STATISTICAL ANALYSIS PLAN

An Open-label, Multicenter Clinical Trial to Assess the Safety and Efficacy of Three Different Doses of OPS-2071 in Patients with Bacterial Enteritis

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An Open-label, Multicenter Clinical Trial to Assess the Safety and Efficacy of Three Different Doses of OPS-2071 in Patients with Bacterial Enteritis

Statistical Analysis Plan

PAREXEL Project Number: 222307

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LIST OF ABBREVIATIONS

AE	Adverse Event
BER	Bacterial Elimination Rate
BMI	Body Mass Index
CDAD	*Clostridium difficile*-associated diarrhea
CDI	*Clostridium difficile* infection
CI	Confidence Interval
CPFX	Ciprofloxacin
CPPS	Clinical Per Protocol Set
CRF	Case Report Form
CRR	Clinical Response Rate
DRC	Data Review Committee
EDC	Electronic Data Capture
FAS	Full Analysis Set
FU	Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
RR	Recurrence Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SS	Safety Set
TEAE	Treatment-Emergent Adverse Event
TPR	Toxin Positive Rate

1 INTRODUCTION

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 *Clostridium Difficile* Infection

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.

This SAP is based upon the following study documents:

- Study Protocol, Version 3.0 (July 15, 2016)
- electronic Case Report Form (CRF), Version 4.0 (May 16, 2016)

2 STUDY 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 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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.

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.

