Statistical Analysis Plan
(SAP)

A Multicenter, Double-Blind, Parallel-Arm, Placebo-Controlled, Phase 2 Study of the Efficacy, Safety, and Tolerability of Oral Full-Spectrum Microbiota™ (CP101) in Subjects with Recurrence of *Clostridium difficile* Infection

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SAP APPROVAL FORM

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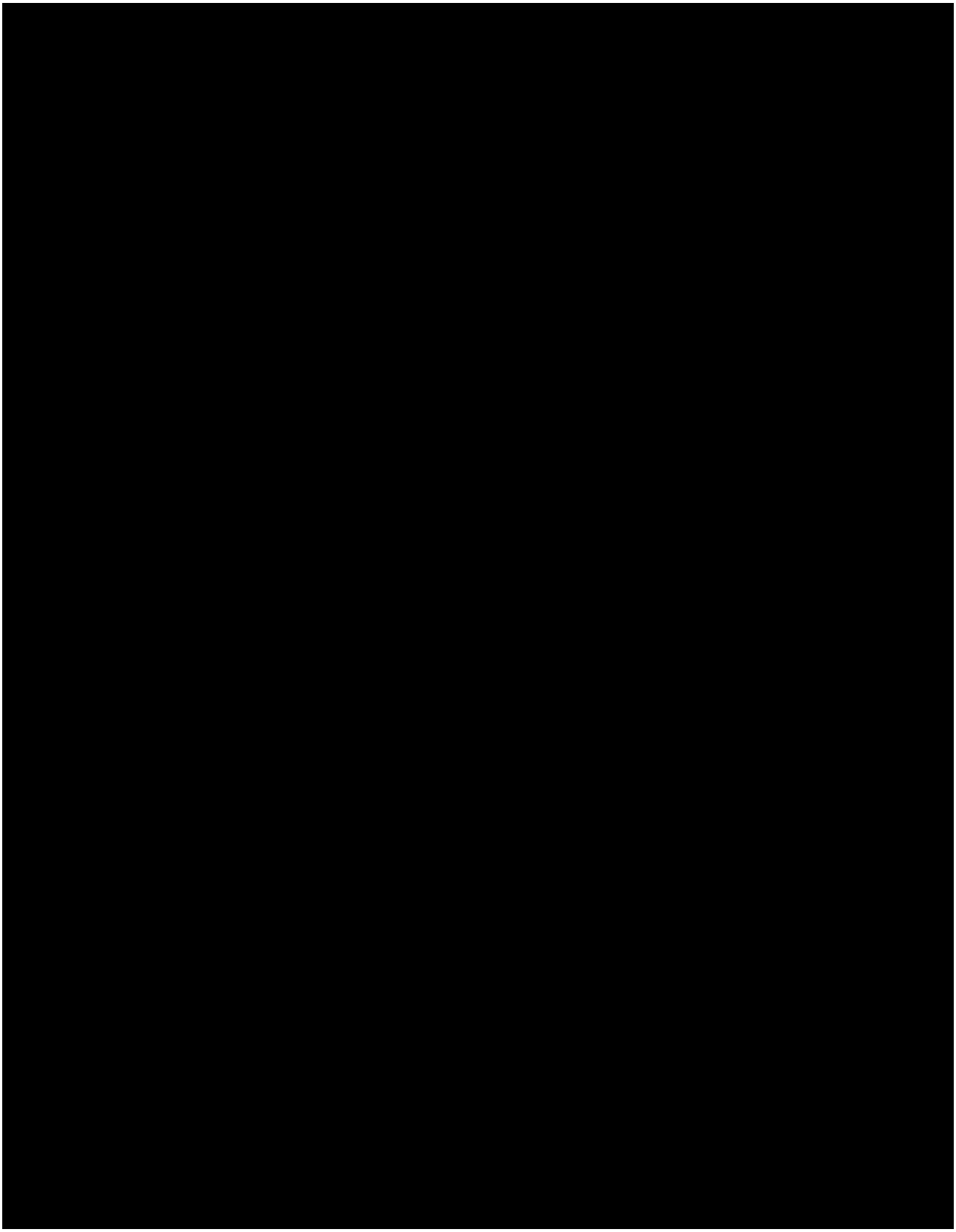
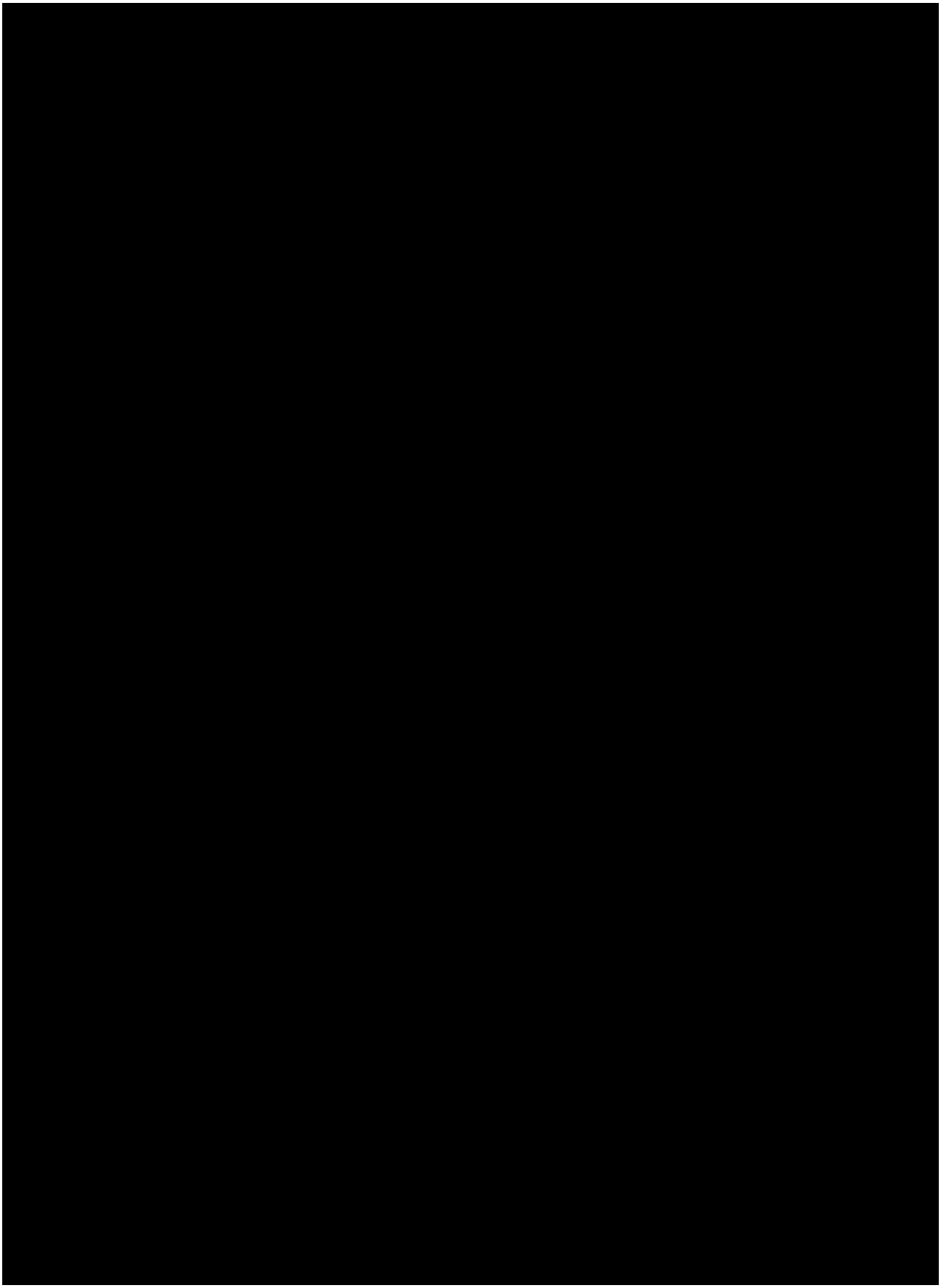
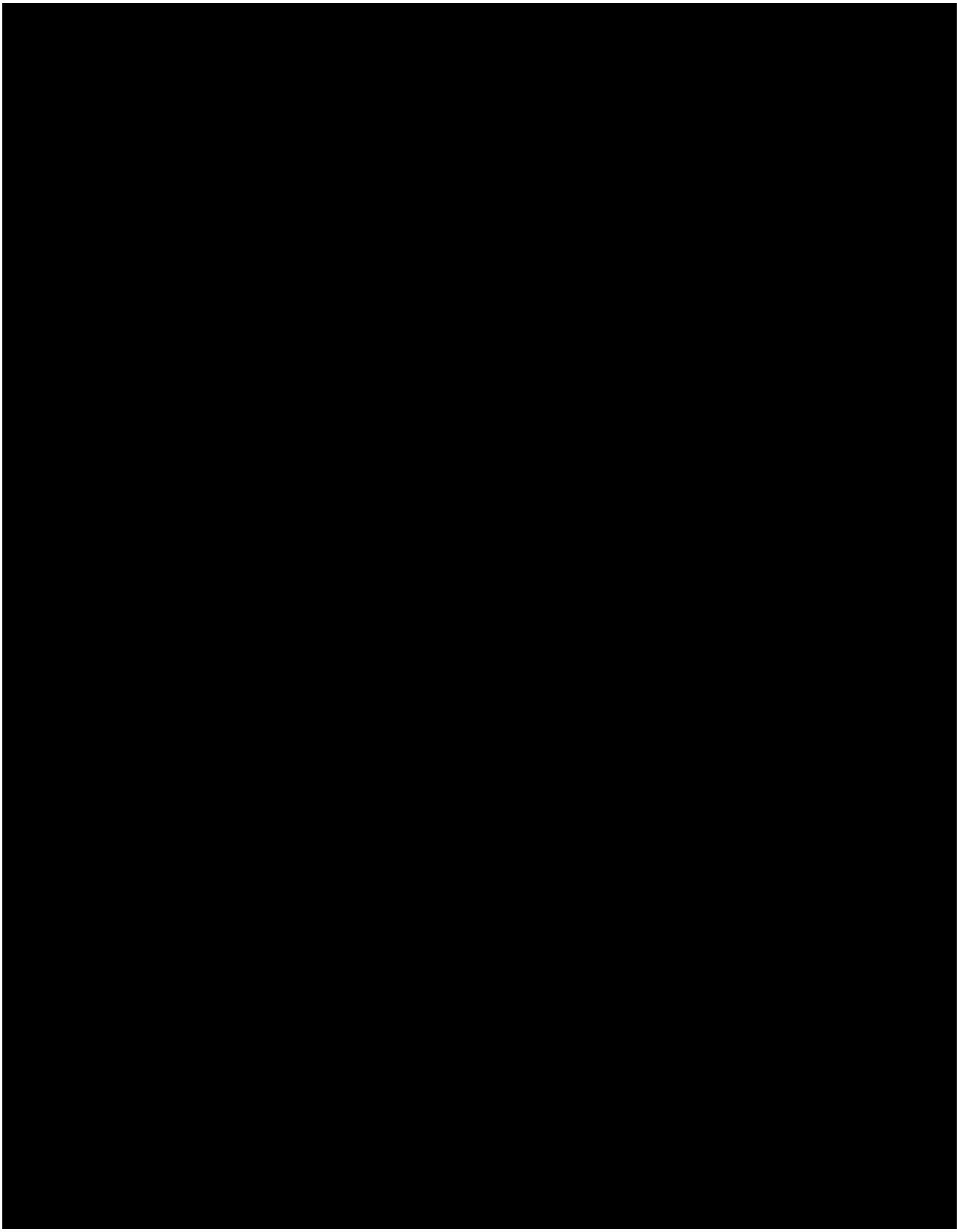
This Statistical Analysis Plan has been reviewed and approved by:

