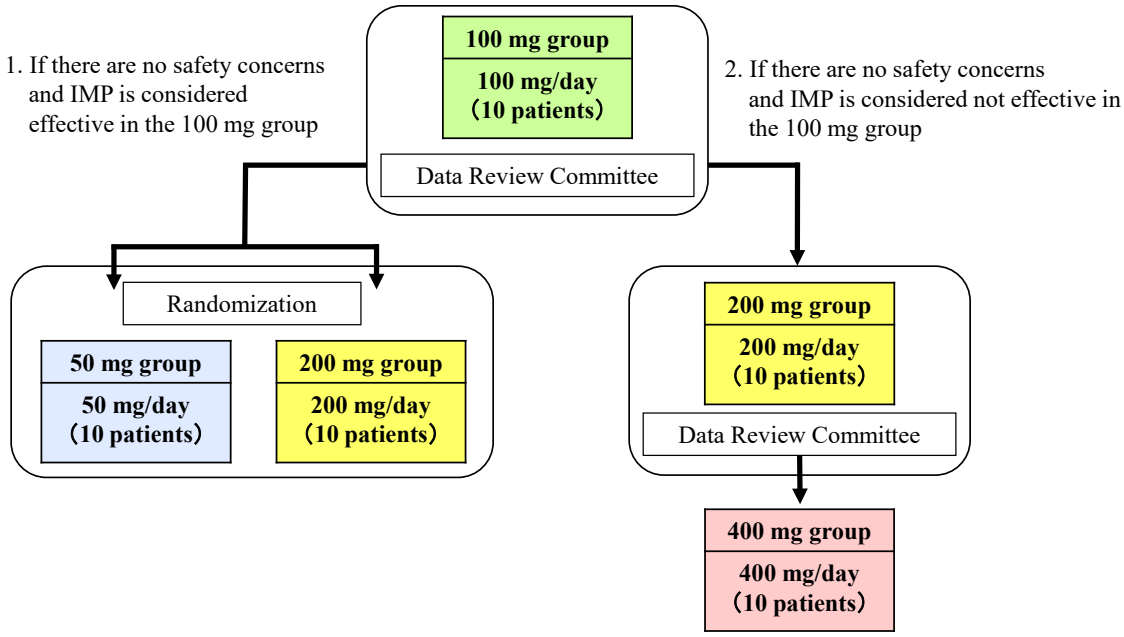

Figure 3.1-1 Outline of Trial Design

Criteria for dose escalation

Start with the 100 mg group. Enroll patients until the target population is achieved in each dosing group with CDI and enteric infection. The DRC will assess the safety and efficacy during the treatment period at 100 mg separately for the CDI and enteric infection groups.

1. If there are no safety concerns and IMP is considered effective in the 100 mg group: The next step is to randomize 10 patients each who were not in the 100 mg group to the 200 mg or 50 mg group. The two groups will be treated in parallel. Treatment will be started in the CDI and enteric infection groups, respectively.
2. If there are no safety concerns and IMP is considered not effective in the 100 mg group:
   The next step is to allocate 10 patients not in the 100 mg group to the 200 mg group. Treatment will be started in the CDI and enteric infection groups, respectively. The DRC assesses the safety of the 200 mg group during the treatment period. When there are no safety concerns in the 200 mg group, the next step is to allocate 10 patients not in the 100 mg or 200 mg group to the 400 mg group. Treatment will be started in the CDI and enteric infection groups, respectively.

3.1.1 Outline of Trial Schedule

The investigator or subinvestigator will obtain written informed consent from patients, register the patients to Interactive Voice Response Services (IVRS) or Interactive Web Response Services (IWRS) to obtain patient numbers, perform screening examination within 2 days before administering IMPs, and assess patient eligibility based on the result of screening examination. Patients assessed as eligible will be allocated to dosing groups via IVRS or IWRS.

Patients in the CDI group will be treated with 50, 100, 200, or 400 mg as the daily dosages of OPS-2071 twice daily for 10 days, and patients in the enteric infection group for 7 days. For both the CDI and enteric infection groups, observation will be performed on Day 4 of dosing, and the day after the final dosing (Day 11 for the CDI group; Day 8 for the enteric infection group). Further, follow-up observation will be conducted on Day 24 and Day 38 for the CDI group and on Day 14 for the enteric infection group.

The trial period of each patient will start on the day of informed consent to the day when scheduled examinations are completed (on Day 38 for the CDI group and on Day 14 for the enteric infection group or at the end of withdrawal examination). This trial will make no distinction between inpatients and outpatients. Trial schedule is shown in Figure 3.1-2.

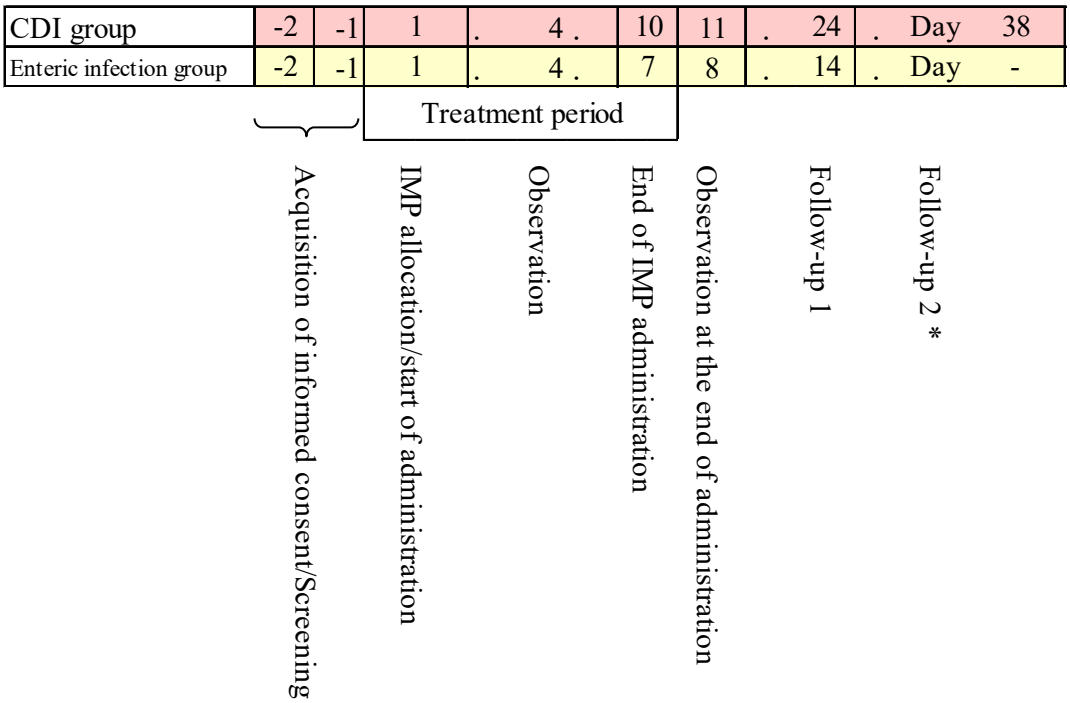

Figure 3.1-2 Trial Schedule

*Performed only in CDI group

3.2 Rationale for Trial Design

1) Design for dose increase/decrease

On the basis of the result of a non-clinical pharmacological study using a hamster CDAD model, 16 to 100 mg of OPS-2071 is expected to have therapeutic effect. Within the range of 16 to 100 mg/day, a dose of 100 mg/day is expected to show the most satisfactory effectiveness and at present 100 mg is considered likely to be the recommended human dose, and therefore the starting dose is set at 100 mg/day. (See Section "6.1 Dose, Regimen, and Treatment Period" for rationale of dose setting.)

If there are no safety concerns and efficacy is confirmed in the 100 mg group, safety and efficacy will be assessed in the 200 mg group. By confirming the safety and efficacy of OPS-2071 in the 50 mg group in parallel, the low dose cohort, at the same time, exploratory information on the recommended dose will be obtained. If efficacy at 100 mg/day is not confirmed and there are no safety concerns, the safety and efficacy of OPS-2071 will be assessed at 200 mg/day and then at 400 mg/day in a sequential ascending manner. Thus, the trial has a dose increase/decrease design.

2) Data Review Committee

This is an open-label trial, and in order to ensure objectivity in efficacy assessment, a DRC will be established as a third-party organization to assess the safety and efficacy at each dose based on a consistent perspective of specialists. The DRC will separately specify their procedures to be followed.

3) Treatment Period

For mild and moderate CDI, American College of Gastroenterology (ACG) 2013 guideline recommends a 10-day administration of VCM or MTZ. A 10-day comparison study between 400 mg/day fidaxomicin (hereafter, FDX) and 500 mg/day VCM confirmed that FDX has a clinical therapeutic effect for CDI comparable to VCM, and FDX is approved to treat CDI with the regimen of twice daily for 10 days. In reference to these, we selected 10 days for the treatment period.

The treatment period for enteric infection is usually 3 to 7 days, although it differs according to the causative pathogen, improvement of clinical symptoms, and type of antimicrobial drug. For an exploratory assessment on how OPS-2071 affects clinical response and microbiological outcome, the trial adopts a 7-day treatment period, regardless of the causative pathogen or the efficacy during the trial so as to confirm the safety and usefulness of OPS-2071.

In the result of the 7-day multiple dose study on OPS-2071 in healthy male adults, some intestinal bacteria decreased because of the repeated administration of OPS-2071.

However, regardless of the dose of OPS-2071, the intestinal bacterial flora returned to the baseline status by the time of follow-up after the end of treatment. There was no apparent effect on intestinal bacterial flora.

4) Follow-up 2 (CDI group)

The problem in the treatment for CDI is its high recurrence rate. CDI responds to the treatment with MTZ or VCM but recurs in approximately 15% to 30% cases. CDI repeatedly recurs, which may result in hospitalization and treatment for a long period. In this trial, for exploratory confirmation of the effect of OPS-2071 to prevent recurrence, presence/absence of recurrence will be confirmed 28 days after the end of treatment (FU2: Day 38) or at withdrawal in patients who achieved "clinical cure" at the end of treatment in the CDI group.

3.3 Endpoints

3.3.1 Safety Endpoints

Adverse events, clinical laboratory tests, vital signs (body temperature, blood pressure, and pulse rate), 12-lead ECG

3.3.2 Efficacy Endpoints

3.3.2.1 Microbiological Outcome

Microbiological outcome will be judged according to the assessment criteria shown in Table 3.3-1 and Table 3.3-2 for the bacterial strain isolated as the causative pathogen based on the data from the microbiological examination. For infection due to multiple causative pathogens, microbiological outcome will be assessed for each individual pathogen.

Table 3.3-1 Assessment Table for Microbiological Outcome

Time of Observation			Assessment of Microbiological Outcome
Baseline	**Day 4**	**End of Treatment**	
+	–	–	Excellent
+	+	–	Good
–			
+	Not applicable		
+	+	+	Poor
–			
+	–		
+	Not applicable		
Others			Unknown/ indeterminate

+: culture positive, −: culture negative
Not applicable: Bacterial culture test was not performed. The causative pathogen was not isolated or identified.

Table 3.3-2 Assessment Criteria for Microbiological Outcome

Assessment of Microbiological Outcome	Definition
Excellent	Pathogen is absent from bacterial culture obtained at Day 4 and at the end of treatment.
Good	Pathogen is still present in bacterial culture obtained at Day 4, and absent from bacterial culture at the end of treatment.
Poor	Pathogen is still present in bacterial culture obtained at the end of treatment.
Unknown/indeterminate	Applicable to none of the above but falls under the cases below for example. • Cultures are not available because of withdrawal from the study or other reasons. • Culture was obtained after the use of prohibited concomitant drugs/therapies. • Any other circumstance, which makes it impossible to define the microbiological response.

