CLINICAL STUDY REPORT

341-13-002

Sponsor:	Otsuka Pharmaceutical Co., Ltd 2-9 Kanda-Tsukasamachi, Chiyoda-ku, Tokyo 101-8535, Japan
Coordinating Investigator	[redacted]
Trial/Protocol No.:	341-13-002
Trial Drug/Product Name:	OPS-2071
Development Phase:	Phase 2a
Indication:	Bacterial enteritis
Date of First Enrollment:	20 Aug 2015
Date of Last Patient Completed:	14 Mar 2017
Date of Report:	20 Sep 2017

The trial was conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

2. CLINICAL TRIAL SYNOPSIS

Name of Company: Otsuka Pharmaceutical Co., Ltd. **Name of Finished Product:** NA **Name of Active Ingredient(s):** OPS-2071	**Volume:** **NA** **Page:**	(For national authority use only)

Title of Trial: An open-label, multi-center clinical trial to assess the safety and efficacy of three different doses of OPS-2071 in patients with bacterial enteritis

Protocol Number: 341-13-002

ClinicalTrials.gov Identifier: NCT02473393

Trial Period: **Date of First Enrollment:** 20 Aug 2015 **Date of Last Completed:** 14 Mar 2017	**Phase of Development:** Phase: 2a **Type of trial:** Dose-ranging trial

Investigators:
Coordinating Investigator:
[redacted]
The complete list of investigators and trial sites can be found in Section 16.1.4 of the clinical study report.

Study Centers:
A total of 19 trial sites in Japan, Republic of Korea, and Singapore.
Japan: Toho University Omori Medical Center and 14 other trial sites
Republic of Korea: Severance Hospital, Yonsei University Health System and 1 other trial site
Singapore: Singapore General Hospital and 1 other trial site
The complete list of trial sites can be found in Section 16.1.4 of the clinical study report.

Publication(s): None to date

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

Trial Design: Multi-center, randomized, open-label trial

Number of Subjects (planned and analyzed):
Planned:
A total of 60 subjects with 20 subjects (10 subjects each in the CDI and the enteric infection groups) in each dosing group were planned to be enrolled in this trial. Three different dosing levels of OPS-2071 were planned. For the assessment of microbiological outcome, 10 subjects in the CDI group were required to be enrolled in each dosing group. For the enteric infection group, at least 5 subjects were required to be enrolled in each dosing group for the assessment of microbiological outcome with the sum of *Salmonella*, *Campylobacter*, and pathogenic *E. coli*. If a sufficient number of subjects were not available for microbiological assessment after enrollment of 10 subjects in each group, more subjects were to be enrolled.

Analyzed:
CDI group:
A total of 5 subjects were included in the full analysis set (FAS): 5 subjects in the 100 mg group.
A total of 2 subjects were included in the microbiological per protocol set (MPPS): 2 subjects in the 100 mg group.
A total of 4 subjects were included in the clinical per protocol set (CPPS): 4 subjects in the 100 mg group.
A total of 5 subjects were included in the safety analysis set (SS): 5 subjects in the 100 mg group.
A total of 1 subject was included in the pharmacokinetics analysis set (PKS): 1 subject in the 100 mg group.

Enteric Infection group:
A total of 36 subjects were included in the FAS: 12 subjects in the 50 mg group, 12 subjects in the 100 mg group, and 12 subjects in the 200 mg group.
A total of 25 subjects were included in the MPPS: 9 subjects in the 50 mg group, 9 subjects in the 100 mg group, and 7 subjects in the 200 mg group.
A total of 32 subjects were included in the CPPS: 10 subjects in the 50 mg group, 10 subjects in the 100 mg group, and 12 subjects in the 200 mg group.
A total of 37 subjects were included in the SS: 12 subjects in the 50 mg group, 13 subjects in the 100 mg group, and 12 subjects in the 200 mg group.
A total of 6 subjects were included in the PKS: 2 subjects in the 50 mg group, 2 subjects in the 100 mg group, and 2 subjects in the 200 mg group.

Diagnosis and Criteria for Inclusion:
Patients who met all of the following criteria were selected.