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

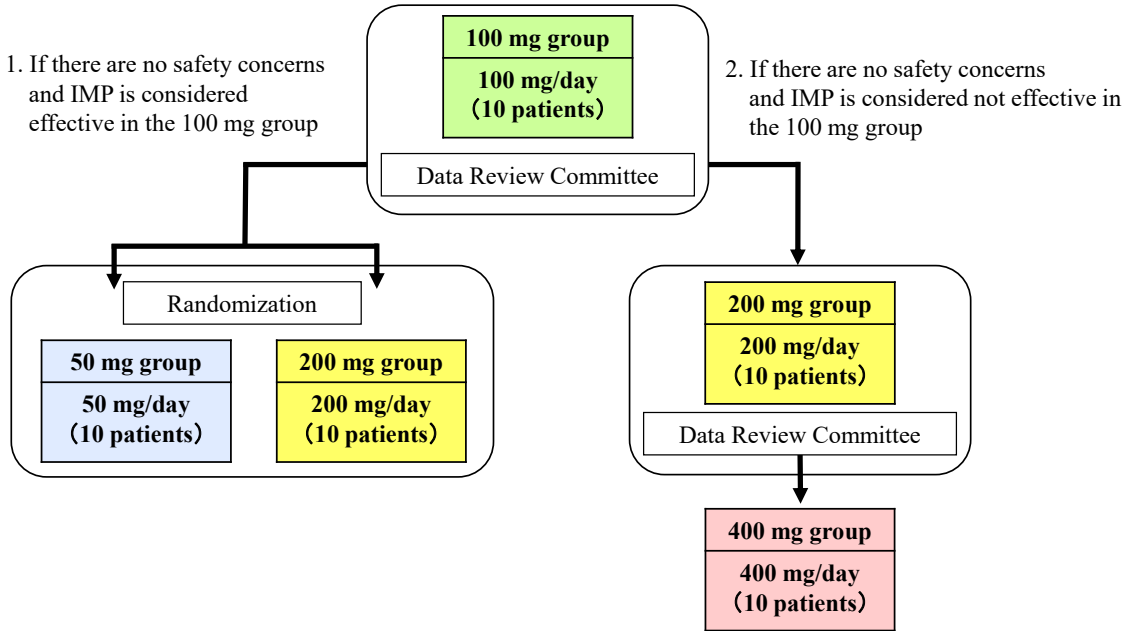

Figure 3.1-1 Outline of Trial Design

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

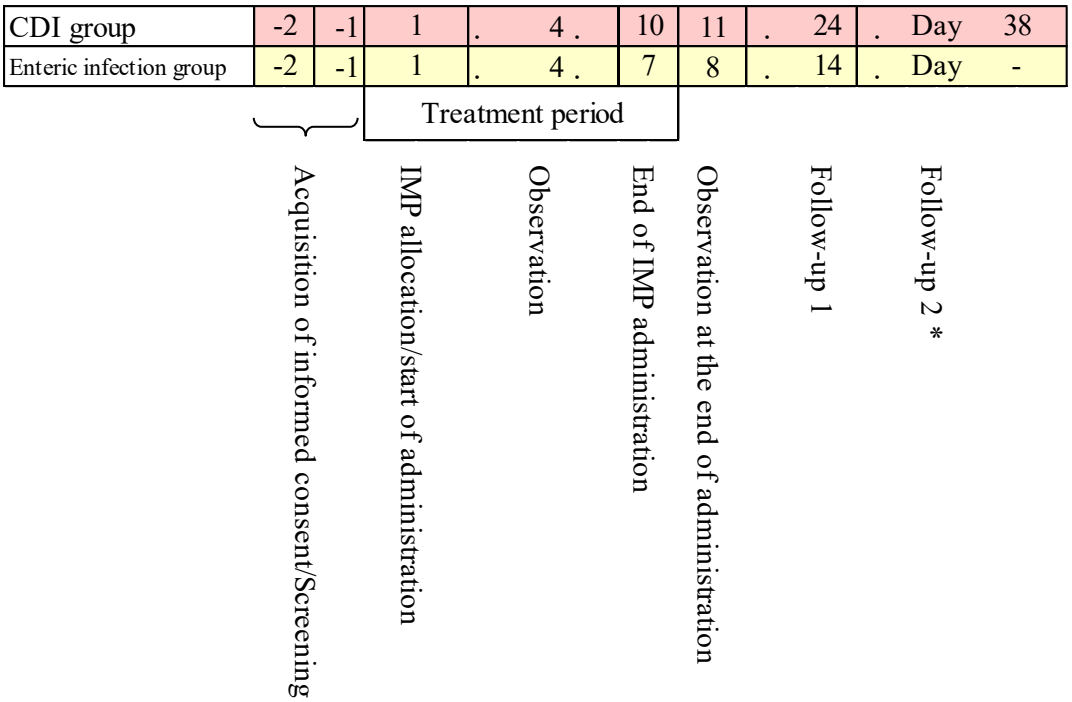

Figure 3.1-2 Trial Schedule

*Performed only in CDI group

For the analysis, the outputs will be prepared under the following plans.
Plan A: Dosage groups 50 mg, 100 mg, 200 mg of each disease group.
Plan B: Dosage groups 100 mg, 200 mg, 400 mg of each disease group.

3.2 Efficacy and Safety Variables

3.2.1 Safety endpoints:

- Adverse events
- Clinical laboratory tests (hematological, biochemical test and urinalysis) ,
- Vital signs (body temperature, blood pressure and pulse rate),
- 12-lead electrocardiogram (ECG)

3.2.2 Efficacy endpoints:

3.2.2.1 Microbiological outcome

Microbiological outcome will be judged according to the assessment criteria shown in Table 3.2-1 and Table 3.2-2 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 3.2-1 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 3.2-2 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.

3.2.2.2 Toxin A/B Assay (CDI Group Only)

Assess positive or negative for toxin A/B.

3.2.2.3 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 3.2-3.

Table 3.2-3 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".

3.2.2.4 Recurrence of CDI (CDI group only)

The investigator or subinvestigator will assess the recurrence of CDI at Follow-up 2 or withdrawal according to the assessment criteria shown in Table 3.2-4 for patients who achieved "clinical cure" at the end of treatment.

Table 3.2-4 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)

3.2.2.5 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.

3.2.2.6 Improvement of clinical symptoms

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

3.2.2.7 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.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently confirmed for consistency, integrity and in accordance with standard PAREXEL procedures.

4.2 General Presentation Considerations

The important terms are defined as below:

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 sub-investigator 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.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.
Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

Confidence intervals will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.2 or a later version in a secure and validated environment.

Baseline

Baseline is defined as the last available screening or pre-treatment assessment.

Allowance window

Assessments taken outside of protocol allowable windows will be displayed only in the listing according to the CRF assessment recorded by the Investigator and will not be included in the summaries.

Unscheduled assessments

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings but not summaries. Listing will include all enrolled subjects in principle.