3.3.2.2 Toxin A/B Assay (*Clostridium Difficile* Infection Group Only)

Assess positive or negative for toxin A/B.

3.3.2.3 Clinical Response

The investigator or subinvestigator will refer to the information from patients (eg, patient diary), and assess clinical response at the time of observation (Day 4 and end of treatment) according to the assessment criteria shown in Table 3.3-3.

Table 3.3-3 Assessment Criteria for Clinical Response

Clinical Response Assessment	Definition
Clinical cure	Meeting all the following criteria within 24 hours before observation • No liquid or unformed stool • No abdominal symptoms and no other symptoms (fever, nausea, vomiting) • No need of medication or therapy to treat CDI or enteric infection
Clinical improvement	Fulfilling at least one of the following criteria within 24 hours before observation • Liquid or unformed stools ≤ 2 times/day • No abdominal symptoms and no other symptoms (fever, nausea, vomiting) • No need of medication or therapy to treat CDI or enteric infection
Clinical failure	Fulfilling none of the above-mentioned clinical improvement criteria. Patients who received medication or therapy to treat CDI or enteric infection prior to the time of observation are to be assessed as "clinical failure".

3.3.2.4 Recurrence of *Clostridium Difficile* Infection (*Clostridium Difficile* Infection Group Only)

The investigator or subinvestigator will assess the recurrence of CDI at FU2 or withdrawal according to the assessment criteria shown in Table 3.3-4 for patients who achieved "clinical cure" at the end of treatment.

Table 3.3-4 Assessment Criteria for Recurrence of *Clostridium Difficile* Infection

Assessment of Recurrence of CDI	Definition
Sustained cure	No recurrence
Recurrence	Meeting all the following criteria • New episode of diarrhea is occurred in the period from the end of treatment to FU2 or withdrawal (liquid or unformed stools ≥ 3 times/day within 24 hours) • Medication or therapy is required to treat CDI in the period from the end of treatment to FU2 or withdrawal • A positive toxin A/B assay at FU2 or withdrawal (positive for either or both toxins)

3.3.2.5 Time to Resolution of Diarrhea

The time from the start of dosing until the first formed stool (except in cases where liquid or unformed stools recurs) will be evaluated as time to resolution of diarrhea.

3.3.2.6 Improvement of Clinical Symptoms

Assess the improvement of clinical symptoms, ie, daily stool count, fecal properties, bloody stool, fever, abdominal pain, nausea, and vomiting.

3.3.2.7 Drug Sensitivity of Isolated Strain

Determine the minimum inhibitory concentration (MIC) of OPS-2071 for the isolated/identified *C. difficile* or the strain identified as the causative pathogen of enteric infection.

3.3.3 Pharmacokinetics Endpoints

3.3.3.1 Plasma Pharmacokinetics

- Plasma concentration of OPS-2071, C_{max}, t_{max}, C_{max}/D

3.4 Target Number of Patients

A total of 60 patients with 20 patients (10 patients each in CDI and enteric infection groups) in each dosing group

Enroll 10 patients in each dosing group of the CDI group to assess microbiological outcome. For the enteric infection group, enroll at least five patients in each dosing group to assess microbiological outcome with the sum of *Salmonella, Campylobacter*, and pathogenic *E. coli*. If a sufficient number of patients are not available for microbiological assessment after enrollment of 10 patients in each group, enroll more patients.

Patients available for microbiological assessment are those assessed as either "excellent," "good," or "poor" according to Table 3.3-2, which means that patients assessed as "Unknown/indeterminate" will not be included in microbiological assessment.

4 Investigational Medicinal Products

4.1 Test Product and Comparator

4.1.1 Test Product

Code Name	OPS-2071
Generic Name	None
Molecular Formula	$C_{20}H_{15}FN_4O_3$
Content and Formulation	A pale yellow film coated tablet containing 25, 50, or 100 mg as OPS-2071
Storage Conditions	To be stored in room temperature

4.2 Packaging and Labeling

4.2.1 Packaging

Blister pack sheets each containing ten 25, 50, or 100 mg IMP tablets are packaged in a box.

4.2.2 Contents of Label

The labels of the package box show the following information requested by regulatory authorities in individual countries: specification that the drug is for use in a clinical trial, code name, protocol number, lot number, expiration date, name and address of the sponsor, and other information as precautions etc.

5 Trial Population

5.1 Target Disease

Bacterial enteritis

5.2 Inclusion Criteria

Patients who meet all of the following criteria will be selected.

1. The patient is an Asian male or female of minimum legal age to provide consent (ie, 21 years for Singapore, 19 years for Korea, and 20 years for Japan at time of informed consent).
2. The patient provides written informed consent before the clinical trial is initiated.
3. The patient has distinctive symptoms and findings of bacterial enteritis (regardless of inpatient or outpatient).
4. The patient has bacterial enteritis with one or more of the following causative pathogens either proven or presumed:
   C. difficile, *Salmonella, Campylobacter*, pathogenic *E. coli*, and other bacteria estimated to cause bacterial enteritis (except for typhoid bacillus, *Salmonella paratyphi A*, enterohemorrhagic *E. coli*, *Shigella*, and *V. cholerae*)
5. The patient and his/her partner are willing to take contraceptive measures from initiation of IMPs to 4 weeks after administration of IMPs.

<u>CDI group:</u>

6. The patient satisfies both the following:
   - ✓ Liquid or unformed stools ≥ 3 times/day within 24 hours before the start of IMP administration
   - ✓ A positive clinical laboratory result in one of the following methods to confirm CDI within 48 hours before the start of IMP administration:
     - Toxin A/B assay (positive for either or both toxins A and B)
     - PCR (detection of toxin genes)
     - Colonoscopy (findings of pseudomembranous colitis)

<u>Enteric infection group:</u>

7. The patient satisfies all the following:
   - ✓ Liquid or unformed stools ≥ 3 times/day within 24 hours before the start of IMP administration
   - ✓ Any of the following clinical findings of enteric infection within 24 hours before the start of IMP administration.

- Either symptom of abdominal pain, nausea, or vomiting

✓ Negative toxin A/B assay or PCR within 48 hours before the start of IMP administration.

5.3 Exclusion Criteria

Patients who fall under any of the following exclusion criteria will be excluded from participation in the trial.

1. Intractable vomiting, inability to take oral medication, patients with feeding tubes
2. The patient has severe or progressive underlying disease or complication, making it difficult to ensure safety in the study or proper efficacy assessment.
3. Complication of chronic bowel diseases such as Crohn's disease, ulcerative colitis, irritable bowel syndrome, or colorectal cancer
4. History of stem cell transplantation, organ transplantation, or bone marrow transplantation (within 6 months before the screening examination)
5. History of total colectomy
6. Suspected viral enteritis
7. History of allergic conditions caused by quinolone antibacterials
8. The patient has a current diagnosis or history of convulsive disorders, such as convulsion and epilepsy
9. The patient has a severe hepatic dysfunction (eg, AST [GOT] or ALT [GPT] ≥ 3 times of the upper limit of normal at the study center, etc)
10. The patient has a severe cardiac dysfunction (eg, cardiac arrest, ischemic disease)
11. The patient has cardiac arrhythmia or congenital or sporadic long QTc syndrome. Or the patient is treated with a drug reported to prolong QTc interval (eg, amiodarone, sotalol, disopyramide, quinidine, procainamide, terfenadine, astemizole, cisapride, pimozide)
12. The patient has a moderate or severe renal dysfunction (eg, serum creatinine level ≥ 2 mg/dL or necessity of renal dialysis, etc)
13. The patient was treated with UGT1A1 inhibitors (atazanavir) within 2 days before the start of IMP administration.
14. Women with confirmed or suspected pregnancy or breast-feeding women

15. The patient was treated with another IMPs within 3 months before the screening examination

16. Patients judged to be ineligible by the investigator for any other reasons

CDI group:

17. The patient was treated with drugs and therapies to treat CDI within 24 hours before the start of IMP administration
18. The patient with severe and complex CDI who has any of the following at the screening examination.
    - Complicated disease: ileus, mental status changes, organ dysfunction (kidney and respiratory organs), septic shock, peritonitis, toxic megacolon, marked dehydration
    - Admission to intensive care unit due to CDI

Enteric infection group:

19. The patient was treated with other antibacterial agent by oral administration or injection within 7 days before the start of IMP administration.

20. Typhoid bacillus, *Salmonella paratyphi* A, enterohemorrhagic *E. coli, Shigella*, or *V. cholerae* was isolated/identified.

21. The patient has marked dehydration at the screening examination.

6 Trial Design

6.1 Dose, Regimen, and Treatment Period

Start with the 100 mg group, and the safety and efficacy during the treatment period will be assessed by the DRC. If the 100 mg has no safety concerns and the efficacy is assessed "effective," 10 patients each who were not in the 100 mg group will be randomized to the 200 mg or 50 mg group, and the two groups will be treated in parallel. If the 100 mg has no safety concerns and the efficacy is assessed "not effective," 10 patients who were not in the 100 mg group will be allocated to the 200 mg group as the next step. After the assessment by the DRC based on the safety of the 200 mg group during the treatment period, start dosing for the 400 mg group. Treatment will be started in the CDI and enteric infection groups, respectively.

Table 6.1-1 shows the dosage and formulations selected for each dosing group.

- Daily dosage: OPS-2071 50 mg, 100 mg, 200 mg, 400 mg
- Number/route of administration: twice daily, morning and evening/oral administration
- Take IMP after meal where possible with at least 10 hours of interval between dosings. Ensure to have evening meal before dosing on the previous day of blood collection for PK and to have breakfast before dosing on the day to perform blood collection for PK.
- Treatment period: 10 days for CDI group and 7 days for enteric infection group

  Note: Whether or not the symptoms improve during the treatment period, use all IMPs prescribed for the predetermined period.

Table 6.1-1 Dosage and Formulations for Each Dosing Group

Dosing Group	Dosage of OPS-2071	Formulation
50 mg group	50 mg/day	25 mg tablet × 1, twice daily
100 mg group	100 mg/day	50 mg tablet × 1, twice daily
200 mg group	200 mg/day	100 mg tablet × 1, twice daily
400 mg group	400 mg/day	100 mg tablet × 2, twice daily

[Rationale for dose and regimen]

It has been confirmed that there are no safety concerns up to 1200 mg in the phase 1 single dose study in healthy male adults and up to 1200 mg per day in the 7-day multiple dose study (twice daily after meals). The barrier function of membranes may be deteriorated because of infection in patients with enteritis, which may increase the absorption of the drug. OPS-2071, with favorable membrane permeability, is unlikely to

increase absorption in patients with enteritis relative to healthy adults.

In a non-clinical pharmacological study, therapeutic effect of OPS-2071, VCM, and FDX was assessed using the hamster CDAD model. Significant therapeutic effect was demonstrated by OPS-2071 at 0.04 to 1 mg/kg, and VCM and FDX at 1 to 5 mg/kg, showing that OPS-2071 has therapeutic effect comparable with or higher than FDX and VCM at doses 1/5 to 1/25 times lower than FDX and VCM. According to the calculation of clinical dose, 16 to 100 mg of OPS-2071 is expected to have therapeutic effect comparable to or higher than VCM (clinical dose 500 mg) and FDX (clinical dose 400 mg).