1. The patient was an Asian male or female of minimum legal age to provide consent (ie, 21 years for Singapore, 19 years for Republic of Korea, and 20 years for Japan at time of informed consent).
2. The patient provided written, informed consent before the clinical trial was initiated.
3. The patient had distinctive symptoms and findings of bacterial enteritis (regardless of inpatient or outpatient.)
4. The patient had 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 were willing to take contraceptive measures from initiation of investigational medicinal products (IMPs) to 4 weeks after administration of IMPs.

CDI group:

6. The patient satisfied both of 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)

Enteric infection group:

7. The patient satisfied 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

Diagnosis and Criteria for Exclusion:

Patients who fell under any of the following exclusion criteria were excluded from participation in the trial.

1. Intractable vomiting, inability to take oral medication, patients with feeding tubes
2. The patient had severe or progressive underlying disease or complication, making it difficult to ensure safety in the trial 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 had a current diagnosis or history of convulsive disorders, such as convulsion and epilepsy
9. The patient had a severe hepatic dysfunction (eg, aspartate aminotransferase [AST] / glutamic oxaloacetic transaminase [GOT] or alanine aminotransferase [ALT] / glutamic pyruvic transaminase [GPT] $\geq$ 3 times of the upper limit of normal at the trial center, etc.)
10. The patient had a severe cardiac dysfunction (eg, cardiac arrest, ischemic disease)
11. The patient had cardiac arrhythmia or congenital or sporadic long corrected QT (QTc) syndrome. Or the patient was treated with a drug reported to prolong QTc interval (eg, amiodarone, sotalol, disopyramide, quinidine, procainamide, terfenadine, astemizole, cisapride, pimozide)
12. The patient had a moderate or severe renal dysfunction (eg, serum creatinine level $\geq$ 2 mg/dL or necessity of renal dialysis, etc.)
13. The patient was treated with uridine diphosphate glucuronosyltransferase (UGT)1A1 inhibitors (atazanavir) within 2 days before the start of IMP administration.
14. Female patient with confirmed or suspected pregnancy or breast-feeding female patient
15. The patient was treated with another IMP 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 had 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 had marked dehydration at the screening examination.

Test Product, Dose and Mode of Administration, and Lot Number(s):

Investigational medicinal products:

OPS-2071 25 mg tablets, 50 mg tablets, 100 mg tablets

Test Product	Content and Dosage Form	Lot Number
OPS-2071 25 mg	A pale yellow film coated tablet containing 25 mg as OPS-2071	14E76A025
OPS-2071 50 mg	A pale yellow film coated tablet containing 50 mg as OPS-2071	14E76A050
OPS-2071 100 mg	A pale yellow film coated tablet containing 100 mg as OPS-2071	14E76A100

Dose and regimen:

Of the planned daily dosages of 50, 100, 200, or 400 mg of OPS-2071, 3 dosages were to be administered: either 100, 50, and 200 mg or 100, 200, and 400 mg. Only one dosage (100 mg) of OPS-2071 was administered to CDI subjects and 3 dosages (100, 50, and 200 mg) were administered to enteric infection subjects. The planned dose at 400 mg of OPS-2071 for both CDI and enteric infection subjects, and the planned dose at 50 or 200 mg of OPS-2071 for CDI subjects were not conducted. The IMP was 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. The IMP was administered after a meal, where possible, with at least a 10-hour interval between dosing. Subjects had an evening meal before dosing on the previous day of blood collection for pharmacokinetic (PK) and had breakfast before dosing on the day blood collection for PK was performed. Whether or not the symptoms improved during the treatment period, all IMPs prescribed for the predetermined period had to be used.

The following algorithm was to be used to decide on dosage.
The administration was started with the 100 mg group. The safety and efficacy during the treatment period were to be assessed by the Data Review Committee (DRC).

1. If there were no safety concerns and IMP was considered effective in the 100 mg group:
   The next step was to randomize 10 subjects each who were not in the 100 mg group to the 200 mg or 50 mg group. The 2 groups were to be treated in parallel.
2. If there were no safety concerns, but IMP was considered not effective in the 100 mg group:
   The next step was to allocate 10 subjects who were not in the 100 mg group to the 200 mg group. The DRC was to assess the safety of the 200 mg group during the treatment period. If there were no safety concerns in the 200 mg group, 10 subjects who were not in the 100 mg or 200 mg group were to be allocated to the 400 mg group as the next step.