Withdrawal assessments

Withdrawal assessments will be summarized according to the CRF assessments recorded by the investigator at the time of withdrawal.

Study day

The first day of IMP administration will be defined as DAY 1.

Study day =

The Date - Date of 1st IMP administration + 1, if the Date >= Date of the 1st IMP administration;

The Date - Date of 1st IMP administration, if the Date < Date of the 1st IMP administration.

4.3 Study Subjects

4.3.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

- A summary of subjects with informed consents, screen failure subjects by major reasons, subjects completed the study, subjects discontinued with reasons under each dosage by disease group and overall.
- A summary of subject disposition per site and country by disease group and overall.

4.3.2 Protocol Deviations

All protocol deviations will be defined in the protocol deviation specification.

The following outputs will be provided.

- A summary of subjects with major protocol deviation in each country/region and site by treatment arm and overall and by type of deviation
- A by-subject listing of all protocol deviations.

4.4 Analysis Populations

4.4.1 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.

4.4.2 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.

4.4.3 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 3.2-2), excluding patients for whom microbiological outcome is assessed as “Unknown/indeterminate”.

4.4.4 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.

4.4.5 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKS) comprises patients in whom plasma drug concentration was measured at least once. Outpatients are not included in PKS.

4.5 Demographic and Other Baseline Characteristics

1) Endpoint:
   - Demographic: Country, Ethnicity, Age, Sex, Body height, Body weight, BMI, History of hospitalization
   - Medical history or concomitant disease
   - Prior and concomitant medication/therapy (WHO Drug Dictionary Enhanced/ATC and Preferred name)
   - Causative strains
   - For CDI group only:
     - Diagnostic procedure of CDI
     - Medical history of CDI: number of episodes so far
   - Confirmation of clinical symptoms:
     - Stool frequency per day
     - Form of stool
     - Presence of symptoms: Bloody stool, Abdominal pain, Nausea, Vomiting , Fever

2) Analysis Population:
   SS, FAS, MPPS, CPPS, PKS

3) Analysis Method:
   Under each disease group, frequency counts and percentage or descriptive statistics for each variable will be calculated according to the nature of the data (continuous or discrete) by dosage group and overall.

   Under each disease group, the following summaries will be provided.
   - A summary of demographic variables by dosage group and overall.
   - A summary of medical history or concomitant disease by dosage group and overall
   - A summary of prior and concomitant medication/therapy by dosage group and overall.
   - A summary of diagnosis and medical history of CDI. (CDI group only)
   - A summary of confirmation of clinical symptoms by dosage group and overall
   - Disposition of subjects by the causative strains (FAS, MPPS, CPPS)
   - A summary of causative strains with MIC values (FAS only)

   The following by-subject listings will also be provided.

- A by-subject listing of demographic characteristics
- A by-subject listing of medical history and concomitant disease
- A by-subject listing of prior and concomitant medication/ therapy
- A by-subject listing of confirmation of clinical symptoms
- A by-subject listing of CDI diagnosis and CDI medical history

4.6 Treatment Compliance

1) Definition:
Under each disease group, the treatment compliance of each dosage group will be defined as the following:

$$Compliance(\%) = \frac{Actual\,total\,dose\ of\ IMP(mg)}{Scheduled\,total\,dose\ of\ IMP(mg)} \times 100$$

The schedule number of IMP administrations will be calculated based on the following

- Treatment period: 10 days for CDI group and 7 days for enteric infection group

Disease / Dosing Group	Dosage of OPS-2071	Scheduled Total Dose
CDI 50 mg	50 mg/day	50 x 10 = 500 mg
CDI 100 mg	100 mg/day	100 x 10= 1000 mg
CDI 200 mg	200 mg/day	200 x 10= 2000 mg
CDI 400 mg	400 mg/day	400 x 10 = 4000 mg
Enteric Infection 50 mg	50 mg/day	50 x 7 = 350 mg
Enteric Infection 100 mg	100 mg/day	100 x 7= 700 mg
Enteric Infection 200 mg	200 mg/day	200 x 7= 1400 mg
Enteric Infection 400 mg	400 mg/day	400 x 7 = 2800 mg

2) Analysis population :
SS, FAS, MPPS, CPPS, PKS

3) Analysis method:

- Under each disease group, a summary of treatment compliance by dosage group and overall.
- A by-subject listing of treatment compliance.