Based on the above, 100 mg/day, the clinically recommended dose at present from which the efficacy can be certainly expected among clinical dose ranging 16 to 100 mg/day is selected for the starting dose. If there are no safety concerns and the efficacy is confirmed in the 100 mg group, the safety and efficacy of OPS-2071 will be assessed at 50 mg/day, the low dose cohort, and at 200 mg/day, 2-fold higher than the clinically recommended dose. If the efficacy at 100 mg/day is not confirmed and there are no safety concerns, the safety and efficacy of OPS-2071 will be assessed at up to 400 mg/day in a sequential ascending manner. Thus, the trial has a dose increase/decrease design.

This trial is designed for twice-daily administration of OPS-2071, the same as in the phase 1 multiple-dose trial, with an interval of at least 10 hours between dosings.

It is demonstrated that OPS-2071 C_{max} is higher by 2.21 times and AUC_{0-t} by 2.04 times in administration after taking high fat meal relative to fasting. Administration after meal is desirable for the assessment of safety and PK at higher exposure. On the other hand, patients with severe symptoms of bacterial enteritis may not be able to take meals. Thus, the IMP should be administered after a meal where possible. However, for PK assessment in a steady state, the IMP must be administered after dinner on the day before blood sampling and after breakfast on the day of blood sampling to avoid any influence on PK assessment.

6.2 Prior and Concomitant Treatment

If a drug other than an IMP has been used during the period from the acquisition of consent to the end of the trial, the name of the drug, purpose of use, mode of administration, daily dose, route of administration, and dates of start and end of administration will be recorded in the source documents and case report form (CRF). For

a non-drug therapy, the name of therapy, purpose, and dates of start and end of that therapy treatment will be recorded in the source documents and CRF. For CDI group, if a drug or therapy from either item 7 in the list of prohibited concomitant drugs and therapies or item 1 in the list of restricted concomitant drugs and foods has been used during the period from 7 days before the start of IMP administration to the start day of the IMP administration, such will also be recorded in the source documents and CRF.

To avoid emergent risks such as the need for treatment of an AE, if it is necessary to treat a patient with a prohibited concomitant drug or therapy, the patient will be withdrawn from this trial according to Section 9.2, Criteria and Procedures for Withdrawal of Individual Patients.

6.2.1 Prohibited Concomitant Drugs and Therapies

The use of following drugs and therapies will be prohibited during the period from the start day of IMP administration to the end day of the trial for items 1 and 7, from screening to the end day of the trial for the following items 2 through 6, and from the start day of IMP administration to the end day of IMP administration for item 8.

1) For enteric infection group only: antibiotic agents/synthetic antibacterial agents (oral, injection, suppository)
2) For enteric infection group only: non-steroidal anti-inflammatory/analgesic drugs (oral, injection, suppository)*
3) For enteric infection group only: corticosteroid preparation (oral, injection, suppository)
4) For enteric infection group only: immunosuppressant medications (oral, injection, suppository)
5) For enteric infection group only: biological preparation (TNF inhibitor)
6) Antidiarrheal drugs, drugs to inhibit bowel motility
7) Other drugs and therapies to treat CDI and enteric infection (eg, fecal microbiota transplantation)
8) UGT1A1 inhibitors (atazanavir)

*: Use for purposes other than treating enteric infection is allowed. (Concomitant use is allowed for treating common cold during the trial period.)

6.2.2 Restricted Concomitant Drugs and Foods

Restricted concomitant drugs and foods among of drugs listed below, concomitant use of drugs listed in 1) in principle are prohibited from the start day of the IMP administration to the day of examination at the end of treatment if the drug is used for a purpose other than treatment of CDI.

However, in cases that drugs are used to treat an underlying disease at the time of screening and cannot be discontinued even after the start day of the IMP administration due to the necessity for continuous drug treatment, such concomitant use is allowed. Drugs listed in items 2) through 5) are allowed to be administered concomitantly as long as the drugs are used at the time of screening and the dose regimen is not changed during the period from screening until the day of examination at the end of treatment.

Drugs listed in item 6) are allowed to administer concomitantly under the following condition: the drugs are used at the time of screening, and the dose regimen is not changed in the period from screening to the end day of trial for CDI groups, or the period from screening to the end day of IMP administration for enteric infection group. If the food described in item 6) is taken, instruct the patient not to change the daily amount of consumption in the period from screening to the end day of the trial.

1) For CDI group only: antibiotic agents/synthetic antibacterial agents (oral, injection, suppository)
2) For CDI group only: non-steroidal anti-inflammatory/analgesic drugs (oral, injection, suppository)*
3) For CDI group only: corticosteroid preparation (oral, injection, suppository)
4) For CDI group only: immunosuppressant medications (oral, injection, suppository)
5) For CDI group only: Biological preparation (TNF inhibitor)
6) Probiotics

*: Use for purposes other than treating CDI is allowed. (Concomitant use is allowed for treating common cold during the trial period.)

[Rationale for establishing the prohibited and restricted concomitant drugs and therapies]

The above defined prohibited and restricted concomitant drugs and therapies were set considering the possible impact on the proper assessment of the efficacy and safety of IMPs. Topical use is allowed for 1) to 4) of the prohibited concomitant drugs.

Since OPS-2071 is metabolized by UGT1A1 and UGT1A9, concomitant use of No. 8) in the list of prohibited concomitant drugs may increase the plasma concentration of OPS-2071. To secure safety, concomitant use of inhibitors that may increase plasma concentrations of OPS-2071 is prohibited.

6.3 Method of Minimizing or Avoiding Bias

If efficacy is confirmed in the 100 mg group and there are no safety concerns, in the next step patients in each group (the CDI group and the enteric infection group) will be randomized to the 200 mg and 50 mg groups by stratified allocation using country (Japan, Korea, or Singapore) as the stratifying variable.

7 Trial Procedures

7.1 Schedule and Procedures

The investigator or subinvestigator will perform observations, examinations, and evaluations in accordance with Table 7-1, Schedule of Observations, Examinations, and Evaluations.

Table 7-1 Schedule of Observations, Examinations, and Evaluations

		Screening	Administration period			End of administration	FU1	FU2	Withdrawal
Observation day	CDI group	-	1	4	10	11	24	38	-
	Enteric infection group	-	1	4	7	8	14	-	-
Allowance range	CDI group / Enteric infection group	-2	0	+1	0	+1	±3	±3	+2
Acquisition of informed consent		X							
Inclusion/Exclusion criteria		X							
Patient background		X							
Height/Body weight		X							
Toxin A/B screening, PCR test, or colonoscopy [a]		X							
Clinical laboratory test (hematological test, biochemical test, urinalysis) [a]		X							
Pregnant test [b]		X							
IMP									
Assignment			X						
Administration			X	X	X				
Confirmation of compliance				X		X			
Safety assessment									
Physical examination		X		X		X	X	X	
Clinical laboratory test (hematological test, biochemical test, urinalysis)		X		X		X	X	X	X
Vital signs (blood pressure, pulse rate, body temperature)		X		X		X	X	X	X
12-lead ECG		X		X		X			X [d]
Adverse events		←	—	—	—	—	—	—	→
Concurrent drugs and combination therapies		←	—	—	—	—	—	—	→
Efficacy assessment of CDI group									
Bacterial culture test		X		X		X		X	X
Toxin A/B test		X		X		X		X	X
Drug sensitivity of isolated strain		X				X		X	
Clinical response				X		X			X [d]
Recurrence of CDI								X	X [c]
Confirmation of patient's clinical symptom		X		X		X	X	X	X
Patient diary			←	—	—	—	—	—	→
Efficacy assessment of enteric infection group									
Bacterial culture test		X		X		X			X [d]
Drug sensitivity of isolated strain		X				X			
Clinical response				X		X			X [d]
Confirmation of patient's clinical symptom		X		X		X	X		X
Patient diary			←	—	—	—	→	-----	---->
Pharmacokinetics assessment									
Plasma drug concentration				X [e]					

[a] To be performed at the trial site to confirm the eligibility, separately from the test for efficacy and safety assessment. Colonoscopy will be performed when necessary only in the CDI group.

[b] Pregnancy test will be performed only in women with childbearing potential

[c] To be performed only in the case of withdrawal after the end of administration.

[d] To be performed only in the case of withdrawal during administration period.

[e] Inpatient: 1 (± 15 minutes), 2 (± 15 minutes), and 4 hours (± 30 minutes) after morning administration.
Outpatient: once within 12 hours after morning administration but before evening administration

7.1.1 Acquisition of Informed Consent

The investigator or subinvestigator will obtain written consent directly from patients before any screening examinations can take place. After obtaining informed consent, the investigator, subinvestigator, or a trial associate will register each patient in either the IVRS or the IWRS to assign a patient number. The patient number (three-digit trial site number + S + five-digit sequential serial number at the trial site) and the date of written informed consent will be recorded on the source documents and CRF. The investigator or subinvestigator will confirm the content of enrollment, and perform screening examination.

7.1.2 Screening Examination: Allowance − 2 Days

The investigator or subinvestigator will perform the following screening examinations, and select patients who meet the inclusion criteria and do not fall under any of the exclusion criteria.

Virus quick test, toxin A/B assay, PCR, colonoscopy, and clinical laboratory tests (hematology test, biochemistry test, and urinalysis) will be performed by the method specified by the trial site. Eligibility will be assessed based on the test result at the trial site. The latest data from colonoscopy performed within 48 hours before administration of IMP can be used for screening, even if they are obtained before informed consent.

For bacterial culture test, toxin A/B assay, PCR, and drug sensitivity test on isolated strains at screening, stool specimens will be collected within 48 hours before the administration of IMP (The latest data performed within 48 hours for CDI group or 24 hours for Enteric infection group before administration of IMP can be used for screening, even if they are obtained before informed consent). Stool specimens and specimens for clinical laboratory tests collected at the screening examination will also be tested by the laboratory for microbiological examination (hereafter, microbiological laboratory), and the central laboratory for clinical laboratory tests (hereafter, central laboratory).

- Height, body weight
- Confirmation of patients' clinical symptoms (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)

- Virus quick test (if considered necessary by the investigator or subinvestigator)*
- Toxin A/B assay*
- PCR or colonoscopy: CDI group only*
- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Toxin A/B assay: CDI group only
  - Drug sensitivity test on isolated strains
- Physical examination
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)*
- hCG pregnancy test
  The pregnancy test will be performed for female patients at the trial site. A pregnancy test will not be required for patients who have undergone bilateral oophorectomy or hysterectomy, or have not experienced menses for at least 12 consecutive months for whatever other medical reasons.
- Vital signs (blood pressure, pulse rate, and body temperature)
- 12-lead ECG
- Confirmation of concomitant drugs and therapies

*Use the test result at the trial site to assess eligibility at the time of screening.

7.1.3 Patient Information

At the time of obtaining informed consent or at the screening examination, the investigator or subinvestigator will check and record the following patient information in the source documents and CRF.

- Disease group (CDI group, enteric infection group)
- Date of informed consent acquisition
- Patient number
- Patient background (sex, date of birth, country where the trial will be conducted, race)
- Inpatient/outpatient (at the time of informed consent)
- Medical history and concomitant disease
- Clinical condition of patients (daily stool count, fecal properties, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Diagnostic procedures of CDI (toxin A/B test, PCR, colonoscopy): CDI group only
- History of CDI: CDI group only
- Number of CDI episodes and date of the latest diagnosis of CDI if there is a history of CDI

7.1.4 Allocation of Patients to Dosing Groups

The investigator or subinvestigator will verify that the patient meets the inclusion criteria and does not fall under any of the exclusion criteria based on the results of the screening examination, and register the information of patients in either the IVRS or the IWRS. The investigator or subinvestigator will obtain the allocated dosage information of IMPs from IVRS or IWRS and administer the allocated dose of IMPs to patients. The investigator or subinvestigator will record the information on the following dose group to the source documents and CRF.