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): NA

Duration of Treatment:

CDI group:
10 days for the treatment period
Enteric infection group:
7 days for the treatment period

Criteria for Evaluation:

Safety endpoints:

- Adverse events (AEs), clinical laboratory tests, vital signs (body temperature, blood pressure, and pulse rate), and 12-lead electrocardiogram (ECG) were evaluated during the trial.

Efficacy endpoints:

- Microbiological outcome based on combined of assessments of bacterial isolates as below:

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

- Microbiological outcome based on Toxin A/B assay for the CDI group only
- Clinical response based on clinical response criteria below at the time of observation

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. Subjects who received medication or therapy to treat CDI or enteric infection prior to the time of observation were to be assessed as "clinical failure".

CDI = *Clostridium difficile* infection

- Recurrence of CDI (for the CDI group only) at the follow-up 2 (FU2), or at withdrawal for subjects who achieved "clinical cure" at end of treatment (EOT) based on the below criteria:

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

CDI = *Clostridium difficile* infection, EOT = end of treatment, FU2 = follow-up 2

- Time to resolution of diarrhea, defined as the time from the start of dosing until the first formed stool (except in cases where liquid or unformed stools recurred)
- Improvement of clinical symptoms (ie, daily stool count, fecal properties, bloody stool, fever, abdominal pain, nausea, and vomiting)
- Drug sensitivity of isolated strain based on the minimum inhibitory concentration (MIC) of OPS-2071

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}], and C_{max} normalized by dose [C_{max}/D]) of OPS-2071 at Day 4 were assessed.

Statistical Methods:

Determination of sample size

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 subjects. It was not selected based on statistical methods but based on the required evaluable subject number.
It was assumed that bacteria were to be detected in almost 100% of the CDI patients, and in 50% of the enteric infection patients. For the assessment of microbiological outcome, 10 patients in the CDI group were required to be enrolled in each dosing group. For the enteric infection group, at least five patients were required for the assessment of microbiological outcome which was a sum of *Salmonella*, *Campylobacter*, and pathogenic *E. coli*. Based on this assumption, the target number of patients in each dosing group was: 10 CDI patients and 10 patients with enteric infection. Three dosing groups of OPS-2071 were planned, ie, 100, 50, 200 mg, or 100, 200, 400 mg, thus a total of 60 patients (10 patients each in the CDI group and the enteric infection group at each dose level) were planned. For both groups, the priority was to enrol those patients for whom microbiological assessment was possible. If a sufficient number of these patients was not attained after enrolling the target number of patients (10 patients), additional patients were to be enrolled.

The dataset analysis populations are listed below:

1. Safety Analysis Set
   The SS included all patients who had received the IMP at least once and from whom data on at least one safety endpoint had been obtained after the start of IMP administration.
2. Full Analysis Set
   The FAS included all patients who had received the IMP at least once and from whom data on at least one efficacy endpoint had been obtained after the start of IMP administration.
3. Microbiological per Protocol Set
   The MPPS comprised those patients in the FAS for whom the causative pathogen was identified and for whom microbiological outcome was assessed as “Excellent”, “Good”, or “Poor” according to the Assessment Criteria of Microbiological Outcome as mentioned above, excluding patients for whom microbiological outcome was assessed as “unknown/indeterminate”.
4. Clinical per Protocol Set
   The CPPS comprised those patients in the FAS for whom all scheduled examinations at all specified observation time points up until EOT or withdrawal had been performed.
5. Pharmacokinetics Analysis Set
   The pharmacokinetics analysis set (PKS) comprised patients in whom plasma drug concentration had been measured at least once. Outpatients were not included in the PKS.

Safety Analysis Method:
Analysis was performed for the entire trial population and by disease group and by dose. AEs that occurred after the start of treatment with IMP were tabulated using Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT), with PT substituted for verbatim terms. The number of subjects who experienced the following events as well as the incidence was tabulated: AEs, adverse drug reactions (ADRs), serious adverse events (SAEs), AEs leading to

withdrawal, and AEs by severity.
Clinical laboratory tests and vital signs (body temperature, blood pressure, and pulse rate) were analyzed by using frequency distributions and descriptive statistics.
Regarding 12-lead ECG, a shift table was prepared for judgment on abnormality at each time point before and after IMP administration.