VERSION HISTORY







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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

[redacted]	[redacted]
AE	Adverse event
ARB	Antibiotic-resistant bacteria
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BSS	Bristol Stool Scale
C. difficile	*Clostridium difficile*
CDI	*Clostridium difficile* infection
CI	Confidence interval
CRE	Carbapenem-resistant Enterobacteriaceae
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EIA	Enzyme immunoassay
ESBL	Extended-spectrum ß-lactamase
FMT	Fecal microbiota transplantation
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
IRT	Interactive response technology
ITT	Intent-to-Treat
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NAP1	North American Pulse-field type 1
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PP	Per-Protocol
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SOC	System Organ Class
TEAE	Treatment-emergent adverse event
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol CDI-001 (Version 7.0 [Amendment 04], March 01, 2019) and describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report. Changes to the primary efficacy hypothesis or analysis prior to database lock would require an amendment to the protocol and SAP.

2. STUDY OBJECTIVES

The objectives of this Phase 2 study are:

- To evaluate the safety and tolerability of CP101 treatment compared to placebo in adults with previously treated recurrent *Clostridium difficile* infection (CDI).
- To evaluate the efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI.

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a double-blind, placebo-controlled, parallel-arm, multicenter study comparing the safety, tolerability, and efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI. Subjects who are experiencing recurrent CDI will undergo screening procedures. Subjects who meet eligibility criteria will be randomized to study drug.