- Dosage groups (50 mg group, 100 mg group, 200 mg group, and 400 mg group)

7.1.5 Examination and Evaluation for *Clostridium Difficile* Infection Group

Collect stool specimens to be used for bacterial culture test, toxin A/B assay, and drug sensitivity test on isolated strains within 24 hours before each test.

7.1.5.1 Day 1

- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.5.2 Day 4: Allowance + 1 Day

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Toxin A/B assay
- Confirmation of IMP compliance
- Confirmation of patients' clinical symptoms on Days 1 to 3 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- Blood sampling for measuring plasma concentration
  - Inpatient: 1 (± 15 minutes), 2 (± 15 minutes), and 4 hours (± 30 minutes) after morning administration
  - Outpatient: once within 12 hours after morning administration but before evening administration.
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, and body temperature)

- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.5.3 Day 11 (End of Treatment): Allowance + 1 Day

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Toxin A/B assay
  - Drug sensitivity test on isolated strains
- Confirmation of IMP compliance
- Confirmation of patients' clinical symptoms on Days 4 to 10 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.5.4 Day 24 (at Follow-up 1): Allowance ± 3 Days

- Confirmation of patients' clinical symptoms on Days 11 to 23 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.5.5 Day 38 (at Follow-up 2): Allowance ± 3 Days

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Toxin A/B assay
  - Drug sensitivity test on isolated strains

- Confirmation of patients' clinical symptoms on Days 24 to 37 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of recurrence of CDI
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.6 Examination and Evaluation for Enteric Infection Group

Collect stool specimens for bacterial culture test and drug sensitivity test on isolated strains within 24 hours before each test.

7.1.6.1 Day 1

- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.6.2 Day 4: Allowance + 1 Day

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
- Confirmation of IMP compliance
- Confirmation of patients' clinical symptoms on Days 1 to 3 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- Blood sampling for measuring plasma concentration
  - Inpatient: 1 (± 15 minutes), 2 (± 15 minutes), and 4 hours (± 30 minutes) after morning administration
  - Outpatient: once within 12 hours after morning administration but before evening administration.
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.6.3 Day 8 (End of Treatment): Allowance + 1 Day

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Drug sensitivity test on isolated strains
- Confirmation of IMP compliance
- Confirmation of patients' clinical symptoms on Days 4 to 7 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.6.4 Day 14 (at Follow-up 1): Allowance ± 3 Days

- Confirmation of patients' clinical symptoms on Days 8 to 13 (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.7 Time of Withdrawal and Withdrawal Examination: Allowance ± 2 Days

The investigator or subinvestigator will perform the following examination, observation, and assessments for patients who withdrew from the trial within 2 days after the day when withdrawal is considered necessary. If the patient refuses to undergo any examinations at the time of withdrawal, or if the investigator or subinvestigator judges that any examinations at the time of withdrawal cannot be performed due to an emergency or other circumstances (eg, SAE or recurrence of CDI), of the examination items specified for the time of withdrawal, only those items that can be performed will be performed. Results of tests and assessment, the date of measurements and assessment,

and the date of blood/urine/stool sampling will be recorded in the source records and CRF.

7.1.7.1 *Clostridium Difficile* Infection Group

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test
  - Toxin A/B assay
- Confirmation of IMP compliance until withdrawal
- Confirmation of patients' clinical symptoms until withdrawal (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response: to be performed only in case of withdrawal during the IMP administration period
- Assessment of recurrence of CDI: to be performed only in case of withdrawal after completing the IMP administration
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- 12-lead ECG: to be performed only in case of withdrawal during the IMP administration period
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination
- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.7.2 Enteric Infection Group

- Collection of stool specimens (the following items will be tested by the microbiological laboratory)
  - Bacterial culture test: to be performed only in case of withdrawal during the IMP administration period
- Confirmation of IMP compliance until withdrawal
- Confirmation of patients' clinical symptoms until withdrawal (daily stool count, stool symptoms, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Assessment of clinical response: to be performed only in case of withdrawal during the IMP administration period
- Clinical laboratory tests (hematology test, biochemistry test, and urinalysis)
- 12-lead ECG: to be performed only in case of withdrawal during the IMP administration period
- Vital signs (blood pressure, pulse rate, and body temperature)
- Physical examination

- Confirmation of adverse events
- Confirmation of concomitant drugs and therapies

7.1.8 Information at Conclusion (Discontinuation) of the Trial

The investigator or subinvestigator will register the necessary items in IVRS or IWRS at the time of conclusion (discontinuation) of the trial for each patient.

7.1.9 Follow-up Investigation

If an AE has not resolved by FU1, FU2, or withdrawal, additional examinations of the AE will be performed in accordance with Section 8.4, Follow-up Investigation of Adverse Events.

7.2 Method of Evaluation

7.2.1 Safety Evaluation

7.2.1.1 Height, Body Weight

Measure height and body weight according to the procedures stipulated by the trial site, and record the date of measurements and results in the source documents and CRF.

7.2.1.2 Physical Examination

The investigator or subinvestigator will examine the patients, record the physical findings in source documents, and evaluate any clinically significant events as AEs, and record the AEs in CRF. In case if abnormal findings are not judged as AEs, enter the reason in source documents.

7.2.1.3 Clinical Laboratory Tests (Hematology Test, Biochemistry Test, and Urinalysis)

At screening, the following clinical laboratory test items will be measured at each trial site according to the procedures stipulated by each trial site. Record the date and result of examination in source documents, not in CRF.

The sample collected at the screening examination will be dispensed in two containers and tested by the trial site and central laboratory.

The central laboratory will determine the following clinical laboratory test items at all the prescheduled time points (including screening examination). Use the container provided by the central laboratory when sampling. The investigator or subinvestigator will record the sampling date in the source documents and CRF, and review the report on clinical

laboratory tests performed by the central laboratory, date, and sign the report. In case if abnormal values are not judged as AEs, enter the reason in source documents.

Follow the separately stipulated procedures for collection, handling, storage, and shipment method of specimens.

Table 7.2-1 Clinical Laboratory Test Items

Hematology test	Hemoglobin (Hb), hematocrit (Hct), red blood cell count (RBC), white blood cell count (WBC), differential leukocyte count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), platelets (PLT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)
Biochemistry test	Aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), total protein (TP), albumin (ALB), total bilirubin (T-BIL), uric acid (UA), urea nitrogen (UN), creatinine (Cr), serum glucose (GLU), triglyceride (TG), cholesterol (TC), γ-glutamyltransferase (γ-GTP), Na, K, Cl, Ca, C-reactive protein (CRP)
Urinalysis	pH, protein, glucose, ketone, bilirubin, urobilinogen, blood, nitrite, leucocytes, and specific gravity

7.2.1.4 Vital Signs (Blood Pressure, Pulse Rate, and Body Temperature)

Systolic and diastolic blood pressures, pulse rate, and body temperature will be measured at rest according to the procedures specified by the trial site, and the date of evaluation and the result will be recorded in the source documents and CRF. In case if abnormal values are not judged as AEs, enter the reason in source documents.

7.2.1.5 12-Lead Electrocardiogram

Measure 12-lead ECG parameters according to the procedures of the trial site with paper feed speed at 25 mm/sec.

The investigator or subinvestigator will record the date of measurement and presence/absence of abnormality in the source documents and CRF. In case if abnormal findings are not judged as AEs, enter the reason in source documents.

The sponsor will retrieve copies of all the ECG charts.

7.2.1.6 Confirmation of Investigational Medicinal Product Compliance Status and Food

The investigator or subinvestigator will distribute patient diary to have them record the information on the compliance with IMP and food intake during the administration period. Based on the information recorded in the patient diary, the investigator or subinvestigator will record in the CRF the patient's IMP compliance during the administration period,

whether or not the IMP was taken after meals, and the time of day that the IMP was taken on the day of blood sampling for PK assessment.

7.2.2 Efficacy Evaluation

7.2.2.1 Microbiological Outcome

1) Timing

CDI group: screening, Day 4, Day 11 (end of treatment), at FU2 (Day 38), at the time of withdrawal

Enteric infection group: screening, Day 4, Day 8 (end of treatment), at the time of withdrawal

2) Method of Examination

Collect approximately 3 g of stool from the patient using the stool sample container provided by the microbiological laboratory. The containers will be labeled with the study number, patient number, and sampling day. Collect stool specimens within 48 hours prior to IMP administration for the screening time point and within 24 hours before the observation day for other time points. Store stool samples at approximately 4°C until a designated courier collects them.

The microbiological laboratory will follow the predetermined procedures and perform the culture and identification by centralized measurement. The isolated strains will be stored in order to enable exploratory investigation in the future on the bacteriological and genetic characteristics other than drug sensitivity of the isolated strains.

If the result of measurement requires notification in line with the Infectious Diseases Control Law, each trial site will submit notification in accordance with relevant laws, regulations, and notifications of each country.

3) Method of Evaluation

The investigator or subinvestigator will identify the causative pathogen on the basis of the microbiological examination results from the microbiological laboratory and record sampling date, the causative pathogen, and pathogen culture results in source documents and CRF. If there is more than one possible causative pathogen, identify all causative pathogens and record the pathogen culture results by causative pathogen in source documents and CRF. The sponsor will collect the microbiological examination results from the microbiological laboratory and judge microbiological outcome by bacterial strain isolated as the causative pathogen based on the change in microbiological examination results according to the assessment criteria shown in Table 3.3-1 and Table

3.3-2. For infection due to multiple causative pathogens, microbiological outcome will be assessed for each individual pathogen.

7.2.2.2 Toxin A/B Assay

1) Timing

CDI group: screening, Day 4, Day 11 (end of treatment), at FU2 (Day 38), at the time of withdrawal

2) Method of Examination

At screening, perform toxin A/B assay according to the procedures specified by the trial site for assessing eligibility on the basis of the test result at the trial site (when PCR and colonoscopy were performed, toxin A/B assay at the trial site is not indispensable). Record the sampling date and the test result in source documents.

At all scheduled time points, including screening, toxin A/B assay will be centrally performed by the microbiological laboratory using the stool specimens for the assessment of microbiological outcome. The microbiological laboratory will perform toxin A/B assay and report the result to the investigator or subinvestigator. (Note: For the enteric infection group, in order to assess patient eligibility, the toxin A/B assay or PCR at screening is also to be performed at the trial site according to the procedure specified by the trial site. Record the sampling date and the test result in source documents.)

3) Method of Evaluation

The investigator or subinvestigator will record the sampling date in source documents and CRF. The sponsor will collect the toxin A/B assay result only of the CDI group tested at the microbiological laboratory. Use the result of toxin A/B assay from the microbiological laboratory.

7.2.2.3 Clinical Response

1) Timing

CDI group: Day 4, Day 11 (end of treatment), at the time of withdrawal

Enteric infection group: Day 4, Day 8 (end of treatment), at the time of withdrawal

2) Method of Evaluation

The investigator or subinvestigator will refer to the information from patients (eg, patient diary), and assess clinical response at the time of observation (Day 4 and end of treatment) according to the assessment criteria shown in Table 3.3-3. The investigator or subinvestigator will record the assessment date and result in source documents and CRF.

