Official Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of the Efficacy, Safety, and Tolerability of a Single Oral Administration of CP101 for the Prevention of Recurrent *Clostridioides difficile* Infection (PRISM4)

NCT#: NCT 05153499

Document: Protocol

Document Date: 04 May 2022

CLINICAL TRIAL PROTOCOL

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Trial Number:	FIN-CDI-301
Version Number:	3.0
Amendment:	2.0
Revised Final	Not applicable
Version Date	04 May 2022

CONFIDENTIALITY STATEMENT

RESPONSIBLE PERSONNEL

Sponsor - Medically Responsible Person

[redacted]

Contract Research Organization

[redacted]

Coordinating Investigator

[redacted]

SYNOPSIS

<table>
<tr><td>NAME OF COMPANY
Finch Research and Development

NAME OF FINISHED PRODUCT
CP101

NAME OF ACTIVE INGREDIENT
Full Spectrum Microbiota
(Complete Consortia)</td><td>Individual Trial Table Referring to Part of the Dossier:

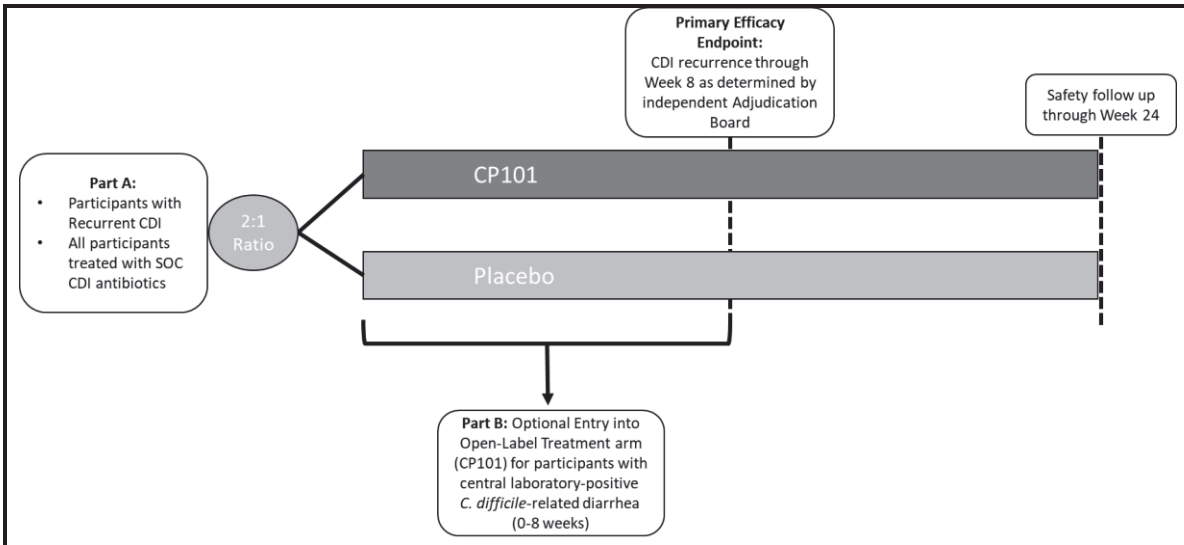
Volume:

Page:</td><td>(FOR NATIONAL AUTHORITY USE ONLY)</td></tr>
<tr><td colspan="3">TITLE OF TRIAL: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of the Efficacy, Safety, and Tolerability of a Single Oral Administration of CP101 for the Prevention of Recurrent Clostridioides difficile Infection (PRISM4)</td></tr>
<tr><td colspan="3">Protocol Number: FIN-CDI-301</td></tr>
<tr><td colspan="3">Indication: Recurrent Clostridioides difficile infection (CDI)</td></tr>
<tr><td colspan="3">TRIAL CENTER(S): Approximately 100 trial sites globally</td></tr>
<tr><td colspan="3">PUBLICATION (REFERENCE): Not applicable</td></tr>
<tr><td colspan="2">STUDIED PERIOD: Approximately 6-week Screening; single-dose treatment, and 24-week Follow-up in Part A

For eligible participants, single-dose, open-label treatment and 24-week Follow-up in Part B</td><td>PHASE OF DEVELOPMENT: 3</td></tr>
<tr><td colspan="3">OBJECTIVES:
The overall objectives of this Phase 3 trial are:
To evaluate the efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI
To evaluate the safety and tolerability of CP101 treatment compared to placebo in adults with previously treated recurrent CDI
See Trial Objectives for full definition.</td></tr>
<tr><td colspan="3">TRIAL DESIGN:

This Phase 3 trial will be conducted in 2 parts: a randomized, double-blind, placebo-controlled trial arm (Part A) and an optional open-label treatment arm (Part B). The trial is designed to evaluate the efficacy, safety, and tolerability of a single oral administration of CP101 for the prevention of recurrent CDI in adult participants. After completing standard-of-care (SOC) CDI antibiotics for their most recent CDI recurrence, participants who meet all eligibility requirements will be randomized in a 2:1 ratio to receive either CP101 or placebo (Part A). Participants will be evaluated for CDI recurrence and safety follow-up through Week 8, the primary endpoint, as well as through Week 24.