Efficacy Analysis Method:
Microbiological Outcome:
Analysis was performed by disease group and by dose, and by MIC values of OPS-2071 for each of the causative strains. The number and proportion of subjects by causative strain, a list of causative strain by subjects, and a list of the result based on bacterial culture at each evaluation time point were prepared.
Concerning microbiological outcome by causative strain, bacteria elimination rate and its 95% confidence interval (CI) were calculated. The bacteria elimination rate was 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, the microbiological outcome of each infections agent was assessed.

Toxin A/B Assay (for the CDI Group Only):
Analysis was performed by dose. Based on the result of Toxin A/B assay performed by the microbiological laboratory, a list was prepared on the result of positive/negative judgment in the Toxin A/B assay at each evaluation time point.
Toxin A/B positive rate and its 95% CI were calculated. Toxin A/B positive rate was the proportion of the number of Toxin positive subjects against the number of evaluable subjects in the CDI group.

Clinical Response:
Analysis was performed by disease group and by dose, by causative strain, and by MIC values of OPS-2071 for the causative strains. Frequency distribution at each evaluation time point was calculated and a list of causative strains by subjects was prepared.
The Clinical Response Rate (CRR) and 95% CI at each evaluation time point were calculated. The CRR was calculated as the proportion of the subjects judged as "clinical cure" or "clinical improvement" against evaluable subjects, except for those with missing data.

Recurrence of CDI (for the CDI group only):
Analysis was performed by dose in the proportion of subjects judged as "clinical cure" at EOT in the CPPS.
The list of result of judgment on CDI recurrence at follow-up (FU2) or withdrawal was prepared.
CDI recurrence rate at FU2 or withdrawal was calculated. CDI recurrence rate was the proportion of the subjects judged as "recurrent" against evaluable subjects, except for those with missing data.

Time to Resolution of Diarrhea:
Analysis was performed by disease group and by dose. Descriptive statistics of days from the start of dosing to first formed stool before the last administration date were calculated (except cases where liquid or unformed stools recurs).

Improvement of Clinical Symptoms:
Analysis was performed by disease group and by dose. Frequency distribution or descriptive statistics for each variable were calculated at each evaluation time point according to the nature of the data (continuous or discrete).

Drug Sensitivity of Isolated Strain:
A list of kinds and number of strains of the identified causative strain was prepared. The MIC value of OPS-2071 for the causative strain at screening and at EOT (and FU2 [Day 38] for the CDI group) were determined to prepare a list.

Pharmacokinetics Analysis Method:

1. Calculation method

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

2. Statistical Analysis Method

For inpatient subjects, descriptive statistics by disease (CDI or enteric infection), by dose, and by blood sampling time point for plasma drug concentration, and by disease (CDI or enteric infection) and by dose for pharmacokinetic parameters was calculated.

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

Efficacy Results:

Only one dosage (100 mg) of OPS-2071 was administered to subjects with CDI and 3 dosages of OPS-2071 (100, 50, and 200 mg) were administered to subjects with enteric infection.

CDI group:

- Microbiological outcome results:

In the MPPS, the Bacterial Elimination Rate (BER) of OPS-2071 for *C. difficile* was 100% (all of 2 isolates from subjects with CDI). The outcomes of microbiological assessments for each of these isolates were "excellent" and "good", respectively.

- Toxin A/B Assay results:

In the MPPS, none of the 2 subjects were positive for Toxin A/B Assay at Baseline, Day 4, EOT or FU2.

- Clinical response results:

In the CPPS, the CRR for the subjects with CDI at both Day 4 and EOT were 100% (all 4 subjects). In the CPPS where *C. difficile* was identified as the pathogen in 2 subjects; neither subject had "clinical cure" at Day 4 and 1 subject had "clinical cure" at EOT.

- Recurrence of *Clostridium difficile* infection results:

In the CPPS, 2 subjects with "clinical cure" at EOT had "sustained cure" at FU2. Neither subject (0 of 2 subjects) had a recurrence, thus the CDI RR was 0.0%.