7.2.2.4 Recurrence of *Clostridium Difficile* Infection (*Clostridium Difficile* Infection Group Only)

1) Timing

CDI group: at FU2 (Day 38), at the time of withdrawal

2) Method of Confirmation

The investigator or subinvestigator will assess the recurrence of CDI at FU2 or withdrawal according to the assessment criteria shown in Table 3.3-3 for patients who achieved "clinical cure" at the end of treatment. The investigator or subinvestigator will record the assessment date and result in source documents and CRF.

7.2.2.5 Time to Resolution of Diarrhea

The sponsor will evaluate the time from the start of dosing until the first formed stool (except in cases where liquid or unformed stools recur), as the time to resolution of diarrhea on the basis of the record of fecal properties in CRF obtained according to the procedure of 7.2.2.6.

7.2.2.6 Improvement of Clinical Symptoms

1) Timing

CDI group: Day 4, Day 11 (end of treatment), at FU2 (Day 38), at the time of withdrawal

Enteric infection group: Day 4, Day 8 (end of treatment), at the time of withdrawal

2) Method

Distribute patient diary to patients and have the patients to record daily stool count, fecal properties, presence/absence of bloody stool, highest body temperature, and presence/absence of abdominal pain, nausea, and vomiting. If the patient is not able to record the information in the patient diary on his/her own, medical personnel or the patient's family will record the information in the diary on behalf of the patient.

3) Method of Evaluation

The investigator or subinvestigator will record the information on the patient diary in CRF. The sponsor will evaluate the change in improvement of clinical symptoms by comparing the record of daily stool count, fecal properties, bloody stool, fever, abdominal pain, nausea, and vomiting described in CRF with those at pre-treatment.

7.2.2.7 Drug Sensitivity of Isolated Strain

1) Timing

CDI group: screening, Day 11 (end of treatment), FU2 (Day 38)

Enteric infection group: screening, Day 8 (end of treatment)

2) Method of Examination

The microbiological laboratory will determine the MIC of OPS-2071 for the isolated/identified *C. difficile* or the strain identified as the causative pathogen of enteric infection. On the basis of the procedures specified by the microbiological laboratory, assess drug sensitivity.

3) Method of Evaluation

The investigator or subinvestigator will record the sampling date in the source documents and CRF. The sponsor will collect the result of drug sensitivity test on isolated strains determined in the microbiological laboratory.

7.2.3 Pharmacokinetic Evaluation

7.2.3.1 Plasma Pharmacokinetics

1) Timing

Inpatient: 1 (± 15 minutes), 2 (± 15 minutes), and 4 (± 30 minutes) hours after morning administration on Day 4

Outpatient: Once within 12 hours after morning administration but before evening administration on Day 4

2) Method

A volume of approximately 5 mL whole blood will be collected into a lithium heparin-containing blood collection tube. Samples will be immediately placed on crushed ice and centrifuged (2000 g for 15 minutes at 4°C) within 1 hour of collection to obtain plasma. Two aliquots of 700 µL plasma will be transferred to two polypropylene tubes and stored approximately at −80°C. The plasma samples will be labeled with the following information: study number, patient number, sampling day and time point, and aliquot type (primary or back-up).

Record sampling day and time point, and date and time of latest medication in the source documents and CRF.

3) Shipment of Samples

Samples will be shipped on dry ice by a designated courier to laboratory performing measurement of drug concentrations (hereafter, bioanalytical laboratory). Back-up samples will be separately sent to the bioanalytical laboratory.

4) Method of Determination

Plasma concentrations of OPS-2071 will be determined using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method by the bioanalytical laboratory.

The bioanalytical laboratory will submit a report on the result of drug concentration measurements to the sponsor. The report submitted to the sponsor is considered as the source documents. Record in the CRF will not be required. Remaining samples after measurement of drug concentrations will be stored approximately at −80°C in the bioanalytical laboratory until the completion of clinical study report. After the completion of clinical study report, the bioanalytical laboratory will promptly discard the remaining samples and record it.

7.3 Measures to Be Taken for Patients Visiting or Planning to Visit Other Hospitals or Departments

At the time of obtaining informed consent, the investigator or subinvestigator will confirm whether or not the patient is receiving treatment at another hospital or department. If the patient is receiving treatment at another hospital or department, the investigator or subinvestigator will inform the attending physician of that hospital or department about the patient's participation in the clinical trial and the IMP being used, with the patient's consent. The investigator or subinvestigator will also obtain and record in source documents and the CRF information on the treatment that the patient is receiving at the other hospital or department (name of disease being treated and information on the type of treatment or measures being implemented) and judge whether or not the patient should participate in the trial.

If a patient visits another hospital or department during the trial period, the investigator or subinvestigator will inform the attending physician of that hospital or department about the patient's participation in the clinical trial and the IMP being used, with the patient's consent. The investigator or subinvestigator will also obtain and record in source documents and the CRF information on the treatment that the patient receives at the other hospital or department (name of disease treated and information on the type of treatment or measures implemented) and judge whether or not the patient should continue to participate in the trial.

8 Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP[notes)]

For this trial, OPS-2071 is regarded as the IMP, and to secure the safety of patients, AEs occurring from the time of signing the ICF to the start of OPS-2071 administration are included in the definition of AEs in addition to the definition given by ICH.

If an event, symptom, or sign existing at the time of acquisition of informed consent worsens after acquisition of informed consent, or if an AE occurring between the acquisition of informed consent and start of OPS-2071 administration worsens after administration of OPS-2071, the exacerbation will be treated as a new AE.

8.1.2 Serious Adverse Event

An SAE is defined as an AE corresponding to one of the events listed in the following list.

The seriousness of AEs occurring during the period from consent to the start of IMP administration will also be judged.

1. An event resulting in death
2. A life-threatening event

   The term “life-threatening” refers to an event in which the patient was at a risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, had it been more severe.
3. An event requiring in-patient hospitalization or prolongation of existing hospitalization for treatment

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notes) "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" Notification No.227 of the Examination Division, issued by the Examination Division Chief, the Pharmaceutical Affairs Bureau as of 20 Mar 1995 (ICH E2A)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

4. An event resulting in persistent or significant disability/incapacity
5. An event causing a congenital anomaly/birth defect
6. A major event resulting in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in 1) to 5) above. Examples of such events are intensive treatment in an emergency room for bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Explanation of hospitalization for treatment of an SAE:

Hospitalization for treatment means that the patient must be hospitalized at a medical institution for treatment of an AE, typically for at least one night. This includes hospitalization for treatment of the AE in which no particular medical procedures are carried out (rest therapy). However, it does not include hospitalization for undergoing tests or treatment for an underlying disease or complication that has not worsened since the patient's entry into the trial, hospitalization for social reasons or convenience not intended for treatment of the AE, or hospitalization for treatment or tests scheduled prior to participation in the trial.

8.2 Response to Occurrence of Adverse Events

8.2.1 Actions to Be Taken for Patients

The investigator or subinvestigator will provide adequate medical care for all clinically significant, trial-related AEs throughout the period of patient participation in the trial as well as thereafter. If treatment for an AE is necessary, the patient will be informed of this.

8.2.2 Expedited Reporting of Serious Adverse Events

(1) Serious Adverse Events Requiring Expedited Reporting

1) Any SAEs occurring during the trial period regardless of causal relationship with the IMP
2) SAEs occurring during the follow-up period (see Section 8.4, Follow-up Investigation of Adverse Events), if a follow-up investigation is performed, for which a causal relationship with the IMP cannot be ruled out, or AEs that become serious during the follow-up period for which a causal relationship with the IMP cannot be ruled out
3) Among SAEs occurring after completion of the trial (after the follow-up investigation, if a follow-up investigation is performed) and reported by patients

to the investigator or subinvestigator, those for which the investigator or subinvestigator cannot rule out a causal relationship with the IMP

(2) Procedures for Expedited Reporting

Countries/Regions other than Japan:

1) When an AE falling under any of the above items (1) 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) orally or by telephone, e-mail, or facsimile (refer to Annex, Emergency Contact).

The notification to the sponsor must include at least the following information.

Patient's date of birth, sex, starting date of IMP, information of AE, causal relationship with the IMP

2) The investigator or subinvestigator will then promptly submit a detailed report on any SAEs occurring after the start of IMP administration to the head of the trial site and the sponsor within the period specified by the applicable regional requirements after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours) by e-mail or facsimile, and additional reporting will be performed if necessary.
3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the IRB to prepare additional information (autopsy report, terminal care report, or other required information) on a reported SAE, the investigator or subinvestigator will respond to the request.

Japan:

1) When an AE falling under any of the above items (1) 1) to 3) occurs, the investigator or subinvestigator will notify the sponsor promptly after becoming aware of the event (within 24 hours, in principle) orally or by telephone, e-mail, or facsimile (refer to Annex, Emergency Contact).

The notification to the sponsor must include at least the following information.

Patient's date of birth, sex, starting date of IMP, information of AE, causal relationship with the IMP

2) The investigator or subinvestigator will then promptly submit a detailed report on any SAEs occurring after the start of IMP administration to the head of the trial site and the sponsor within 10 days after becoming aware of them using the report form of the trial site or sponsor. Any additional information will also be promptly relayed to the sponsor (within 24 hours) by telephone, e-mail, or facsimile, and additional reporting will be performed if necessary.
3) When the investigator or subinvestigator is requested by the sponsor, the head of the trial site, or the IRB to prepare additional information (autopsy report, terminal care report, or other required information) on a reported SAE, the investigator or subinvestigator will respond to the request.

8.2.3 Expedited Reporting of Non-serious Adverse Events Resulting in Discontinuation of Investigational Medicinal Product Administration

When a non-serious AE occurs and the investigator or subinvestigator judges that IMP administration should be discontinued, the investigator or subinvestigator will notify the sponsor within 3 working days in principle after their judgment by telephone, e-mail or facsimile (refer to Annex, Emergency Contact).

8.3 Assessment of Adverse Events

The investigator or subinvestigator will assess AEs for the following items.

8.3.1 Terms for Adverse Events

If the disease responsible for an AE can be specified, the name of the diagnosed disease will be recorded and not the individual symptoms.

8.3.2 Date and Onset and Recovery

(1) Date of onset:

The date of onset of an AE or date of confirmation of an AE will be recorded in the source documents and CRF. If an event, symptom, or sign existing at the time of acquisition of informed consent worsens, "the date of exacerbation" will be recorded as "date of onset of AE." Also, if an AE occurring between the acquisition of informed consent and start of IMP administration worsens after administration of the IMP, the exacerbation will be recorded as a new AE with "the date of exacerbation" recorded as "date of onset of exacerbated AE."

(2) Date of recovery:

The date of recovery of an AE or date of confirmation of recovery of an AE will be recorded.

8.3.3 Severity

Severity of AEs will be classified into the following three categories.

1) Mild: Discomfort noticed, but no disruption to daily activity
2) Moderate: Discomfort sufficient to limit or affect normal daily activity
3) Severe: Inability to work or perform normal daily activity

8.3.4 Causal Relationship With Investigational Medicinal Product

The causal relationship between the IMP and AEs occurring after the start of IMP administration will be judged according to the following two categories.