Participants who experience an on-trial, central laboratory-positive C. difficile-related diarrhea (see Inclusion Criteria Part B for full definition) through Week 8 are eligible for open-label treatment (OLT) with CP101 (Part B). Participants in Part B will be evaluated for CDI recurrence and safety follow-up through Week 8, as well as through Week 24.</td></tr>
</table>



Abbreviations: CDI = *Clostridioides difficile* infection; SOC = standard-of-care.

NUMBER OF PARTICIPANTS (PLANNED): Approximately 324 participants

PARTICIPANT POPULATION AND ELIGIBILITY CRITERIA:

Population:

Part A:

- Recurrent CDI defined as:
  - Participants with a history of **≥ 3 episodes of CDI**, with 2 episodes occurring within the previous 6 months (inclusive of the current episode); OR
  - Participants with a history of **2 episodes of CDI** occurring within the previous 6 months (inclusive of the current episode) may be eligible if **65 years of age or older**.

Part B:

- Participants who have an on-trial, central laboratory-positive *C. difficile*-related diarrhea within 8 weeks after receiving CP101 or placebo in Part A of the trial, and consent to having open-label administration of CP101.

Eligibility Criteria:

Inclusion Criteria Part A (Screening):

1. Participant or legal representative voluntarily agreed to participate by signing and dating the written informed consent form after trial has been fully explained.
2. Participant 18 years of age or older.
3. History of recurrent CDI defined as:
   - 3.1 ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 6 months (inclusive of the current episode); OR
   - 3.2 Participants with a history of 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) may be eligible if 65 years of age or older.
4. For the Qualifying CDI episode, the following criteria (4.1-4.4) must be satisfied:
   - 4.1 History of diarrhea (> 3 unformed stools per day) for 2 or more consecutive days that is clinically consistent with CDI.

   AND
   - 4.2 Documented positive stool test by local laboratory for toxigenic *C. difficile* (toxin enzyme immunoassay [EIA] or polymerase chain reaction [PCR]-based testing) for the current CDI episode and within 45 days prior to Randomization.

AND

4.3 Received a course of SOC CDI antibiotics for the most recent CDI episode (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator).

AND

4.4 Demonstrated an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to Randomization.

***NOTE**: ALL qualifying CDI episodes require CLINICAL and LABORATORY CONFIRMATION of eligibility by Medical Monitor.*

5. Females (assigned at birth) must fulfill at least 1 of the following criteria:
   - 5.1 Postmenopausal, defined as amenorrhea ≥ 1 year; or
   - 5.2 Surgically sterile: hysterectomy, bilateral oophorectomy, or tubal ligation; or
   - 5.3 Abstinent or willing to use adequate contraception from Screening through the Week 24 visit per Section 7.2.9.1.

6. Males (assigned at birth) must fulfill the following criteria: Abstinent or willing to use adequate contraception from Screening through the Week 24 visit per Section 7.2.9.1.

Exclusion Criteria <u>Part A</u> (Screening):