4.7 Efficacy Evaluation

4.7.1 Microbiological Outcome

1) Endpoint:
Bacterial Elimination Rate (BER)

Definition: Bacterial elimination rate is defined as the proportion of causative strains assessed as either “excellent” or “good” except for those assessed as “Unknown/indeterminate”.

$$\text{BER (\%)} = \frac{Number\ of\ subjects\ assessed\ as\ Excellent\ or\ Good}{All\ subjects\ in\ MPPS\ population} \times 100$$

2) Analysis Population:
FAS, MPPS

3) Analysis Method:
Under each disease group, the following summaries will be provided.

- A summary of BER (%) by the MIC value of OPS-2071 and causative strains by dosage group and overall. (MPPS only)

- A summary of assessment of criteria and BER (%) by the MIC value against each causative strain, dosage group and overall.

- A summary of BER (%) and its 95% CI by causative strains, dosage group and overall. (MPPS only)

- A summary of assessment criteria, BER (%) and its 95% CIs by causative strains, dosage group and overall.
- A summary of subject disposition by causative strains.

  - For CDI, causative strain is *C.difficile*
  - For enteric infection group, a summary of 3 causative strains (*E.coli, Salmonella sp.* and *Campylobacter*) and all causative strains will be generated.

  - All 95% CIs described will be calculated using the exact method based on the relationship between Binomial distribution and F-distribution (Clopper-Pearson method). [1][2]

$$\text{Lower limit}=\frac{1}{1+\frac{n-x+1}{x}F_{2(n-x+1),2x,0.025}}\times 100$$

$$\text{Upper limit}=\frac{\frac{x+1}{n-x}F_{2(x+1),2(n-x),0.025}}{1+\frac{x+1}{n-x}F_{2(x+1),2(n-x),0.025}}\times 100$$

Where n is the number of all subjects evaluated and x is the number of subjects assessed as Excellent or Good. Also, upper 2.5% point of F-distribution will be used for calculation.

- MIC value is defined as the lowest concentration of antimicrobial agent that inhibited growth of the organism in the ager spots, after confirming the growth in the drug-free ager as growth control.
- MIC value measures in reports: >128, 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03, 0.015, 0.008, 0.004, 0.002 and ≤0.001 μ g/ml.

The following listing will be provided.

- A by-subject listing of causative strains and bacterial culture outcome evaluated at each time point.

The following graph will be provided.

- Bar chart group of BER (%) by dosage group of each causative strain in each disease group.(MPPS only)

4.7.2 Toxin A/B Assay (CDI Group Only)

1) Endpoint:
Toxin Positive Rate (TPR)

Definition: Toxin positive rate is defined as the proportion of the number of Toxin positive patients against the number of evaluable patients in CDI group.

$$\text{TPR (\%)} = \frac{Number\ of\ Toxin\ positive\ subjects}{All\ subjects\ in\ MPPS\ population} \times 100$$

2) Analysis Population:
FAS, MPPS (CDI group only)

3) Analysis Method:
The following summaries will be provided.

- A summary of TPR (%) and its 95% CI at each time point by dosage group and overall.

The following listing will be provided.

- A by-subject listing of toxin A/B assay outcome at each time point.

4.7.3 Clinical Response

1) Endpoint:
Clinical Response Rate (CRR)

Definition: Clinical response rate is defined as the proportion of the patients judged as "clinical cure" or "clinical improvement" against evaluable patients except for those with unknown outcome.

$$\text{CRR (\%)} = \frac{Number\ of\ subjects\ assessed\ as\ \text{Clinical Cure or Improvement}}{All\ subjetcs\ in\ CPPS-Unknown} \times 100$$

2) Analysis Population:
CPPS

3) Analysis Method:
Under each disease group, the following summaries will be provided.

- A summary of CRR (%) and its 95% CI by dosage group and overall at each time point.
- A summary of assessment criteria, CRR (%) and its 95% CI by dosage group and overall at each time point.

- A summary of assessment criteria, CRR (%) and its 95% CI by causative strains, dosage group and overall at each time point.
- A summary of CRR (%) by the MIC value of OPS-2071 and the causative strains by dosage group and overall.
- A summary of assessment of criteria and CRR (%) by the MIC value against each causative strain, dosage group and overall

The following listing will be provided.