1) Relationship is ruled out

For reasons such as the following, the possibility of a relationship between occurrence of an AE and OPS-2071 is not reasonably conceivable.

a) The event can be assumed to be caused by an underlying disease, complication(s) (a current condition(s) if the trial patient is a healthy adult patient), or previous disease(s).
b) The event can be assumed to be associated with age, sex, or some other demographic factor.
c) A temporal relationship between IMP administration and occurrence of the AE is unlikely.
   Example: An AE that occurs after a considerable lapse of time from the conclusion of IMP administration.
d) Considering the time course of the AE and IMP administration, a relationship with the IMP is unlikely.
   Example: Despite continuous administration of the IMP, the AE disappeared spontaneously without any treatment (except cases in which it is judged that the patient became habituated to the IMP during continued administration).
e) The event can be assumed to be caused by some other drug besides the IMP
f) The event can be assumed to be incidental (such as an accident or incidental disease).
   Example: "femoral bone fracture" occurring in a traffic accident.
g) A relationship with the IMP can be ruled out for other reasons based on medical consideration.

2) Relationship cannot be ruled out

For reasons such as the following, the possibility of a relationship between occurrence of an AE and the IMP is reasonably conceivable.

a) A relationship is predictable from the pharmacological and toxicological effects of the IMP.
   Examples: Occurrence of "pancytopenia" when effects on the hematopoietic system have been observed in non-clinical studies, or the occurrence of "dehydration" when the drug has a diuretic effect.
b) The event has been observed in previous nonclinical trials and/or clinical trials.
   Example: An AE with high incidences in phase 1 trials.
c) A temporal relationship is suspected between IMP administration and onset of the AE.
   Example: "Allergic dermatitis" occurring several days after the start of IMP administration.

d) A relationship is suspected based on the outcome of an adverse event after discontinuation or dose reduction of the IMP.
Example: Prompt disappearance of "nausea" after discontinuation of the IMP.

e) A relationship with the IMP cannot be ruled out for other reasons based on medical consideration.

8.3.5 Actions to Be Taken Regarding Investigational Medicinal Product Administration

Actions to be taken regarding IMP administration following the occurrence of an AE after initiation of IMP administration will be selected from among the following.

- No change
- Discontinuation of IMP administration
- Unknown
- Not applicable

8.3.6 Actions to Be Taken for Adverse Events

The performance of medical treatments (medications and/or other treatments) for AEs and details of the treatments will be entered in the source documents and CRF.

8.3.7 Outcome

The outcome of an AE will be selected from the following six categories (one only).

If the patient died, the date of death will be recorded in the CRF; if the patient's condition was recovering/resolving, not recovered/not resolved, or unknown, the date of outcome confirmation will be recorded in the CRF.

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown (for some reason, a follow-up investigation could not be performed even once)

8.4 Follow-up Investigation of Adverse Events

The term "recovered" used below means that a patient who had an AE prior to the start of IMP administration returned to his or her original condition, or a patient who had an AE

after the start of IMP administration returned to his or her condition before the start of IMP administration.

1) If an AE has not resolved by the day of trial completion or the day of withdrawal, the investigator or subinvestigator will explain to the patient the need for follow-up investigation after the end of the trial and will request the patient's cooperation. The investigator or subinvestigator will conduct a follow-up investigation within 4 weeks after the end of the trial and record information regarding the AE in the source documents. If an AE is not resolved by the day of trial completion or the day of withdrawal, the investigator or subinvestigator will record the outcome in CRF as "recovering/resolving," "not recovered/not resolved," or as otherwise appropriate.
2) If an AE has not resolved by the day of the follow-up investigation and a causal relationship with the IMP cannot be ruled out, follow-up investigation will be continued until the event resolves or becomes stable and information regarding the AE will be recorded in the patient's source documents. If a causal relationship between the AE and the IMP can be ruled out, no further follow-up will be made beyond the day of the initial follow-up investigation.
3) If, between the day of trial completion or day of withdrawal and the day of the follow-up investigation, a new SAE for which a causal relationship with the IMP cannot be ruled out occurs, or if an AE is not resolved by the day of trial completion or the day of withdrawal and for which a causal relationship with the IMP cannot be ruled out becomes serious, follow-up investigation will be conducted until the AE resolves or becomes stable, and information regarding the AE will be recorded in the source documents.
4) If a serious AE for which a relationship with the IMP cannot be ruled out is discovered after the day of trial completion or the day of withdrawal, or after the day of the initial follow-up investigation (if performed), follow-up investigation will be conducted until the AE resolves or becomes stable or until follow-up of the patient becomes impossible and information regarding the AE will be recorded in the source documents.

8.5 Pregnancy

If women of childbearing potential or male patients whose partners are capable of becoming pregnant participate in the trial, the investigator or subinvestigator will attend to the following.

- Information on reproductive and developmental toxicity of the IMP
- Drug interactions between the IMP and hormonal contraceptives
- Information regarding pregnancy in the ICF
- Explanation of contraceptive methods
- Reporting and follow-up of cases of pregnancy

8.5.1 Guidance to Patients Including Contraceptive Methods

1) Before the start of the trial, the investigator or subinvestigator will explain to the patients the importance of using contraception and the risks associated with pregnancy of a female patient or partner of a male patient and, after patients have read the written information for patients and understood it, the investigator or subinvestigator will have patients sign the ICF.
2) If women of childbearing potential or male patients whose partners are capable of becoming pregnant wish to participate in the trial, the investigator or subinvestigator will instruct them to practice contraception during the period specified in the trial protocol.
3) Contraceptive methods must be highly effective, ie, have a failure rate of less than 1%. Contraceptive methods include condoms, pills, pessaries, intrauteric device (IUD), implantable contraceptive devices, spermicide, vasectomy, and tubal ligation. However, if a female patient or male patient's partner is without question unable to become pregnant (ie, has undergone bilateral ovariectomy or hysterectomy or has not experienced menses for at least 12 consecutive months for whatever other medical reasons, or the male patient/partner has undergone bilateral orchidectomy), or if the patient and his/her partner remain abstinent, use of contraception is unnecessary.
4) The investigator or subinvestigator will instruct the patients that if the contraceptive measures fail and evidence of pregnancy of the female patient or male patient's partner such as delay in menstruation is observed, this should be promptly reported to the investigator or subinvestigator.

8.5.2 Actions to Be Taken by the Investigator or Subinvestigator When Pregnancy Is Suspected

If the investigator or subinvestigator or a patient suspects that the patient has become pregnant before initiation of IMP administration, initiation of IMP administration will be withheld and a pregnancy test will be performed. If the test result is positive, the trial patient will be withdrawn without receiving IMP administration. If a pregnancy is suspected after initiation of IMP administration, IMP administration will be discontinued (refer to section 9.2 Criteria and Procedures for Withdrawal of Individual Patients).

8.5.3 Actions to Be Taken by the Investigator or Subinvestigator When a Patient Is Discovered to Be Pregnant

When a female patient is found to be pregnant, the investigator or subinvestigator will withdraw the patient from the trial and perform follow-up investigation until delivery or end of pregnancy, and report this in writing to the sponsor.

After discontinuation of IMP administration, the investigator or subinvestigator will perform the withdrawal examinations and follow-up observation stipulated in the protocol, in so far as they do not affect the pregnancy.

8.5.4 Expedited Reporting of Pregnancy

When a female patient or a partner of a male patient is found to be pregnant during the trial, the investigator or subinvestigator will promptly report this to the sponsor orally or by telephone or e-mail (refer to Annex, Emergency Contact). The investigator or subinvestigator will then provide any additional information requested by the sponsor.

8.5.5 Follow-up Investigation of Pregnancy

If a female patient becomes pregnant, the investigator or subinvestigator will perform follow-up investigation of the pregnancy up to delivery or the end of pregnancy and report the results of follow-up in writing to the sponsor. When a patient or patient's partner has delivered, it is best that the neonate be observed for at least 6 months after delivery.

9 Withdrawal of Individual Patients From the Trial

Any patient may discontinue participation in the trial at any time without medical disadvantage. The investigator or subinvestigator may withdraw a patient from the trial at any time if it is considered necessary for medical treatment of that patient.

9.1 Screen Failure

If a patient is a screen failure, the following information should be recorded in the source documents and CRF:

date of investigation (the start date of the screening examination), date of informed consent acquisition, date of birth, sex, country where the trial was conducted, race, and reason for screen failure.

9.2 Criteria and Procedures for Withdrawal of Individual Patients

In any of the events listed below, the investigator or subinvestigator will discontinue IMP administration, perform the tests to be performed at withdrawal stipulated in Section 7.1, Schedule and Procedures of the Trial, and promptly inform the sponsor of the withdrawal (Annex, Emergency Contact). The investigator or subinvestigator will record the date and reason for withdrawal in the source documents and CRF.

If withdrawal is necessitated by problems with safety, such as the occurrence of an AE or aggravation of the underlying disease, the investigator or subinvestigator will promptly take appropriate measures and perform follow-up if necessary (refer to Section 8.4 Follow-up Investigation of Adverse Events).

1. If the patient wishes to withdraw
2. If it is found after the start of the trial that the patient did not meet all the inclusion criteria or fell under any of the exclusion criteria
3. If a drug or therapy from either item 1 or item 7 in the list of prohibited concomitant drugs and therapies is used or judged to be required
4. If an AE making continuation of trial participation difficult occurs
5. If the female patient is found to be pregnant
6. If symptoms of the primary disease exacerbate, and the investigator or subinvestigator judges that it is not appropriate to continue the trial participation
7. If it becomes impossible to comply with the protocol for any another reason or if the investigator or subinvestigator judges that it is necessary to discontinue the trial participation for any another reason

9.3 Follow-up Investigation of Patients Who Do not Visit the Trial Site

When a patient stops visiting the trial site for unknown reasons, the investigator or subinvestigator will promptly contact the patient or patient's family by phone or other means to check for AEs and to ask the patient to visit.

1) When the patient has visited

A withdrawal examination will be performed (see Section 7.1.7).

2) When the patient has not visited

The following items will be recorded in the source documents.

- The date of investigation
- The method of investigation
- Whether or not the patient was contacted
- The reason why the patient does not (or cannot) visit the trial site
- Occurrence or non-occurrence of AEs. If an AE has occurred, record name of the event, date of onset and of recovery, severity, relationship to the IMP, measures taken regarding IMP administration, and treatment of AE, outcome.
- If follow-up investigation is impossible, record the reason why.

10 Collection of Case Report Form Data and Specification of Source Data

10.1 Collection of Case Report Form Data

1) Electronic Data Capture (EDC) will be used in the trial.
2) Patient data will be entered directly into the database from the trial site via a Web browser. These data collected by EDC will constitute the CRF. The results of clinical laboratory tests, microbiological examination, toxin A/B test, drug sensitivity test, and drug concentration measurement with centralized measurement will be directly transferred from respective laboratories to the sponsor.
3) For every patient who provides consent to participate in the trial, a CRF will be created on an EDC data entry screen that conforms to the items of CRF data collection described in the trial protocol.
4) The investigator, subinvestigator, or trial associate will entry the data according to the manual provided by the sponsor. If source documents are available and the objectivity of the data can be ensured, then the data may be recorded in a CRF by a trial associate.
5) When entering data into CRFs from the trial site, a predetermined check will be automatically performed. The investigator, subinvestigator, or a trial associate will make corrections as necessary.
6) The sponsor will verify CRFs in comparison to source documents and conduct data reviews. If additional query is necessary, the sponsor will issue an intra-system query and the investigator, subinvestigator, or a trial associate will perform data correction or provide a response to the sponsor's query as necessary.
7) A history of all revisions made after the initial data entry is saved on the server will be automatically recorded within the system (date and time of revision, name of person making revision, pre- and post-revision data, reason for revision, date and time of query, name of person issuing query, details of query, etc).
8) After completion of all CRF data entry and confirmation that the content is correct and complete, including confirmation of the audit trail, the investigator will attach an electronic signature.
9) Details concerning data collection will be specified in a separate manual prepared in advance.