1. Known stool sample testing positive for enteric pathogen(s) (e.g., *Salmonella*, *Shigella*, diarrhoeagenic *E. coli*, *Campylobacter*, *Giardia*) within 28 days prior to Screening.
2. Inability to ingest capsules (e.g., severe nausea, vomiting, gastroparesis, gastric outlet obstruction, dysphagia and/or history of chronic aspiration).
3. Active or suspected ileus, toxic megacolon, or bowel obstruction.
4. Historical or current diagnosis of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, indeterminate colitis, or microscopic colitis).
5. Recent diagnosis (< 6 months prior to Screening) of diarrhea-predominant irritable bowel syndrome (post-infection or not related to an enteric infection). Participants with diarrhea-predominant irritable bowel syndrome ≥6 months prior to Screening may be randomized following confirmation of eligibility.
6. Current diagnosis of chronic diarrheal illness with pre-CDI baseline diarrhea. This includes but is not limited to celiac disease, bile salt diarrhea, chronic pancreatitis, and short gut syndrome.
7. Past administration of bezlotoxumab (Zinplava™), or past enrollment in a *C. difficile* vaccine trial where participant received active investigational product (IP) within 12 months prior to Randomization. Participants blinded to treatment assignment or with unknown status are excluded. Participants who only received placebo would not be excluded.
8. Participation in PRISM3 (CDI-001) or PRISM-EXT (CP101-CDI-E02) where participant received active IP or received CP101 at any time in the past. Participants who only received placebo would not be excluded.
9. Fecal transplant or other live microbiome therapeutics for any condition, regardless of route of administration, within 12 months prior to Randomization.
10. Initiation of any systemic cancer treatment (e.g., chemotherapy, radiotherapy, biologic, immunotherapy, others) for active malignancy that is planned 8 weeks prior to Randomization or during the 8 weeks following Randomization. Participants on maintenance treatment for malignancy may be randomized following confirmation of eligibility. NOTE: Participants on hormone therapy alone are eligible.
11. Known primary or secondary immunodeficiency, including but not limited to, IgA deficiency, common variable immunodeficiency, severe combined immunodeficiency, or human immunodeficiency virus/acquired immune deficiency syndrome.
12. History of solid organ transplantation or stem cell transplant.

13. Initiation or dose escalation of systemic immunosuppressive agents, at the discretion of the Investigator, for any condition during the 8 weeks prior to Randomization or planned during the 8 weeks following Randomization. Examples may include but are not limited to corticosteroid agents given orally or intravenously, cyclosporine, tacrolimus, or tumor necrosis factor inhibitors. Participants on stable low dose of systemic immunosuppressive agents or short courses (< 2 weeks) may be randomized following confirmation of eligibility.
14. Major intra-abdominal surgery (e.g., bowel resection) within the past 60 days prior to Screening (excluding appendectomy or cholecystectomy) and/or planned invasive surgery/hospitalization during the trial.
15. History of total colectomy or ileostomy.
16. Use of a systemic antibiotic for any condition (other than CDI) during the Screening period, or any anticipated use of a systemic antibiotic for any condition other than CDI during the trial for 8 weeks after Randomization. This includes participants who have a known medical procedure that requires antibiotic prophylaxis (e.g., elective surgical procedure or dental procedure requiring prophylactic antibiotics) scheduled during the trial.
17. Active drug, chemical, or alcohol dependency as determined by the Investigator.
18. Enrollment in any other investigational drug, device, or observational trial within 30 days or 5 half-lives of the last dose, prior to Randomization (Day 1) or at any time during this trial.
19. Pregnant, breast-feeding, or planning to become pregnant during the trial.
20. Clinically significant abnormal laboratory values including, but not limited to, white blood cell count $\geq 15 \times 10^9$ /L, absolute neutrophil count of $< 1 \times 10^9$ neutrophils/L, or laboratory evidence of acute kidney injury at Investigators discretion, at Screening.
21. Screening nasal PCR test is positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
22. Any acute, chronic, or unstable medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety. Examples include but not limited to acute myocardial infarction, acute stroke, uncompensated congestive heart failure, or decompensated liver disease.

    ***NOTE*:** Trial participants may be screened while an inpatient in an acute care facility/hospital but must be discharged from inpatient medical admission prior to Randomization.
23. Life expectancy < 24 weeks.
24. Known hypersensitivity to CP101 or any component of its formulation or history of severe adverse reactions or other common drug class effects during prior exposure to similar compounds per the judgment of the Investigator.

To be eligible for Randomization, the above listed inclusion/exclusion criteria as well as the following additional Inclusion Criteria Part A - Randomization (Day 1) must be satisfied:

Inclusion Criteria Part A Randomization (Day 1)

1. An outpatient prior to Randomization;

   NOTE: Participant may be screened while an inpatient in an acute care facility/hospital but must be discharged from inpatient medical admission prior to Randomization. Participants residing in an assisted living center, long-term care facility, or rehabilitation ward/center may be randomized.
2. Has received a course of SOC CDI antibiotics for the Qualifying CDI episode (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator).
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to Randomization.
4. [redacted]
5. [redacted]

Inclusion Criteria Part B of the trial (Screening):

1. Previously enrolled in Part A: Participants who have an on-trial, central laboratory-positive *C. difficile*-related diarrhea within 8 weeks after receiving CP101 or placebo in Part A defined as:

   a) Diarrhea (> 3 unformed stools in 24 hours for 2 or more consecutive days) or diarrhea that does not meet the definition, but the Investigator has a strong clinical suspicion of *C. difficile*-related diarrhea and Medical Monitor has confirmed per study Figure 8;

   AND

   b) A stool specimen testing positive for *C. difficile* by central laboratory testing algorithm (or local laboratory-positive under extenuating circumstances such as central lab closure);

   AND

   c) Participant has received a course of SOC CDI antibiotics for the most recent CDI event (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator).