- A by-subject listing of causative strains and clinical response assessment at each time point.

The following graph will be provided.

- Bar chart group of CRR (%) by dosage group of each causative strain in each disease group at each time point.

4.7.4 Recurrence of Clostridium Difficile Infection (CDI group only)

1) Endpoint:
CDI Recurrence Rate (RR)

$$\text{CDI RR(\%)} = \frac{Number\ of\ subjects\ assessed\ as\ \text{Recurrence}}{All\ subjetcs\ judged\ as\ \text{"Clinical cure"}in\ CPPS} \times 100$$

2) Analysis Population:

Analysis will be performed on subjects that are judged as “clinical cure” at the end of IMP administration in CPPS. (CDI group only)

3) Analysis Method:
The following summaries will be provided.

- A summary of CDI RR (%) at FU2 or withdrawal by dosage group and overall.

The following listing will be provided.

- A by-subject listing of recurrence outcome at FU2 or withdrawal.

4.7.5 Time to Resolution of Diarrhea

1) Endpoint:
Duration (days) from 1st day of IMP administration to the first formed stool that occurred before the last administration date.
Date of first formed stool- Date of first IMP administration + 1
Where recurrence of liquid stool or unformed stool prior to the last administration date will be excluded.

2) Analysis Population:
CPPS

3) Analysis Method:

Under each disease group, the following summaries will be provided.

- A summary of descriptive statistics of days to resolution by dosage group and overall.

The following listing will be provided.

- A by-subject listing of days to resolution of diarrhea.

4.7.6 Improvement of Clinical Symptoms

1) Endpoint:
Stool count, fecal properties, bloody stool, highest body temperature, abdominal pain, nausea, vomiting

2) Analysis Population:
CPPS

3) Analysis Method:
Under each disease group, the following summaries will be provided.

- A summary of descriptive statistics or frequency distributions (according to the nature of the data) for each variable by dosage group and overall at each time point.

The following listing will be provided.

- A by- subject listing of all the clinical symptoms.

Under each disease group, the following graph will be provided.

- Trend diagram of average stool count (with SD) at each time point by disease/dosage group
- Trend diagrams of stool count of all subjects at each time point by disease/dosage group.

4.7.7 Drug Sensitivity of Isolated Strain

1) Endpoint:
MIC values

2) Analysis Population:
MPPS, FAS

3) Analysis Method:

The following summary will be provided.

- Microbiological test for causative strains.

The following listing will be provided.

- A listing of MIC values against each causative strains at screening and at the end of treatment.

4.8 Safety Evaluation

4.8.1 Extent of Exposure

1) Definition:
Days of IMP administered, total dose administered, total number of IMP administrations

2) Analysis Population:
SS, FAS, CPPS, MPPS, PKS

3) Analysis Method:
Under each disease group, the following summaries will be provided.
- A summary of descriptive statistics of extent of exposure by dosage group and overall.

The following listing will be provided.
- A by-subject listing of exposure extent.

4.8.2 Adverse Events

1) Definition:
AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be tabulated by System Organ Class (SOC) and Preferred term (PT) with PT substituted for verbatim terms.

Treatment-emergent AEs will be tabulated and are defined as those AEs that either start or worsen in severity on or after the date of first dose of IMP administration.

An adverse drug reaction (ADR) is defined as a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function. (WHO definition)

When dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to the first dose of IMP administration.

SAE, death and AEs leading to discontinuation will be considered separately.

2) Analysis Population:
SS

3) Analysis Method:
Under each disease group, the following summaries will be provided.

- A summary of the number and percentage of subjects reporting a treatment-emergent AE or ADR by dosage group and overall, SOC and PT

- A summary of the most common treatment-emergent AEs or ADRs by dosage group and overall, SOC and PT (reported by ≥30% of subjects in any group)
- A summary of the number and percentage of subjects reporting a treatment-emergent AE or ADR by dosage group and overall, severity, SOC and PT
- A summary of the number and percentage of subjects reporting a treatment-emergent AE or ADR leading to death by dosage group and overall, SOC and PT.
- A summary of the number and percentage of subjects reporting a serious treatment-emergent AE or ADR by dosage group and overall, SOC and PT.
- A summary of the number and percentage of subjects reporting a treatment-emergent AE or ADR leading to discontinuation by dosage group and overall, SOC and PT.
- A summary of all the above.