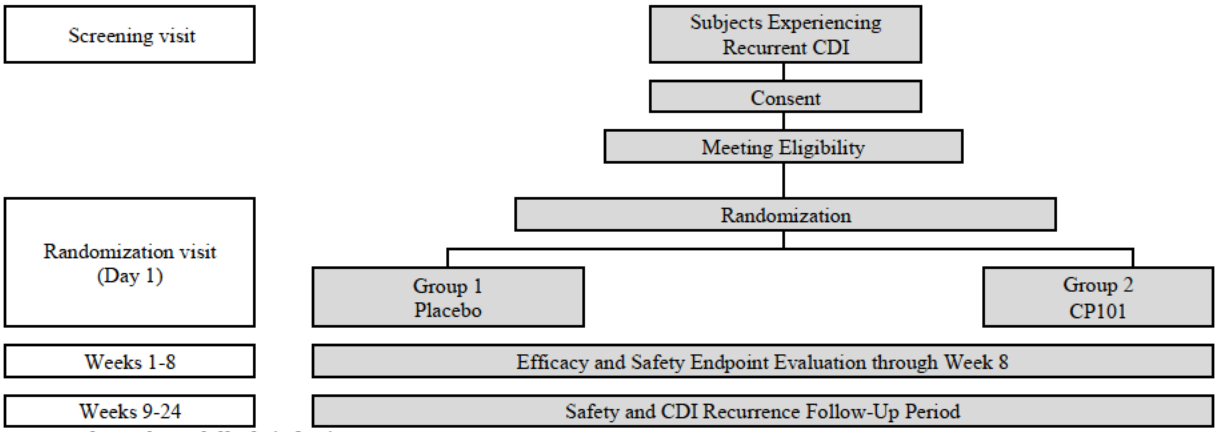
[redacted] Subjects will be monitored for recurrence of CDI, safety, and tolerability for 24 weeks following Randomization. The primary efficacy and safety endpoints will be evaluated at 8 weeks post-treatment, and all subjects will continue to be followed for an additional 16 weeks for safety and recurrence of CDI.

[redacted]

To qualify for the study, subjects must be experiencing recurrent CDI defined as: a) ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 12 months (inclusive of the current episode); OR b) 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) AND 65 years of age or older. Additionally, to qualify, recurrent CDI subjects must have received standard-of-care CDI antibiotics for the most recent CDI episode (for 10-42 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator) and have an adequate

clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during standard-of-care CDI antibiotics prior to Randomization.

Figure 1. Study Design



CDI = *Clostridium difficile* infection.

The primary clinical outcome is recurrence of CDI and is defined as a) diarrhea (> 3 unformed stools [Bristol Stool Scale (BSS) score of 6 or 7] per day) for 2 or more consecutive days; b) a stool specimen testing positive for *Clostridium difficile* (*C. difficile*) by a testing algorithm (see figure below); and c) requiring a course of standard-of-care CDI antibiotics. Secondary outcomes include assessment of decolonization of antibiotic-resistant bacteria (ARB) [redacted]

Figure 2. [redacted]

After the Randomization visit, subjects will return to the clinic at Weeks 4, 8, and 24 for safety and efficacy assessments. Telephone contact, including concomitant medication and adverse event reporting, will occur after the Screening visit at Weeks 1, 2, 3, 7, 11, 12, and 23.

Subjects will be issued a paper Memory Aid at the time of informed consent and given training on its use in order to aid in capturing the following information: occurrence of GI symptoms, frequency of stools, fecal urgency, stool incontinence, BSS, and any new medications taken (including antibiotics for treatment of CDI). Subjects will return the Memory Aid to the clinic and will review it with the coordinator at the Screening visit and Randomization (Day 1) after drug administration. At Week 1 telephone call, the Memory Aid data will be discussed, and subjects will be reminded to bring it to the Week 4 visit. In the event of suspected CDI recurrence, the Memory Aid recorded after Week 1 will be discussed at unscheduled visit(s).

Clinical signs and symptoms of recurrent CDI, including frequency and consistency of stools, will be confirmed by a *C. difficile* stool testing algorithm. North American Pulse-field type 1 (NAP1)/BI/027 subtyping will be performed if symptoms are consistent with recurrent CDI. [redacted]

Safety will be assessed via adverse event monitoring, concomitant medication use, physical examinations, vital signs, electrocardiograms (ECGs), clinical safety laboratory evaluations, and pregnancy testing (if female is of childbearing potential).

[redacted]

[redacted]

If a subject discontinues from the study early, the subject will be asked to return to the clinic within 14 days after discontinuation to undergo the scheduled Week 24 assessments prior to study discharge. All other subjects will have their final visit at Week 24 ± 14 days.

3.2. Study Population

Approximately 200 subjects 18 years of age or older, who experience recurrent CDI, and who respond to a standard-of-care CDI antibiotic regimen for the most recent CDI episode will be randomized to the study drug.

3.3. Randomization

[redacted]

3.4. Blinding

The study drug blind will be maintained through Week 8. Subjects, the Sponsor, Investigators, and all study site personnel involved with the study, carrying out study procedures, evaluating subjects, entering study data, and/or evaluating study data will remain blinded to treatment allocations until all subjects have completed the Week 8 assessments and the database has been locked for the analysis at Week 8. The Investigators, study site personnel, and subjects will remain blinded until Week 24.

Active study drug and placebo will be identical with the exception of a unique identification number on the bottle label.

Investigators shall not break the study blind during the study, and Investigators should treat all subjects as if they had received CP101. However, in situations in which knowledge of the subject's study drug is necessary for clinical management, the Investigator must first attempt to contact the Medical Monitor or designee, to discuss and agree to the need for unblinding to occur. The Medical Monitor or designee will answer calls 24 hours a day, 7 days a week, and 365 days of the year. In situations in which the Investigator has tried, but is unable to reach the Medical Monitor or designee, he/she should use best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the Medical Monitor or designee.

Once a subject’s treatment assignment has been unblinded, the Medical Monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., date and time of the call to the Medical Monitor by the Investigator, reason for unblinding, and date and time of unblinding) shall be clearly recorded in the subject’s study file and in the electronic data capture (EDC) system, as part of relevant standard operating procedures. In addition, the Investigator should consider whether the clinical event prompting unblinding

should be considered an adverse event or serious adverse event (SAE), according to the regulatory definitions or criteria for adverse events or SAEs, and if so, submit an adverse event/SAE report to Sponsor or designee.

Sponsor or designee will also unblind any SAE reports that are unexpected, and considered to be related to the study drug, in accordance with safety reporting guidance and regulations.