10.2 Source Documents

1) Source documents are defined as those documents that are the source of data transcribed into CRFs as trial results.

Medical records and other records (eg, medical records, nursing records, prescription records), patient diary, registration verification forms, patient

screening list, ICFs, clinical laboratory test and other measurement reports, ECG charts, IMP management records, and other documents

2) The investigator or the trial site will retain all trial-related documents and records except CRFs in such a manner that enables the sponsor or the regulatory authority to have direct access to the documents and records.
3) After completion of the trial, the sponsor will retain the original CRFs on CD-ROM or some other appropriate electronic medium and the investigator or the trial site will retain copies.
4) The original ICFs will be retained according to the method specified by each trial site.
5) The bioanalytical laboratory will retain the original reports on the results of drug concentration measurement and documents related to the measurement.

10.3 Case Report Form Items to Be Treated as Source Data

Not applicable

10.4 Data to Be Collected by the Sponsor

1) CRFs (data following acquisition of informed consent)
2) Copies of reports on results of drug concentration measurement
3) Results of clinical laboratory tests, microbiological examination, toxin A/B test, and drug sensitivity test
4) Copies of 12-lead ECG charts

11 Statistical Analysis

Details of the planned statistical analysis will be presented in the Statistical Analysis Plan (SAP).

11.1 Statistical Analysis Sets

11.1.1 Safety Analysis Set

The safety analysis set (SS) includes all patients who received the IMP at least once and from whom data on at least one safety endpoint was obtained after the start of IMP administration.

11.1.2 Full Analysis Set

The full analysis set (FAS) includes all patients who received the IMP at least once and from whom data on at least one efficacy endpoint was obtained after the start of IMP administration.

11.1.3 Microbiological per Protocol Set

The microbiological per protocol set (MPPS) comprises those patients in the FAS for whom the causative pathogen is identified and for whom microbiological outcome is assessed as “Excellent”, “Good”, or “Poor” according to the Assessment Criteria of Microbiological Outcome (Table 3.3-2), excluding patients for whom microbiological outcome is assessed as “Unknown/indeterminate”.

11.1.4 Clinical per Protocol Set

The clinical per protocol set (CPPS) comprises those patients in the FAS for whom all scheduled examinations at all specified observation time points up until the end of treatment or withdrawal have been performed.

11.1.5 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKS) comprises patients in whom plasma drug concentration was measured at least once.

11.2 Handling of Data

Baseline values are defined as the last non-missing values at screening or before IMP administration. No imputation will be performed for missing data. If a problematic patient or data are encountered, the sponsor will decide how to handle the patient or data, with advice from the expert, as necessary.

11.3 Analysis Items and Method

11.3.1 Safety Analysis

1) Endpoints

Adverse events, clinical laboratory tests, vital signs (body temperature, blood pressure and pulse rate), 12-lead ECG

2) Analysis Set

SS

3) Analysis Method

Analysis will be performed for the entire study population and by disease group and by dose. AEs that occurred after the start of treatment with IMP will be tabulated using MedDRA by System Organ Class (SOC) and Preferred Term (PT), with PT substituted for verbatim terms. The number of patients who experienced the following events as well as and the incidence will be tabulated: adverse events, adverse drug reactions, serious adverse events, adverse events leading to withdrawal, and adverse events by severity.

Clinical laboratory tests and vital signs (body temperature, blood pressure, and pulse rate) will be analyzed by using frequency distributions and descriptive statistics.

Regarding 12-lead ECG, a shift table will be prepared for judgment on abnormality at each time point before and after IMP administration.

11.3.2 Demographic and Other Baseline Characteristics

1) Endpoints

Country, race, age, sex, height, body weight, BMI, inpatient/outpatient, previous medical history, complications, diagnostic method for CDI (CDI group only), history of CDI (CDI group only), concomitant drugs, and clinical symptoms

2) Analysis Sets

SS, FAS, MPPS, and CPPS

3) Analysis Method

Analysis will be performed by disease group and by dose. Frequency distribution or descriptive statistics for each variable will be calculated according to the nature of the data (continuous or discrete).

11.3.3 Treatment Period

1) Endpoints

Number of days when IMP was administered, total dose, total number of administrations

2) Analysis Sets

SS, FAS, and CPPS

3) Analysis Method

Analysis will be performed by disease group and by dose. Descriptive statistics will be calculated for number of days when IMP was administered, total dose, and total number of administrations.

11.3.4 Efficacy Analysis

11.3.4.1 Microbiological Outcome

1) Endpoints

Bacteria elimination rate

2) Analysis Set

MPPS

3) Analysis Method

Analysis will be performed by disease group and by dose, and by MIC values of OPS-2071 against the causative strain. The number and proportion of patients by causative strain, a list of causative strain by patient, and a list of the result based on bacterial culture at each evaluation time point will be prepared.

Concerning microbiological outcome by causative strain, bacteria elimination rate and its 95% CI will be calculated. The bacteria elimination rate is the proportion of causative strains assessed as either "excellent" or "good" except for those assessed as "Unknown/indeterminate". In case of infection of multiple bacteria, assess the microbiological outcome of each infections agent.

$$\text{Bacterial elimination rate (\%)} = \frac{\text{"Excellent"} + \text{"Good"}}{\text{Number of patients assessed for microbiological outcome}} \times 100$$

11.3.4.2 Toxin A/B Assay (*Clostridium Difficile* Infection Group Only)

1) Endpoint

Toxin positive rate

2) Analysis Sets

MPPS (CDI group only)

3) Analysis Method

Analysis will be performed by dose. Based on the result of Toxin A/B assay performed by the microbiological laboratory, prepare a list on the result of positive/negative judgment in the Toxin A/B assay at each evaluation time point.

Calculate Toxin A/B positive rate and its 95% CI. Toxin A/B positive rate is the proportion of the number of Toxin positive patients against the number of evaluable patients in CDI group.

$$\text{Toxin positive rate (\%)} = \frac{\text{Number of toxin positive patients}}{\text{Number of patients assessed for microbiological outcome}} \times 100$$

11.3.4.3 Clinical Response

1) Endpoint

Clinical response

2) Analysis Set

CPPS

3) Analysis Method

Analysis will be performed by disease group and by dose, by causative strain, and by MIC values of OPS-2071 against the causative strain. Calculate frequency distribution at each evaluation time point and prepare a list of causative strains by patients.

Calculate the clinical response rate and 95% CI at each evaluation time point. Clinical response rate will be calculated as the proportion of the patients judged as “clinical cure” or “clinical improvement” against evaluable patients except for those with missing data.

$$\text{Clinical response rate (\%)} = \frac{\text{Patients judged as “clinical cure” + “clinical improvement”}}{\text{Evaluable patients except for those with missing data}} \times 100$$

11.3.4.4 Recurrence of *Clostridium Difficile* Infection (*Clostridium Difficile* Infection Group Only)

1) Endpoint

CDI recurrence rate

2) Analysis Set

CPPS

3) Analysis Method

Analysis will be performed by dose in the proportion of patients judged as “clinical cure” at the end of treatment in CPPS.

Prepare the list of result of judgment on CDI recurrence at FU2 or withdrawal.

Calculate CDI recurrence rate at FU2 or withdrawal. CDI recurrence rate is the proportion of the patients judged as “recurrent” against evaluable patients except for those with missing data.

$$\text{Recurrence rate (\%)} = \frac{\text{Patients judged as “recurrent”}}{\text{Evaluable patients except for those with missing data}} \times 100$$

11.3.4.5 Time to Resolution of Diarrhea

1) Endpoint

Days from the start of dosing to first formed stool

2) Analysis Set

CPPS

3) Analysis Method

Analysis will be performed by disease group and by dose. Calculate descriptive statistics of days from the start of dosing to first formed stool (except cases where liquid or unformed stools recurs).

11.3.4.6 Improvement of Clinical Symptoms

1) Endpoints

Stool count, fecal properties, blood stool, highest body temperature, abdominal pain, nausea, vomiting

2) Analysis Set

CPPS

3) Analysis Method

Analysis will be performed by disease group and by dose. Frequency distribution or descriptive statistics for each variable will be calculated at each evaluation time point according to the nature of the data (continuous or discrete).

11.3.4.7 Drug Sensitivity of Isolated Strain

1) Endpoint

MIC values

2) Analysis Set

C. difficile isolated/identified or the strain identified as enteric infection agents by the microbiological laboratory

3) Analysis Method

Prepare a list of kinds and number of strains of the identified causative strain. Determine MIC value of OPS-2071 for the causative strain at screening and at the end of treatment (and FU2 [Day 38] for CDI group) to prepare a list.

11.3.5 Pharmacokinetics Endpoints

11.3.5.1 Plasma Pharmacokinetics

1) Endpoints

    1) Plasma OPS-2071 concentration
    2) OPS-2071 pharmacokinetic parameters (C_{max}, t_{max} and C_{max}/D)

2) Analysis Set

PKS

3) Analysis Method

1) Calculation method

- Plasma concentration below lower limit of quantification (0.200 μg/L) will be considered as 0 (μg/L), and used for calculation of pharmacokinetic parameters and descriptive statistics.
- C_{max}, t_{max} and C_{max}/D will be calculated for inpatients.
- The highest concentration among all blood sampling time points will be adopted as C_{max}.
- C_{max}/D will be calculated by dividing C_{max} by dose.
- t_{max} will be calculated using actual time after administration.

2) Statistical Analysis Method

For inpatients, calculate descriptive statistics by dose and by blood sampling time point for plasma drug concentration, and by dose for pharmacokinetic parameters.

Descriptive statistics include number of patients, arithmetic mean, standard deviation (SD), coefficient of variation, minimum, median, and maximum for plasma drug concentration, and number of patients, arithmetic mean, SD, coefficient of variation, geometric mean, minimum, median, and maximum for pharmacokinetic parameters.

11.4 Procedures for Reporting Deviations From the Original Statistical Analysis Plan

For deviations from the analysis method stipulated by the protocol, the detail and reason will be entered in SAP or pharmacokinetics analysis plan and clinical trial report.

11.5 Rationale for Target Number of Patients

There will be three dosing groups of OPS-2071, ie, 100, 50, 200 mg, or 100, 200, 400 mg. For each dosing group, 10 patients in CDI group will be secured for assessing microbiological outcome. For enteric infection group, at least five patients will be secured for assessing microbiological outcome as a total of *Salmonella, Campylobacter*, and pathogenic *E. coli*. It is assumed that bacteria will be detected almost 100% in CDI patients, and 50% in patients with enteric infection. Based on the assumption, the target number of patients in each dosing group was selected: 10 CDI patients and 10 patients with enteric infection. The target sample sizes were selected for investigation of the safety, efficacy, and pharmacokinetics of OPS-2071 while limiting the exposure to a minimum number of patients. The target number of patients is not selected by statistical methods, but selected as an evaluable sample size.

For both the groups, the priority is to enroll patients for whom microbiological assessment is possible. If a sufficient number of patients for whom microbiological

assessment is possible is not attained after enrolling the target number of patients (10 patients), additional patients will be enrolled.

12 Quality Control and Quality Assurance for the Trial

To ensure the quality of the trial, trial sites, contract research organizations, microbiological laboratory, bioanalytical laboratory, central laboratory, and the sponsor will perform quality control for the trial according to their respective Standard Operating Procedures.