By-subject listings of all AEs (including non-treatment-emergent events) will be generated.

- A by-subject listing of all AEs
- A by-subject listing of all deaths that occurred during the study
- A by-subject listing of all SAEs
- A by-subject listing of all AEs that led to withdrawal.

For by-severity summaries, for each subject reporting multiple AEs, the worst severity recorded will be used.

4.8.3 Clinical Laboratory Evaluation

1) Definition:
   A subject will be defined as having a potentially clinically abnormality if any of the following conditions are satisfied for a specific laboratory parameter.
   - A laboratory result within the normal range at baseline and either a result below the lower limit of the normal range or above the upper limit of the normal range at any post-baseline time point.
   - A laboratory result below the lower limit of the normal range at baseline and a laboratory result above the upper limit of the normal range at any post-baseline time point.
   - A laboratory result above the upper limit of the normal range at baseline and a laboratory result below the lower limit of the normal range at any post-baseline time point.
2) Analysis Population:
   SS
3) Analysis Method:
   Under each disease group, the following summaries will be generated:
   - A summary of each laboratory parameter and its change from baseline by dosage group and overall at each time point.
   - A summary of the number and percentage of subjects experiencing low, normal and high values by dosage group and overall at baseline and at each post-baseline time point. (shift table)

- A summary of incidences of potentially clinically abnormalities by dosage group and overall.

The following listing will be provided.

- A by-subject listing of all laboratory data will be generated with reference range provided and abnormal values will be marked.

4.8.4 Vital Signs, Physical Findings and Other Observations Related to Safety

1) Definition:
Vital signs (blood pressure, pulse rate, body temperature), 12-lead ECG.

2) Analysis Population :
SS

3) Analysis Method:
Under each disease group, the following summaries will be provided.

- A summary of descriptive statistics or frequency distributions (according to the nature of the data) for each vital sign variable by dosage group and overall at each time point.
- A summary of the number and percentage of subjects experiencing normal, not clinically significant abnormal and clinically significant abnormal ECG result by dosage group and overall at baseline and at each post-baseline time point. (shift table)

The following listing will be provided.

- A by-subject listing of vital signs and 12-lead ECG.

4.8.5 Data Review Committee [DRC]

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 specialist. The DRC procedures will be specified in a separate document.

4.9 Determination of Sample Size

There will be three dosing groups of OPS-2071, i.e., 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.

4.10 Changes in the Conduct of the Study or Planned Analysis

PK analysis will be performed by sponsor and it is not included in this SAP. In PKS, outpatients are not included.

In the following analysis section, some analysis populations are added to the populations described in the protocol.
4.5 Demographic and Baseline Characteristics: PKS

4.6 Treatment Period: MPPS, PKS
4.7.1 Microbiological Outcome: FAS
4.7.2 Toxin A/B Assay: FAS
4.7.7 Drug Sensitivity of Isolated Strain: FAS

Regarding time to resolution of diarrhea, only the period from 1st day of IMP administration to the last administration date will be considered.

5 REFERENCES

[1] Blyth, C.R., Approximate Binomial Confidence Limits, Journal of the American Statistical Association,1986; 81(395):843-855.
[2] Clopper, C. and Pearson, E.S. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 1934; 26, pp. 404-413

DOCUMENT CHANGE RECORD

Version Number	Document Date	Summary of Changes Made
1.1	2015/10/16	4.6 Treatment compliance Changed the definition of compliance (tablets→total dose).
1.2	2016/3/15	4.4.5 Pharmacokinetics Analysis Set Added the exclusion of outpatients.
2.0	2016/3/18	Version 2
2.1	2017/2/20	4.5 Demographic and Other Baseline Characteristics Added causative strains 4.7.1 Microbiological Outcome Specified Analysis population 4.10 Changes in the Conduct of the Study or Planned Analysis Additional Analysis populations are described.
2.2	2017/3/01	Corrected typo 4.5 Demographic and Other Baseline Characteristics
3.0	2017/3/03	Version 3