- Time to resolution of diarrhea results:

In the CPPS, the mean (SD) of days to the resolution of diarrhea was 3.7 (1.53) days in subjects with CDI after the administration of OPS-2071.

- Improvement of clinical symptoms results:

In the CPPS, the mean (SD) of stool frequency/day in the subjects with CDI decreased from an average of 5.3 (3.30) times/day at Screening to less than 3 times at Day 1 and was maintained less than 3 times/day through Day 41.

Formed stool was found starting on Day 2 in 1 of 4 subjects (25.0%), and subsequently in 1 to 2 subjects through Day 41. At Screening, all 4 subjects (100.0%) had liquid or unformed stool for 3 and more times/day. However, from Day 1 through Day 41, the number of subject with liquid or unformed stool for 3 or more times/day reduced to 2 or less subjects. None of the subjects had bloody stool from the Screening through Day 41.

At Screening, 2 of 4 subjects (50.0%) had abdominal pain and from Day 1 through Day 41, 1 subject or less had abdominal pain. The number of subjects who had nausea and vomiting after Day 1 was very low (1 subject or less). The median of the body temperature from Screening to Day 41 was less than 37.5°C. However, the maximum body temperature was above 37.5°C at times.

- Drug sensitivity of isolated strain:

At Screening, for the MPPS, the MIC values of OPS-2071 for *C. difficile* from 2 isolates were 0.03 μg/mL and 0.06 μg/mL. At Screening, the MIC values of vancomycin (VCM) were 0.5 μg/mL for both isolates. The MIC value of OPS-2071 for *C. difficile* in 1 isolate remained the same as that at Screening (0.06

μg/mL) and the MIC value of VCM for this isolate at FU2 remained the same as that at Screening (0.5 μg/mL).

Enteric Infection group:

- Microbiological outcome results:

In the MPPS, the BER of OPS-2071 in subjects with enteric infection (all 3 dose groups) against all strains was 82.8% (24 of 29 isolates from subjects with enteric infection), and the BER of OPS-2071 against 3 strain species (*Salmonella species*, *E. coli* pathotypes [ie, enteroaggregative, enteroinvasive, enteropathogenic, enterotoxigenic] and *Campylobacter species* including *jejuni* and *coli*) was 82.4% (14 of 17 isolates). The BER for all strains in each dose group were 72.7% (8 of 11 isolates) in the 50 mg group, 90.0% (9 of 10 isolates) in the 100 mg group, and 87.5% (7 of 8 isolates) in the 200 mg group. The BER against 3 strain species by dose group were 80.0% (4 of 5 isolates) in the 50 mg group, 83.3% (5 of 6 isolates) in the 100 mg group, and 83.3% (5 of 6 isolates) in the 200 mg group. The BER against all strains in each dose group and against 3 strain species in all dose groups were similar.

- Clinical response results:

In the CPPS, the CRR for the subjects with enteric infection at Day 4 was 100% (all 32 subjects) and at EOT was 96.9% (in 31 of 32 subjects). The CRR of the subjects with enteric infection at Day 4 by dose group were 100.0% (10 of 10 subjects) in the 50 mg group, 100.0% (10 of 10 subjects) in the 100 mg group, and 100.0% (12 of 12 subjects) in the 200 mg group. The CRR of the subjects with enteric infection at EOT by dose group were 100.0% (10 of 10 subjects) in the 50 mg group, 90.0% (9 of 10 subjects) in the 100 mg group, and 100.0% (12 of 12 subjects) in the 200 mg group. The CRR of the subjects with enteric infection at Day 4 and at EOT in all dose groups were similar. In the CPPS, based on the isolated strain, the clinical responses were predominantly "clinical cure" or "clinical improvement", thus the CRR was mostly 100% at Day 4 and EOT. Except for *C. perfringens*, the CRR at EOT was 50.0% in the 100 mg group due to 1 subject having "clinical failure" at EOT.

- Time to resolution of diarrhea:

In the CPPS, the mean (SD) of days to the resolution of diarrhea was 4.4 (1.55) days after the administration of OPS-2071. The mean (SD) of number of days to the resolution of diarrhea was similar in all dose groups: 4.3 (1.34) days in the 50 mg group, 4.4 (2.01) days in the 100 mg group, and 4.6 (1.42) days in the 200 mg group in subjects with enteric infection.