The audit division of the sponsor company will carry out audits within the company and, as necessary, at the trial site and contract research organizations or organizations entrusted to perform related activities, and check whether quality control of the trial is appropriately performed according to the Standard Operating Procedures.

13 General Items of Caution Pertaining to the Trial

13.1 Ethics and Good Clinical Practice Compliance

This trial must be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki, the ICH-GCP Guideline, all applicable regional regulatory requirements, and the protocol.

13.2 Institutional Review Board

Each trial site will seek approval from an IRB/IEC according to regional regulations. The IRB/IEC will investigate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling CRFs, the investigator, subinvestigator, and their staff must take measures to ensure adequate care in protecting patient privacy.

13.3 Patient Consent

13.3.1 Procedures for Obtaining Consent

1) Prior to the start of the screening examination, the investigator or subinvestigator will fully explain the matters listed in Section 13.3.2 to each patient who will be included in the trial, using the ICF, and give the ICF to the patient. The patient will be provided sufficient time to make a decision regarding participation. After confirming that the patient has properly understood the explanation, the investigator or subinvestigator will obtain written voluntary consent for participation in the trial from the patient.
2) The investigator or subinvestigator who has provided the explanation and the patient will each put their printed name and personal seal or signature on the ICF, and write the date on which they sign or stamp the form. If a trial associate has provided a supplemental explanation of the trial, he/she will also put his/her printed name and personal seal or signature on the form and write the date on which he/she signs or stamps the form.
3) The original of the ICF that was signed or stamped and dated will be retained by the investigator or subinvestigator according to the regulations of the trial site. A copy of the original ICF will be given to the patient.
4) After obtaining informed consent from a patient, the investigator or subinvestigator will write the date of informed consent acquisition and patient number in the documents for enrolled patients.
5) If new information becomes available that may influence the willingness of the patient to continue participation in the trial, the investigator or subinvestigator will promptly inform the patient of such information and confirm the willingness of the patient to continue participation in the trial, and then record the result in the source documents. If there is guidance regarding the recording of re-consent stipulated by the trial site, it will be followed.

13.3.2 Contents of Informed Consent Form

1) An explanation that the trial involves research
2) The type of IRB that reviews the appropriateness of trial conduct, matters to be reviewed by the IRB, and other relevant descriptions of the activity of the IRB
3) The purpose of the trial
4) The trial procedures (including research-related aspects of the trial, inclusion criteria for patients, and, if random allocation is performed, the probability of randomization to each treatment arm)
5) The expected duration of the patient's participation in the trial.
6) The planned number of patients involved in the trial
7) The foreseeable IMP-related physical and mental benefits (if no benefits are expected, this should be indicated) as well as risks or inconveniences to the patient
8) The existence of alternative treatments for the patient, and their important potential benefits and risks
9) The treatment and compensation available to the patient in the event of trial-related injury to health
10) That the patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which he or she would otherwise be entitled
11) An explanation that the patient will be informed in a timely manner if information becomes available that may be relevant to his or her willingness to continue participation in the trial
12) The circumstances or reasons under which the patient's participation in the trial should be terminated
13) An explanation that the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the patient's original medical records without violating the confidentiality of the patient, and that by signing the ICF, the patient is authorizing such access
14) An explanation that if the results of the trial are published, the patient's identity will remain confidential
15) The anticipated expenses to the patient for participating in the trial
16) The anticipated payment, if any, to the patient for participating in the trial (agreements on payment, etc)
17) The name, position, and contact address of the investigator or subinvestigator
18) The persons at the trial site to contact for further information regarding the trial and the rights of trial patients, and whom to contact in the event of trial-related injury to health
19) Matters to be observed by patients

13.3.3 Amendments to the Informed Consent Form

If revision of the ICF becomes necessary due to newly obtained information, the investigator will promptly revise the ICF to include that information after conferring with the sponsor.

The investigator, when revising the ICF, will report this to the head of the trial site and submit the revised document to the IRB designated by the trial site to obtain its approval.

If new information becomes available that may influence the willingness of patients to continue participation in the trial and the ICF has been revised according to the new information, the investigator or subinvestigator will again obtain patients' written informed consent to continue participation in the trial.

13.4 Management of Investigational Medicinal Products

1) The sponsor will issue the "Procedures for Handling of Investigational Medicinal Products" to the persons designated by the trial site.
2) The sponsor will issue the "Document on Investigational Medicinal Products Storage Conditions" to the investigator or subinvestigator, trial associates, and IMP manager.
3) The sponsor will deliver the IMPs to the trial site following the start of the trial period contracted with the trial site.
4) The IMP manager will manage OPS-2071 appropriately according to the "Procedures for Handling of Investigational Medicinal Products" prepared by the sponsor.
5) The IMP manager will prepare and retain the "Record of Management and Storage of Investigational Medicinal Products."

13.5 Direct Access to Source Documents and Monitoring

13.5.1 Direct Access to Source Documents

The head of the trial site and the investigator must accept monitoring and audits to be performed by the sponsor and inspection by the IRB and Japanese and foreign regulatory authorities, and must make source documents and all other trial-related records available to these agencies for direct access (including copying). Patients authorize such direct access by signing the written ICF.

13.5.2 Monitoring

The sponsor bears responsibility for ethical, legal, and scientific conduct of the trial. The sponsor will perform monitoring according to the "Procedures for monitoring" specified for this trial. Monitoring includes periodic visits, phone calls, or other contact with the

trial site for the provision, obtaining, and recording of updated trial-related information by monitors designated by the sponsor.

The sponsor may entrust a portion of monitoring activity to a contract research organization.

13.5.3 Documents to Be Retained by the Investigator

The trial-related documents to be retained by the investigator will be kept in the investigator's file, which will be managed by the investigator.

13.6 Deviations From and Changes or Amendments to the Trial Protocol

13.6.1 Deviations From the Trial Protocol

1) The investigator or subinvestigator should not deviate from the protocol or change it without prior written agreement between the investigator and the sponsor and the written approval of the IRB of the trial site based on prior review.
2) In unavoidable medical circumstances such as the need to avoid emergent risk to a patient, the investigator or subinvestigator may deviate from the protocol or change the protocol without prior written agreement from the sponsor and prior approval of the IRB. In such an event, the investigator will promptly submit a document providing the details of and reason for the deviation or change to the sponsor and the head of the trial site and obtain approval from the IRB. In addition, the investigator will obtain written approval from the head of the trial site and the written agreement of the sponsor by way of the head of the trial site.
3) The investigator or subinvestigator will record all deviations from the protocol.

13.6.2 Amendments to the Trial Protocol

1) The investigator will promptly submit to the sponsor, the head of the trial site, and the IRB by way of the head of the trial site, a written report on any changes in the trial that may significantly affect conduct of the trial or increase risks to the trial patients.
2) The sponsor, after conferring with the investigator, will agree with the investigator on the contents of the revised protocol and compliance with the revised protocol.
3) The sponsor will promptly submit the revised protocol to the head of the trial site.

13.7 Archiving of Records

1) The trial site will retain all the trial-related documents and records for the period of time indicated in a) or b) below, whichever is longer. However, if the sponsor requires a longer period of archiving, the head of the trial site will consult with the sponsor on the period and procedures of record retention.
   a) The date an Application for Approval of a Pharmaceutical Product for OPS-2071 is granted; or, if the head of the trial site receives notification from the sponsor that development has been terminated or that results of the trial will not be submitted with the approval application, the date 3 years after receipt of such notification.
   b) The date 3 years after termination or completion of the trial.
2) The investigator will retain the trial-related documents and records as directed by the head of the trial site.
3) If it becomes no longer necessary to retain the trial-related documents and records at the trial site, the sponsor will notify the head of the trial site.

13.8 Termination or Interruption of Part or All of the Trial

13.8.1 Termination or Interruption of the Trial at Individual Trial Sites

1) In the event of termination or interruption of the trial, the investigator will promptly provide the head of the trial site with written notification and a written explanation of the details of the termination or interruption of the trial.
2) When the sponsor has been informed by the head of a trial site that the investigator has terminated or interrupted the trial, the sponsor will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site.

13.8.2 Termination or Interruption of the Entire Trial

1) When the entire trial is to be terminated or interrupted by the sponsor, the sponsor will promptly provide the heads of all trial sites involved in the trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination or interruption of the trial.
2) When the investigator has received notification of termination or interruption of the entire trial by the sponsor from the head of the trial site, the investigator will obtain a detailed written explanation of the termination or interruption of the trial from the head of the trial site, promptly notify the trial patients currently receiving IMP administration, and take necessary measures such as switching to appropriate alternative treatment(s).
3) When development of OPS-2071 is terminated by the sponsor, the sponsor will promptly provide the heads and the investigators of all trial sites involved in the

trial and the regulatory authority with written notification and a detailed written explanation of the reason for the termination of development.

13.9 Protection of Patients' Personal Information

In completion and handling of CRFs, the investigator and subinvestigator will take adequate care to ensure protection of the personal information of patients. Individual patients will be identified by patient numbers. The sponsor will not provide the information obtained to any third party.

13.10 Compensation for Injury to Health

Trial patients will be compensated for health damages according to the criteria established by the trial sponsor with reference to applicable regional regulatory requirement(s) for this trial will comprise medical costs and medical benefits.

13.11 Agreement on Publication

The sponsor may use the findings obtained from this trial for purposes such as an "Application for Approval of a Pharmaceutical Product" for OPS-2071.

When the results of this trial and relevant data are to be published in scientific journals or at academic meetings, the investigator will obtain prior written approval from the sponsor.

14 Trial Administrative Structure

The administrative structure of this trial is shown in Annex.

15 Scheduled Duration of the Trial

01 Jul 2015 through 31 Mar 2017

16 References

1 World Health Organization. The top 10 causes of death [updated May 2014]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/

2 Chan M, WHO Director-General. Combat drug resistance: no action today means no cure tomorrow.[updated 2011 Apr; cited 2013 Jan]. Available from: http://www.who.int/mediacentre/news/statements/2011/whd_20110407/en/index.html.

3 Tribble DR, Sanders JW, Pang LW, Mason C, Pitarangsi C, Baqar S, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. Clin Infect Dis. February 1, 2007; 44(3):338-46.

4 Cody AJ, Clarke L, Bowler IC, Dingle KE. Ciprofloxacin-resistant campylobacteriosis in the UK. Lancet. December 11, 2010; 376(9757):1987.

5 Hookman P, Barkin JS. Clostridium difficile associated infection, diarrhea and colitis. World J Gastroenterol. April 7, 2009; 15(13):1554-80.

6 Asha NJ, Tompkins D, Wilcox MH. Comparative analysis of prevalence, risk factors, and molecular epidemiology of antibiotic-associated diarrhea due to Clostridium difficile, Clostridium perfringens, and Staphylococcus aureus. J Clin Microbiol. August 2006; 44(8):2785-91.

7 Pepin J, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: A cohort study during an epidemic in Quebec. Clin Infect Dis. 2005; 41:1254-60.

8 Ananthakrishnan AN. Clostridium difficile infection: epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol. 2011; 8:17-26.

9 Saima Aslam, Richard J Hamill, Daniel M Musher; Treatment of Clostridium difficile- associated disease: old therapies and new strategies; Lancet Infect Dis 2005; 5: 549–57.

10 Oka D. Antibacterial spectrum of OPS-2071. Otsuka Study No. 034501, Otsuka Report No. 028199, 2012.

11 Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108:478-98.