3.5. Study Assessments

Table 1 presents the schedule of observations.

Table 1. Schedule of Observations

	Screening[1]	Rand. Visit[2]	Efficacy and Safety Assessment Period						Safety and CDI Recurrence Follow-Up Period			
Study time point/ activities — Week / Day	Prior to study drug (On-site)	0 (On-site)	1 (Tel)	2 (Tel)	3 (Tel)	4 (On-site)	7 (Tel)	8 (On-site)	11 (Tel)	12 (Tel)	23 (Tel)	Week 24 or early termination visit[3] (On-site)
		1	7 ± 2	14 ± 2	21 ± 2	28 ± 3	49 ± 3	56 ± 3	77 ± 3	84 ± 7	161 ± 7	168 ± 14
Screening/Administrative Assessments												
Informed consent[4]	X											
Inclusion/Exclusion Criteria	X	X[5]										
Demographics	X											
Medical history (including BMI)[6]	X											
Memory Aid data recording[7, 8]	X	X	X	<——— (X) ———>								
Memory Aid distribution, training, and/or review[8]	X	X	X	<——— (X) ———>								
Telephone contact[9]	X[1]		X	X	X		X		X	X	X	
Randomization[10]		X[5]										
Start/continue treatment of standard-of-care CDI antibiotics[11]	X											
[redacted]	X	X[5,12]						X				X
Study drug administration		X[13]										
Safety Assessments												
Complete physical examination[14]		X[5]										
Symptom-directed physical examination[8,15]	X					X		X				X
Vital signs[8,16], height[17], and weight[8,18]	X	X[19]				X		X				X
12-lead ECG (per standard-of-care)[20]	X							X				X[20]
Clinical safety laboratory evaluations[21]	X	X[5]				X		X				X
Drug screen (as needed)[22]	X											
Pregnancy testing[23]	X	X[5]						X				X
Concomitant medications[8]	X	X[5]	<——— X ———>									
Adverse events[8,24]	X	X	<——— X ———>									
Stool Assessments												
Stool sample collection[8]	X	X[5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Bristol Stool Scale[8]	X	X[5]	X	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
[redacted]	X	X[5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X

	Screening [1]	Rand. Visit [2]	Efficacy and Safety Assessment Period						Safety and CDI Recurrence Follow-Up Period			
Study time point/ activities — Week	Prior to study drug (On-site)	0 (On-site)	1 (Tel)	2 (Tel)	3 (Tel)	4 (On-site)	7 (Tel)	8 (On-site)	11 (Tel)	12 (Tel)	23 (Tel)	Week 24 or early termination visit [3] (On-site)
Day		1	7 ± 2	14 ± 2	21 ± 2	28 ± 3	49 ± 3	56 ± 3	77 ± 3	84 ± 7	161 ± 7	168 ± 14
Assessment for ARB [8,26]	X	X [5]	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X
NAP1/BI/027 subtyping [8]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
C. difficile stool testing algorithm [8]			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

ARB = antibiotic-resistant bacteria; BMI = body mass index; *C. difficile* = Clostridium difficile; CDI = Clostridium difficile infection; ECG = electrocardiogram; GI = gastrointestinal; hCG = human chorionic gonadotropin; NAP1 = North American Pulse-field type 1; rand. = randomization; RNA = ribonucleic acid; Tel = telephone assessment.
(X) = in the event of suspected recurrent CDI

1 The Screening visit includes the entire Screening period up to the time of Randomization. The Screening period is limited to 60 days between the signing of informed consent and Randomization. Where referenced as the Screening visit, study-required tests and procedures may be performed on 1 day or across multiple days, but preferably closest to the time of Randomization. During the Screening visit, potential study subjects will be fully informed regarding the nature of the study and possible adverse events, and will receive a copy of the informed consent form for review. All subjects must have a stool specimen documented as testing positive for *C. difficile* performed at the site or local laboratory within the previous 60 days from Randomization. After the Screening visit, 1 phone call will be made to the subject as a reminder for the upcoming Randomization visit.
In the event that the Screening period is planned for > 30 days, additional clinical safety laboratory evaluations may be conducted at the discretion of the Investigator.

2 [redacted] If the subject experiences diarrhea for 2 or more consecutive days during the washout period, the Investigator should contact the Medical Monitor.

3 If a subject discontinues from the study early, the subject will be asked to return to the clinic within 14 days after discontinuation to undergo the Week 24 assessments prior to study discharge. All other subjects will have their final visit at Week 24 ± 14 days.

4 The signing of the informed consent form initiates the screening process. Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act). Informed consent must be in place prior to performing any study procedures.

5 To be performed prior to study drug administration. NOTE: Missing stool sample does not preclude the subject from Randomization.

6 Includes CDI history (e.g., number of prior episodes) and a pre-CDI medically documented weight or BMI will be obtained.

7 Subjects will be issued a paper Memory Aid at the time of informed consent and given training on its use. The Memory Aid data will be discussed at the Screening visit and Randomization visit (Day 1) after drug administration. At Week 1 telephone call, the Memory Aid data will be discussed and subjects will be reminded to bring it to the Week 4 visit.

8 To be performed in the event of a suspected CDI recurrence at the timepoints marked as (X). For stool sample, instructions for at-home stool sample collection, handling, storage, and transportation/shipping are included in the Laboratory Manual and an instruction sheet will be distributed to subjects.

9. Subjects will be contacted by telephone. Subjects will be asked about any adverse events, including occurrence of diarrhea. If a subject reports diarrhea, the study staff will review the timing of those episodes and the subject may be asked to submit a stool sample for *C. difficile* testing. Subjects will be asked about their general well-being, changes in their health status, medications, and over-the-counter remedies, and will be reminded about their next study visit. From Screening through study completion, subjects will be reminded to record all relevant information on their Memory Aid, as applicable. If a solicitated adverse event is Grade 2 or greater on telephone contact at Week 1, an unscheduled visit will be arranged as soon as possible for evaluation and confirmation of the event. For all subsequent telephone contacts adverse events will be managed according to good clinical practice at the discretion of the treating physician.
At Week 4, 8, 24 visits every effort will be made to conduct an on-site assessment. However, under extenuating subject circumstances that make an on-site visit not feasible and after all reasonable measures to enable the subject's on-site visit have been exhausted, a telephone assessment will be conducted.

10 Randomization will occur [redacted] Eligible subjects will be allocated to 1 of 2 treatment groups in a 1:1 ratio.

11 For the most recent CDI episode, the subject will have received standard-of-care CDI antibiotics (10-42 days; with exact duration, antibiotic type, and dose at the discretion of the Investigator).