- Improvement of clinical symptoms

In the CPPS, the mean (SD) of stool frequency/day in the subjects with enteric infection in all dose groups decreased from 7.9 (3.48) times/day at Screening to 3.3 (2.16) times/day at Day 3. Stool frequency was maintained less than 3 times/day from Day 4 through to Day 17.

Formed stool was observed in 8 of 32 subjects (25.0%) on Day 3 and in 24 of 32 subjects (75%) on Day 8. At Screening, all 32 subjects (100.0%) had liquid or unformed stool for 3 or more times/day. On Day 3, it was reported in 13 of 32 subjects (40.6%), on Day 8 in 2 of 32 subjects (6.3%), and at later time points in 0 to 4 subjects. At Screening, 7 of 32 subjects (21.9%) had bloody stool, however, from Day 3 through Day 17 none of the subjects had bloody stool.

At Screening, abdominal pain was reported in all 32 subjects (100.0%), on Day 3 in 17 of 32 subjects (53.1%), on Day 8 in 3 of 32 subjects (9.4%), and at later time points in 0 to 5 subjects. At Screening, the number of subjects who had nausea and vomiting was 15 of 32 subjects (46.9%) and 5 of 32 subjects (15.6%), respectively, and on Day 3, 4 of 32 subjects (12.5%) and 0 of 32 subjects (0.0%), respectively. On Day 4 or later, the incidences of both events were very low (in 1 subject or less). From Screening through Day 17, the median of the body temperature was less than 37.5°C. However, the maximum body temperature was above 37.5°C at times.

- Drug sensitivity of isolated strain:

In the MPPS, the MIC values of OPS-2071 for all isolated/identified strains at Screening ranged from ≤ 0.001 to 16 μg/mL. Out of 29 isolates, only in 1 isolate of *K. oxytoca*, the MIC value of OPS-2071 was 16 μg/mL. The MIC values of OPS-2071 for other isolates were less than 1 μg/mL. The MIC values of the ciprofloxacin (CPFX) for all isolated/identified strains at Screening ranged from 0.015 to 32 μg/mL, where the MIC values in 9 of 29 isolates was above 16 μg/mL. The most common strain isolated/identified from the enteric infection subjects was *C. jejuni* (13 isolates). At Screening the MIC values of OPS-2071 in these 13 isolates ranged from 0.008 to 0.5 μg/mL which was lower than the MIC values of CPFX, which ranged from 0.12 to 32 μg/mL. At EOT, the MIC values of OPS-2071 for 2 isolates of *C. jejuni* were 2

and 8 μg/mL, while the MIC values of CPFX was 64 μg/mL for both isolates.

Pharmacokinetic Results:

The C_{max} of OPS-2071 on Day 4 of multiple oral administrations at 100 mg in 1 subject with CDI (inpatient subject) was 64.0 ng/mL. The mean C_{max} of OPS-2071 on Day 4 of multiple oral administration in the inpatient subjects with enteric infection was 29.2 ng/mL at 50 mg, 42.4 ng/mL at 100 mg, and 81.9 ng/mL at 200 mg, showing a dose-dependent increase.

The t_{max} of OPS-2071 on Day 4 of multiple oral administrations at 100 mg in 1 subject with CDI (inpatient subject) was 4.15 h. The individual t_{max} of OPS-2071 on Day 4 of multiple oral administrations at 50 mg to 200 mg in the inpatient subjects with enteric infection ranged from 0.92 hour to 4.12 hours.

Individual plasma OPS-2071 concentrations within 12 hours after morning administration on Day 4 of multiple oral administrations at 100 mg in outpatient subjects with CDI ranged from 41.6 ng/mL to 153 ng/mL. Individual plasma OPS-2071 concentrations within 12 hours after morning administration on Day 4 of multiple oral administrations in outpatient subjects with enteric infection ranged from 10.6 to 92.6 ng/mL at 50 mg, 14.5 to 54.1 ng/mL at 100 mg, and 58.4 to 200 ng/mL at 200 mg.