   AND

   d) Participant has had an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to investigational product (IP) administration.

   NOTE: *Confirmation of eligibility by Medical Monitor is required before entry into Part B.*

Exclusion Criteria Part B (Screening):

1. New onset of any acute, chronic, or unstable medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety. Examples include but not limited to acute myocardial infarction, acute stroke, uncompensated congestive heart failure, and decompensated liver disease.
2. Pregnant, breast-feeding, or planning to become pregnant during the trial.
3. Screening nasal PCR test is positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and participant exhibits symptoms that in the opinion of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety.

Inclusion Criteria Part B Open-Label Treatment (Day 1):

The following criteria must be satisfied prior to OLT in Part B of the trial:

1. An outpatient prior to OLT.

   NOTE: Participant may be screened while an inpatient in an acute care facility but must be discharged from inpatient medical admission prior to IP administration. Participants residing in an assisted living center, long-term care facility, or rehabilitation ward/center are eligible for Part B.

2. Has received a course of SOC CDI antibiotics for the on-trial, central laboratory-positive *C. difficile*-related diarrhea (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator).
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to IP administration.
4. [redacted]
5. [redacted]

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Part A and Part B:

Part A: IP (CP101 [redacted] or matching placebo) will be administered after Randomization on Day 1 (single administration) as an oral dose [redacted]

Part B: All participants will be treated with a single dose of CP101 administered orally by capsules.

CRITERIA FOR EVALUATION

Efficacy:

The primary clinical outcome is CDI recurrence confirmed by an independent Adjudication Board (AB). The primary efficacy endpoint is CDI recurrence through Week 8. Determination of the primary endpoint utilizes a 3-step process:

1. **A new episode of diarrhea**: Participants are required to promptly report a new episode of diarrhea to trial site personnel (defined as > 3 unformed stools in 24 hours for 2 consecutive days). Additionally, surveillance for a new episode of diarrhea will include daily prompts to participants via a diary to record either the presence or absence of any unformed stool from Screening through Week 8. Thereafter participants will be required to contact the trial site if they experience a new episode of diarrhea between Week 8 and Week 24. At any time during the trial, if the number of unformed stools recorded in the diary by the participant meet the definition of a new episode of diarrhea, the trial site will be notified.
2. **Investigator evaluation**: The onset of a new episode of diarrhea will trigger an Investigator evaluation for CDI. Investigator evaluation will include a) review of diarrhea data (> 3 unformed stools in 24 hours, for 2 or more consecutive days); b) assessment of stool *C. difficile* testing by central laboratory testing algorithm (see Figure 1 below); and c) the clinical decision to start a course of SOC CDI antibiotics.
3. **Adjudication board:** The determination of the Investigator evaluation prompts review of the event by an independent AB. The purpose of the independent AB is to confirm if the event is a CDI recurrence. The AB decision will be included in the dataset for the statistical analysis of the primary efficacy endpoint of the trial.

Figure 1: Central Laboratory Testing Algorithm

Key secondary outcome includes determination of the participant's intestinal microbiome profile by 16S ribosomal ribonucleic acid (rRNA) gene amplicon sequencing before and after IP administration.

Safety:

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

In addition to collection of all AEs, the following AEs will be specifically solicited using a daily participant diary for 7 days following IP administration (Day 1 to Day 7): abdominal distention or bloating, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, nausea, vomiting, and fever. The diary will be reviewed at the Week 1 visit.

Endpoints:

Part A:

Primary Endpoints:

- Proportion of participants experiencing a CDI recurrence through Week 8.
- Incidence of TEAEs through Week 8.

Key Secondary Endpoints

- Improvement in intestinal microbiome diversity at Week 1.

Other Secondary Endpoints:

- Proportion of participants experiencing toxin EIA-positive recurrent CDI through Week 8;
- Proportion of participants experiencing toxin EIA-positive recurrent CDI through Week 24;
- Time-to-first recurrent CDI episode during the trial (Day 1 through Week 8);
- Proportion of participants experiencing a CDI recurrence through Week 24;
- Time-to-first recurrent CDI episode during the trial (Day 1 through Week 24);
- [redacted]

Exploratory Endpoints

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

Safety:

- Incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs);
- Clinical safety laboratory tests and vital signs will be summarized.