12 [redacted]

13 Subjects will have completed a mandatory washout [redacted] Study drug will be administered under direct supervision of clinic staff as an oral dose [redacted] Subjects will remain in the clinic for observation for at least 1 hour post-dose.

14 A complete physical examination will be performed (including evaluation of general appearance/mental status; head, eyes, ears, nose, throat; and the following body systems: skin, heart, lungs, abdomen, and extremities).

15 The Investigator will perform symptom-directed physical examinations based on subjects' signs and symptoms.

16 Vital signs (blood pressure, heart rate, and temperature) will be measured per standard-of-care. Body temperature should be taken at all visits where vital signs are measured. Vital signs and body temperature should also be measured at time of recurrence, if any.

17 Height will be measured at the Screening visit only per standard-of-care.

18 Subjects should be weighed per standard-of-care. Height and weight will be used to calculate BMI. BMI will be calculated from weight collected at Week 8 and Week 24 as well.

19 Vital signs will be measured before and after (within 60 minutes) study drug administration.

20 Single 12-lead ECG will be performed per standard-of-care at Screening and at Week 8. Evidence of clinically significant abnormalities during the Screening visit may result in exclusion from the study. At Week 24, the 12-lead ECG will be performed only if there are findings at the Week 8 ECG, or if the subject has symptoms requiring an ECG.

21 [redacted]

22 Optional (at the discretion of the Investigator) drug screen includes cotinine (not exclusionary), amphetamines, barbiturates, benzodiazepines, cannabinoids (not exclusionary), cocaine, opiates (not exclusionary), and alcohol.

23 Women of childbearing potential enrolled in this study will have serum hCG pregnancy testing administered during Screening and urine pregnancy testing thereafter, at the discretion of the Investigator. Women who are post-menopausal for ≥ 1 year or surgically sterile will not undergo pregnancy testing.

24 The adverse event reporting period will begin with informed consent and will continue through study completion or, in the case of withdrawal, until the outcome is determined. Adverse events will be collected after study drug administration on Day 1. Subjects will be asked about any adverse events, including occurrence of diarrhea. If a subject reports diarrhea, the study staff will review the timing of those episodes and the subject may be asked to submit a stool sample for *C. difficile* testing. Subjects will be asked about their general well-being, changes in their health status, medications, and over-the-counter remedies.

25 [redacted]

26 Stool sample collection for the assessment for ARB, defined as vancomycin-resistant enterococci, extended-spectrum ß-lactamase organisms, or carbapenem-resistant Enterobacteriaceae, will be performed on samples obtained at Screening, Randomization (Day 1) prior to study drug administration, Week 8, and Week 24. Assessment for ARB may also be performed at any other visit or time point (e.g., time of recurrence, if any).

4. SAMPLE SIZE JUSTIFICATION

[redacted]

5. EFFICACY ENDPOINTS

5.1. Primary Endpoints

The primary endpoints are:

- Proportion of subjects experiencing sustained clinical cure, defined as absence of recurrent CDI, through Week 8, and
- Incidence of adverse events through Week 8.

5.2. Secondary Endpoints

The secondary endpoints are:

- Proportion of subjects experiencing recurrent CDI with ribosomal NAP1/BI/027 *C. difficile* subtype through Week 8;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 8);
- Proportion of subjects experiencing sustained clinical cure at Week 24;
- Proportion of subjects experiencing CDI Recurrence through Week 24;
- Time-to-first recurrent CDI episode during the study (Day 1 through Week 24);
- Incidence of hospitalization due to recurrent CDI through Week 8 and through Week 24;
- Incidence of decolonization of antibiotic resistant bacteria (ARB), defined as Vancomycin-resistant enterococci (VRE), Extended spectrum ß-lactamase (ESBL) organisms, or Carbapenem-resistant Enterobacteriaceae (CRE) at Week 8 and Week 24 among co-colonized subjects;
- [redacted]
- Change in BMI by Week 8 and Week 24 relative to medically documented pre-CDI BMI; and

- Incidence of newly diagnosed autoimmune disease through Week 8 and Week 24.

5.3. Other Safety Endpoint

The other safety endpoint is:

- Incidence of adverse events through Week 24.

5.4. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

6. SAFETY ASSESSMENT

6.1. Adverse Events

The adverse event reporting period will begin with informed consent and will continue through study completion or, in the case of withdrawal, until the outcome is determined. Adverse events will be assessed at each visit and through telephone contact with the subject. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.1).

The intensity of an adverse event will be graded according to the scale below in addition to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) for Grading the Severity of Adult Adverse Events. The clinical significance of the adverse event is determined by the Investigator.

Grade	Description
Grade 1 (Mild):	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate):	Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3 (Severe):	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4 (Life-Threatening):	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death):	Death related to adverse event

In this study, diarrhea is considered an adverse event and is defined as > 3 unformed stools (BSS score of 6 or 7) per day. If a subject has diarrhea for 2 or more consecutive days and is accompanied by a positive test for *C. difficile* by a testing algorithm, and received additional standard-of-care CDI therapy, then diarrhea will not be recorded as an adverse event. Instead, it will be considered an on-study recurrent CDI episode and will be included in the determination of efficacy.

6.2. Clinical Safety Laboratory Evaluations

Samples of blood and urine are scheduled for collection at Screening, at Randomization (Day 1) prior to study drug administration, and at Weeks 4, 8, and 24; specific tests performed at each visit are shown in Table 2. The total volume of blood collected at scheduled study visits will be approximately 123 mL. Additional follow-up samples for clinical laboratory testing should be obtained as clinically indicated. A 3-mL serum aliquot will be collected at each time point and archived for safety testing as may be required by emergence of adverse conditions.

Subjects with a white blood cell count $\geq 15 \times 10^9$, laboratory evidence of acute kidney injury, or an absolute neutrophil count of $< 1 \times 10^9$ neutrophils at Screening are to be excluded from the study.

All clinical laboratory testing, with the exception of optional drug testing or on-site urine pregnancy testing during the treatment period for females of childbearing potential, will be performed by the central clinical laboratory.

Table 2. Clinical Laboratory Safety Tests

Category	Analyte
Hematology	Complete blood count with differential.
Chemistry	[redacted]
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio.
Urinalysis	[redacted]
Screening only Drug Screen (Optional, at discretion of the Investigator) Pregnancy	Optional drug screen including cotinine (not exclusionary), amphetamines, barbiturates, benzodiazepines, cannabinoids (not exclusionary), cocaine, opiates (not exclusionary), and alcohol. Serum hCG for women of childbearing potential.

hCG = human chorionic gonadotropin.