Safety Results:

- Overall, 36 Treatment-emergent Adverse Events (TEAEs) were reported in 19 of all 42 subjects (45.2%) including CDI group and enteric infection groups. Eight TEAEs were reported in 3 of 5 subjects (60.0%) in the CDI group (in the 100 mg group). Twenty-eight TEAEs were reported in 16 of 37 subjects (43.2%) in the enteric infection groups.
- By dose groups in the enteric infection group, 7 TEAEs were reported in 4 of 12 subjects (33.3%) in the 50 mg group, 13 TEAEs were reported in 8 of 13 subjects (61.5%) in the 100 mg group, and 8 TEAEs were reported in 4 of 12 subjects (33.3%) in the 200 mg group.
- The most frequently reported TEAE (reported in 2 or more subjects) including the CDI group and the enteric infection groups were headache (4 TEAEs in 3 of 42 subjects [7.1%]), alanine aminotransferase increased (3 TEAEs in 3 of 42 subjects [7.1%]), eosinophilia (2 TEAEs in 2 of 42 subjects [4.8%]), and pyrexia (2 TEAEs in 2 of 42 subjects [4.8%]).
- In the CDI group, none of the TEAEs occurred in more than 1 subject. In subjects with enteric infection, the most frequently reported TEAE (reported in 2 or more subjects) by dose group were as follows: alanine aminotransferase increased (2 TEAEs in 2 of 12 subjects [16.7%]) in the 50 mg group; pyrexia (2 TEAEs in 2 of 13 subjects [15.4%]) and headache (3 TEAEs in 2 of 13 subjects [15.4%]) in the 100 mg group; no TEAE was reported in more than 1 subject in the 200 mg group.
- Overall, 13 potentially drug-related TEAEs were reported in 9 of all 42 subjects (21.4%) including CDI group and enteric infection groups. All 13 potentially drug-related TEAEs were reported in 9 of 37 subjects (24.3%) in the enteric infection groups.
- The most frequently reported potentially drug-related TEAE (reported in 2 or more subjects) in the enteric infection group were as follows: no potentially drug-related TEAE reported in 2 or more subjects in the 50 mg group; pyrexia (2 potentially drug-related TEAEs in 2 of 13 subjects [15.4%]) and headache (3 potentially drug-related TEAEs in 2 of 13 subjects [15.4%]) in the 100 mg group; and no potentially drug-related TEAE reported in 2 or more subjects in the 200 mg group.
- All TEAEs were mild or moderate, and no severe TEAEs were reported in subjects with CDI and enteric infection.
- No deaths due to TEAEs occurred in the trial and no subjects reported TEAEs leading to discontinuation of IMP.
- Only 1 serious TEAE of pyrexia was reported in this trial, in 1 subject with enteric infection in the 100 mg group. This event was considered a potentially drug-related serious TEAE.
- There were no safety concerns from the assessments of clinical laboratory results, physical examination, vital signs, and ECG.
- In this trial, OPS-2071 at 50 mg, 100 mg, and 200 mg doses were safe and well tolerated in subjects with enteric infection. OPS-2071 at 100 mg dose was safe and well tolerated in subjects with CDI.

Conclusions:

- For the CDI group, OPS-2071 was administered to 5 subjects at a dose of 100 mg twice a day. The microbiology assessments and clinical assessments results showed improvement. None the subjects who were judged as "clinical cure" at EOT, had a relapse at FU2.
- No meaningful efficacy conclusions can be made in subjects with CDI due to the low number of the subjects.
- For the enteric infection groups, OPS-2071 administered at doses of 50 mg, 100 mg, and 200 mg twice a day resulted in improvements of microbiology assessments and clinical assessments results. There was no observed dose-relationship in the efficacy of OPS-2071 in the enteric infection groups: efficacy was observed at a dose as low as 50 mg.
- The absorption of OPS-2071 in subjects with bacterial enteritis associated with CDI or enteric infection in this trial did not increase relative to that in healthy adults in the Phase 1 trial.
- In this trial, OPS-2071 at 50 mg, 100 mg, and 200 mg doses was safe and well tolerated in subjects with enteric infection. OPS-2071 at 100 mg dose was safe and well tolerated in subjects with CDI.

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