6.3. Physical Examinations

A complete physical examination (including evaluation of general appearance/mental status; head, eyes, ears, nose, throat; and the following body systems: skin, heart, lungs, abdomen, and extremities) will be performed at the time points listed in the Schedule of Observations (Table 1).

The Investigator will perform the symptom-directed physical examinations based on subjects' signs and symptoms at the time points listed in the Schedule of Observations (Table 1).

6.4. Vital Signs, Height, and Weight

Vital signs (blood pressure, heart rate, and temperature) will be assessed per standard-of-care as listed in the Schedule of Observations (Table 1). Vital signs will be measured before and after (within 60 minutes) study drug administration. Body temperature should be taken at all visits where vital signs are measured. Vital signs and body temperature should also be measured at time of recurrence, if any.

Body weight and height (Screening only) will be measured per standard-of-care. Height and weight will be used to calculate BMI. A pre-CDI medically documented weight or BMI will be obtained. BMI will be calculated from weight collected at Week 8 and Week 24 as well.

6.5. Electrocardiograms

Single 12-lead ECGs will be performed per standard-of-care at the time points listed in the Schedule of Observations (Table 1). Evidence of clinically significant abnormalities during the Screening visit may result in exclusion from the study. A 12-lead ECG will only be performed at Week 24 if there are findings at the Week 8 ECG or if the subject has symptoms requiring an ECG.

6.6. [redacted]

[redacted]

6.7. [redacted]

7. ANALYSIS POPULATIONS

7.1. Intent-to-Treat Population (ITT) or All Randomized

All subjects randomized into the study. The ITT population will be analyzed according to the treatment group to which subjects were randomized.

7.2. Modified ITT Population (mITT or Full Analysis population)

All subjects in the ITT population who receive at least 1 capsule of study drug at Randomization (Day 1). The mITT population will be the primary analysis population for all efficacy analyses.

7.3. Per-Protocol (PP) Population

All subjects in the mITT population who have received at least 80% of study medication, completed 8 weeks of follow up or had documented CDI recurrence prior to the 8-week follow-up and did not have any major protocol deviation that affect the efficacy or safety of the study drug.

7.4. Week 24 Per-Protocol (PP) Population

All subjects in the mITT population who have received at least 80% of study medication, completed 24 weeks of follow up or had documented CDI recurrence prior to the 24-week follow-up and did not have any major protocol deviation that affect the efficacy or safety of the study drug. The Week 24 PP Population will be used for all analyses of the Week 24 endpoints where the PP Population is specified.

7.5. Safety Population

All enrolled subjects who received at least 1 capsule of study drug. Unless otherwise stated, the Safety population will be the default analysis population for all safety analyses. Analyses of safety will be performed based on treatment received, even if different from the treatment group to which subjects were randomized.

8. STATISTICAL ANALYSIS

8.1. General Statistical Considerations

8.1.1. General Analysis Approach

- All table summaries and listings will present the results by study drug (CP101 and placebo).
- For purposes of all analysis and reporting, days will be numbered relative to the first day of dosing. Day 1 will be defined as the date on which a subject receives the first dose of study drug, as recorded on the electronic case report form (eCRF). The day prior to the first dose of study drug is Day -1;
- Descriptive statistical methods will be used to summarize study data, with hypothesis testing performed for the primary efficacy endpoints at Week 8. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data, and refers to frequencies and percentages for categorical data, along with 95% confidence interval (CI) as appropriate. For categorical data summary, number of subjects with missing data will be included and percentages will be calculated based on the total number of subjects in the specified analysis population. For some data that may be presented as continuous variables, there may be scientific reasons to present those data in constructed categories as well (e.g., BMI). Reasons for the categories will be described in the Clinical Study Report.
- Individual data listings of all data represented on the eCRF will be presented. Sort order for data listings will be subject identification number, visit, and time point where appropriate.
- The SAP will be finalized and approved by signatures and dates prior to database lock for Week 8 and Week 24. The SAP will take precedence over the protocol for details about the statistical analyses for the study except the primary efficacy analyses which would require a protocol amendment. In addition to the analyses specified in the SAP, other exploratory analyses and graphical representations of the results may be produced after review of the data (post-hoc).
- Verbatim terms recorded for medical history conditions, surgical history procedures, and adverse events will be mapped to a SOC and preferred term using MedDRA, and all prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (B3 September 2018).

8.1.2. [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

- [redacted]

- [redacted]

8.1.3. Baseline Definition

For all efficacy and safety endpoints, baseline is defined as the last measurement or assessment prior to the administration of study drug.

8.1.4. Multiplicity

All comparisons of the secondary endpoints will be performed at a 2-sided 0.05 significance level, and no corrections for multiple testing will be made.

8.1.5. Derived Data

- Age will be calculated using the subject's date of birth and the date the subject signed informed consent [integer part of (informed consent date - birth date)/365.25].
- Change from baseline values will be calculated as the value at a post-baseline time point minus the baseline value.
- The Day on which an AE occurrence is noted will be calculated relative to the date of the first dose of study drug; Day = (date of AE – date of first dose) if date of AE is before date of first dose, Day = (date of AE – date of first dose + 1) if date of AE is on or after date of first dose.
- Other derived variables summarized in tables (with individual values provided in listings) will be described in footnotes of the tables where appropriate.

The detailed derivation for the efficacy and safety data will be documented in a separate derived datasets specification.

8.2. Study Subjects

8.2.1. Subject Disposition

The number of subjects who are randomized, treated, complete the study, and discontinue from the study will be summarized by treatment group and in total for the ITT population. Subject disposition will also be summarized by study site.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]
  - [redacted]
- [redacted]

For screen failures, a summary will be provided by reason of screen failure. [redacted]

In addition, the total number of subjects for each defined population will be tabulated. Reasons for exclusions from analyses populations will be tabulated.

8.2.2. Protocol Deviations

The number of subjects with at least one reportable protocol deviation, and the number of subjects with at least one reportable deviation in each deviation category defined in the study protocol deviation plan will be presented based on the ITT and mITT populations. In addition, the protocol deviations related to COVID-19 pandemic will be categorized and summarized separately.

Protocol deviations will also be listed by subject.

8.2.3. Demographic and Baseline CDI Characteristics

The following demographics will be summarized:

- Age (years) and age categorized as <65 vs. ≥65 years, and <70, 70-79, or ≥80 years;
- Sex;
- Race;
- Ethnicity;
- Pre-CDI weight (kg);
- Height (cm);
- Pre-CDI BMI (kg/m^2);
- Charlson comorbidity index (CCI)[1] and CCI categories (<3 and ≥3).

The following baseline CDI characteristics will be summarized:

- CARDS score[2] and score categories (<5, 5-9, 10-14, and ≥15);
- GEIH-CDI score[3] and score categories (≤3 and >3);
- Previous CDI-associated hospitalization;
- Previous CDI episodes
    - Total number of CDI episode in previous 12 months
- Recurrent CDI category
    - ≥ 3 episodes with 2 episodes occurring in the previous 12 months
    - 2 episodes of CDI occurring in the previous 6 months AND 65 years or older
- [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]

- Recurrent CDI history – Standard-of-care CDI antibiotics for most recent study entry-qualifying episode
    - Vancomycin and length categories (≤10, 10-14, 15-42, and ≥43 days)
    - Fidaxomicin and length categories (≤10, 10-14, 15-42, and ≥43 days)
    - Metronidazole and length categories (≤10, 10-14, 15-42, and ≥43 days)
    - CDI antibiotic combination and length categories (≤10, 10-14, 15-42, and ≥43 days)
    - Other and length categories (≤10, 10-14, 15-42, and ≥43 days)
- Medications (at Randomization)
    - Proton pump inhibitor vs no proton pump inhibitor
    - Immunosuppressive agents vs no immunosuppressive agents

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment group in all analysis populations.

8.2.4. Medical and Surgical History

Medical and surgical history terms will be coded using MedDRA (Version 20.1). Medical and surgical history will be summarized by treatment group and MedDRA SOC and preferred term in all analysis populations.

All Medical and surgical history will be listed by subject.

8.2.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (B3 September 2018). Prior medications will include medications used before the administration of study drug. Any medications used on or after the administration of study drug will be included as concomitant medications.

The number and percentage of subjects taking prior medications will be summarized in all analysis populations by Anatomical Therapeutic Chemical (ATC) class and preferred term for each treatment group.

The number and percentage of subjects taking concomitant medications will be summarized in the same manner.

All prior and concomitant medications and procedures will be listed by subject.

8.2.6. Study Drug Compliance

[redacted] In addition, summary tables will be provided to show the number and percentage

of subjects in each treatment group with compliance in the following categories: <80% and ≥80%.

[redacted]

8.3. Efficacy Analyses

8.3.1. Primary Efficacy Analyses

The primary efficacy endpoint is defined as the proportion of subjects with sustained clinical cure* (Table 3) through Week 8 calculated as the number of subjects with sustained clinical cure through Week 8 divided by the total number of subjects in the analysis population. [redacted]

Table 3. [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The proportion of subjects with sustained clinical cure through Week 8 will be summarized by treatment group in the mITT population and tested using a Chi-Square test for treatment group differences. The difference in proportions will be presented together with 95% confidence intervals.

For the primary efficacy analysis, the active treatment group will be compared to the placebo group. The null hypothesis will be tested at a two-sided significance level of 0.05. In addition, the 95% two-sided confidence interval of the treatment difference will be presented based on Wilson's Score method.

Null Hypothesis: There is no difference between the proportions of subjects with sustained clinical cure, defined as absence of recurrent CDI through Week 8 in the CP101 group compared to the placebo group. The null and alternative hypotheses are the following:

H_0: $p_1 = p_2$
H_1: $p_1 \neq p_2$

Where:

p_1 = the primary efficacy outcome in the CP101 group

p_2 = the primary efficacy outcome in the placebo group

[redacted]

- [redacted]

- [redacted]

8.3.2. Secondary Efficacy Analyses

All comparisons of the secondary endpoints will be performed at a 2-sided 0.05 significance level, and no corrections for multiple testing will be made.

Proportion of subjects with sustained clinical cure through Week 8 in the PP Population

Analysis of proportion of subjects with sustained clinical cure through Week 8 will be performed for the PP Population.

Proportion of subjects experiencing recurrent CDI through Week 8 by ribosomal NAP1/BI/027 subtype at CDI recurrence

The proportion of subjects experiencing recurrent CDI at Week 8 will be summarized by ribosomal NAP1/BI/027 *C. difficile* subtype at CDI recurrence for the mITT and PP populations and compared using Chi-Square or Fisher's exact test, as appropriate, within each subtype (NAP1/BI/027 vs. not NAP1/BI/027).

[redacted]

[redacted]

Proportion of subjects experiencing sustained clinical cure at Week 24

The proportion of subjects experiencing sustained clinical cure through Week 24 is defined as the number of subjects with sustained clinical cure through Week 24 divided by the total number of subjects in the analysis population. Investigator reported suspected CDI recurrence will be adjudicated by an independent Adjudication Board in a blinded fashion prior to database lock. The determination of "sustained clinical cure" is defined in Table 4. The proportion of subjects experiencing sustained clinical cure at Week 24 will be summarized by treatment group for the mITT and PP populations and tested using a Chi-Square test for treatment group differences. The difference in proportions will be presented together with 95% confidence intervals.

Table 4. [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Proportion of subjects experiencing CDI Recurrence through Week 24

The proportion of subjects experiencing CDI recurrence through Week 24 is defined as the number of subjects with CDI recurrence through Week 24 divided by the total number of subjects in the analysis population. Investigator reported suspected CDI recurrence will be adjudicated by an independent Adjudication Board in a blinded fashion prior to database lock for Week 24 and will constitute the determination of "CDI recurrence" as defined in column 4 of Table 4.

The proportion of subjects with recurrence through Week 24 will be summarized by treatment group in the mITT and PP populations and tested using a Chi-Square test for treatment group differences. The difference in proportions will be presented together with 95% confidence intervals.

[redacted]

Incidence of hospitalization due to recurrent CDI through Week 8 and Week 24

Incidence of hospitalization (including emergency room visits) due to recurrent CDI is defined as the number of subjects who were hospitalized due to recurrent CDI divided by the total number of subjects in the analysis population. Incidence of hospitalization due to recurrent CDI at Week 8 and Week 24 will be summarized by treatment group for the mITT and PP populations and tested using Chi-Square or Fisher's exact test as appropriate. In addition, duration of hospitalization will be summarized by treatment group. Duration of hospitalization will be summarized by treatment group for the mITT and PP populations and tested using a T-test for treatment group difference. Duration of hospitalization is calculated as the total number of days of hospitalization.

Incidence of decolonization of ARB at Week 8 and Week 24

Incidence of decolonization of ARB is defined as the number of subjects who experienced decolonization of ARB (VRE, ESBL organisms, or CRE) divided by the total number of subjects with ARB at baseline in the analysis populations. Incidence of decolonization of ARB at Week 8 and Week 24 will be summarized by treatment group for the mITT and PP populations and tested using a Chi-Square or Fisher's exact test as appropriate.

[redacted]

Change in BMI at Week 8 and Week 24

Change from pre-CDI BMI will be calculated at the specified study visit as the value at the specified study visit minus the pre-CDI value. Change in BMI at Week 8 and Week 24 relative

to medically documented pre-CDI BMI will be summarized by treatment group in the mITT and PP populations.

8.3.3. [redacted]

[redacted]

8.3.4. Subgroup Analyses

The following subgroups based on baseline characteristics will be used for subgroup analyses for the primary efficacy endpoint in the mITT and PP populations.

- Age group (<65 years vs. ≥65 years)
- Age group (<70, 70-79, and ≥80 years)
- Gender group (male vs. female)
- Race group (Caucasian vs. others)
- Charlson Comorbidity Index (<3 vs. ≥3)

- CARDS score (<5, 5-9, 10-14, and ≥15)
- GEIH-CDI score (≤3 vs. >3)
- Previous CDI episodes - total number of CDI episode in previous 12 months
- Recurrent CDI category
    - ≥3 episodes of CDI with 2 occurring in within the previous 12 months
    - 2 episodes of CDI occurring within the previous 6 months and 65 years old or greater
- Previous CDI-associated hospitalization
- [redacted]
- [redacted]
- [redacted]
- Ad-hoc Analyses

Additional analyses may be performed and will be considered as ad-hoc analyses and exploratory in nature.

8.4. Safety Analyses

All safety summaries and analyses will be performed on the Safety population. All subjects will be summarized according to the treatment actually received.

Safety will be evaluated by presenting summaries of AEs, vital signs, laboratory evaluations and ECG parameters. For each safety parameter, unless otherwise stated, the last assessment made prior to the administration of study drug will be used as the baseline value for all analyses.

8.4.1. Adverse Events

Any event reported on the eCRF that occurs during or after the administration of study drug is defined as treatment-emergent adverse event (TEAE). Additionally, it will be assumed that an adverse event that was reported to have started at Randomization (Day 1) without an associated onset time may have occurred after the administration of study drug. Hence, adverse events occurring at Randomization (Day 1) with no associated onset time are assumed to be treatment-emergent.

For the primary safety endpoint, the incidence rate of TEAEs will be presented by treatment group through Week 8.

For the other safety endpoints, the incidence rate of TEAE will be presented by treatment group through Week 24.

In addition, an overview of TEAEs will be provided which summarizes the incidence of the following information:

- All TEAEs
- Drug-related TEAEs
- Maximum severity of TEAEs
- Deaths
- Serious adverse events (SAEs)

The number and percentage of subjects who experienced at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAEs, withdrawals due to TEAEs, and all SAEs will be summarized in the same manner.

Although a subject may have two or more TEAEs, the subject is counted only once within a System Organ Class and Preferred Term category. The same subject may contribute to two or more preferred terms in the same System Organ Class category.

A list of subjects who have SAEs, and a list of subjects who discontinue from study drug will be provided. All adverse events will be listed.

Newly diagnosed autoimmune disease will be reported as an AE. Newly diagnosed autoimmune disease is defined autoimmune disease occurs on or after the administration of study drug. Incidence of newly diagnosed autoimmune disease at Week 8 and Week 24 will be summarized by treatment group for the Safety population. The number and percentage of subjects who experienced treatment-emergent autoimmune disease will be presented by system organ class and preferred term.

The solicited signs and symptoms collected will be entered in the eCRF and will be graded for severity. The number and percentage of subjects who experienced solicited signs and symptoms will be presented by treatment group and severity.

8.4.2. Clinical Laboratory Evaluations

Descriptive statistics for clinical laboratory tests for hematology, chemistry, and coagulation listed in Table 2 will be presented by study visit as well as the change from baseline.

Laboratory abnormalities will be graded according to NCI CTCAE Version 4.03 (for analytes where CTCAE grading applies). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group and severity grade. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided by treatment group. For laboratory parameters with no CTCAE grading, shift tables (with categories of low, normal, high) from baseline to worst post-treatment value will be provided by treatment group. Both scheduled and unscheduled post-treatment values during the treatment period will be considered.

All clinical laboratory data will be listed. Values outside the normal ranges will be identified in the data listings with flags for low (L) and high (H).

8.4.3. Vital Signs

Descriptive statistics for vital signs (temperature, heart rate, blood pressure and respiratory rate) will be presented by study visit and for the change from baseline. Descriptive statistics for weight will be presented by study visit and for the change from pre-CDI weight.

A listing of all vital signs will be provided by subject.

8.4.4. Electrocardiograms (ECG)

Descriptive statistics will be provided for 12-lead ECG findings (heart rate, QRS, PR, RR, and QT, and QTcF) and changes from baseline for each scheduled visit in the Safety Population.

QTcF will be calculated as follows:

All ECG measurements and the overall interpretation will be listed by subject.

8.4.5. Physical Examination

Physical examination findings will be summarized for any abnormal findings that are considered clinically significant in the opinion of the Investigator. These will be recorded as adverse events or be captured on the medical history if they are already present during Screening.

Physical examination findings will be listed by subject.

9. TIMING OF PRIMARY ENDPOINT ANALYSIS

Selected analysis will be performed after database lock for Week 8. After week 8 database is locked, the database will be unblinded by the independent unblinded personnel at Medpace

only. The unblinded analysis results will be delivered to the Sponsor and blinding procedures will continue to be adhered to as described in the protocol.

10. REFERENCES

1. Suidan RS, Leitao MM Jr, Zivanovic O, Gardner GJ, Long Roche KC, Sonoda Y, Levine DA, Jewell EL, Brown CL, Abu-Rustum NR, Charlson ME, Chi DS. Predictive value of the Age-Adjusted Charlson Comorbidity Index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer. *Gynecol Oncol*. 2015; 138(2):236-251.

2. Kassam Z, Cribb Fabersunne C, Smith MB, Alm EJ, Kaplan GG, Nguyen GC, Ananthakrishnan AN. Clostridium difficile associated risk of death score (CARDS): a novel severity score to predict mortality among hospitalised patients with C. difficile infection *Aliment Pharmacol Ther*. 2016; 43(6):725-733.

3. Cobo J, Merino E, Martinez C, Cozar-Listo A, Shaw E, Marrodan T, Calbo E, Bereciartua E, Sanchez-Munoz LA, Salavert M, Perez-Rodriguez MT, Garcia-Rosado D, Bravo-Ferrer JM, Galvez-Acebal J, Henriquez-Camacho C, Cuquet J, Pino-Calm B, Torres L, Sanchez-Porto A, Fernandez-Felix BM, Nosocomial Infection Study Group. Prediction of recurrent Clostridium difficile infection at the bedside: the GEIH-CDI score. *Int J Antimicrob Agents*. 2018; 51(3):393-398.