Part B:

Efficacy and Safety Endpoints

- Proportion of participants experiencing CDI recurrence through Week 8 and Week 24;
- Incidence of TEAEs and TESAEs through Week 8 and Week 24.

Other Endpoints

The remaining secondary and exploratory endpoints are identical to Part A and will be described in further detail in the statistical analysis plan (SAP).

STATISTICAL METHODS:

This trial is a randomized, double-blind, placebo-controlled, Phase 3 trial with an approximate sample size of 324 participants. An interim analysis (IA) is planned when 8-week data are available for approximately 217 participants (67% information fraction) in the intent-to-treat (ITT) population, including those that discontinued earlier than 8 weeks (e.g., due to lost-to-follow-up, withdrawal of consent). This IA is intended to evaluate whether the data are sufficient to declare success for efficacy early based on primary efficacy endpoint, but not for evaluating futility. [redacted]

Determination of Sample Size

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AB	Adjudication Board
AE	Adverse event
BMI	Body mass index
CBC	Complete blood count
CDAD	*Clostridioides difficile*-associated diarrhea
CDI	*Clostridioides difficile* infection
[redacted]	[redacted]
[redacted]	[redacted]
CRA	Clinical research associate
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EDC	Electronic data capture
EIA	Enzyme immunoassay
[redacted]	[redacted]
FDA	Food and Drug Administration
FMT	Fecal microbiota transplantation
GCP	Good Clinical Practice
[redacted]	[redacted]
hCG	Human chorionic gonadotropin
IA	Interim analysis
ICF	Informed consent form
ICH	International Council for Harmonization
[redacted]	[redacted]
IEC	Independent ethics committee
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent to treat
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition
mITT	Modified intent-to-treat
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OLT	Open-label treatment
PCR	Polymerase chain reaction
PP	Per-protocol
PRO	Patient-reported outcome
rRNA	Ribosomal ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	Standard-of-care
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WBC	White blood cell
[redacted]	[redacted]

1 BACKGROUND INFORMATION

1.1 Investigational Product

CP101 is an investigational oral microbiome drug designed to deliver a complete and functional microbiome to durably repair intestinal dysbiosis and restore microbiome diversity, which is known to be disrupted in participants with recurrent *Clostridioides difficile* infection (CDI), and key in the pathogenesis of CDI recurrence.

1.2 Background

*Clostridioides difficile (*formerly *Clostridium difficile; C. difficile)* is a toxin-producing, spore-forming bacterium that causes severe and persistent diarrhea in infected individuals. *C. difficile* expresses toxins that lead to inflammation of the colon, severe diarrhea, and abdominal pain, as well as potentially more serious clinical outcomes including toxic megacolon, perforation of the colon, and death. Commonly patients with CDI experience recurrent CDI after completing a course of standard-of-care (SOC) CDI antibiotics (McDonald et al. 2018). Clinically, recurrent CDI is often associated with more severe symptoms and more frequent complications, and serious complications of recurrent CDI have increased significantly over the past decade (Cohen et al. 2010; Khanna et al. 2012). Recurrent CDI occurs when 2 conditions are met in an individual: 1) the causative microorganism (*C. difficile*) is present, and 2) there is an abnormal microbiome, or dysbiosis. As SOC antibiotics exacerbate dysbiosis, there is an urgent need for therapeutics that address intestinal dysbiosis, which underlies the pathogenesis of CDI recurrence. CP101 is an investigational oral microbiome drug designed to deliver a complete and functional microbiome to durably repair intestinal dysbiosis, which is being evaluated for the prevention of recurrent CDI. The proposed use of CP101 is for prevention of recurrent CDI in individuals with recurrent CDI.

1.2.1 Epidemiology

CDI is the most common healthcare-associated infection and it is recognized by the United States Centers for Disease Control as one the most urgent antibiotic-resistant bacterial threats in the United States. Recurrent CDI represents a major unmet medical need. In the United States, Desai and colleagues estimate greater than 165,000 episodes of recurrent CDI in 2014 (Desai et al. 2016). Due to few effective treatments, and an absence of therapeutics that address the underlying dysbiosis underpinning the pathogenesis of recurrent CDI, there has been a rise in multiply recurrent CDI. Ma and colleagues report the incidence of multiply recurrent CDI has dramatically increased, with an 188.8% increase in annual incidence between 2001 and 2012 (Ma et al. 2017). Overall, recurrent CDI is a major unmet medical need.

1.2.2 Pathophysiology

The underlying pathophysiology of recurrent CDI is distinct. Recurrent CDI is driven by intestinal dysbiosis characterized by 1) a lack of colonization resistance conferred by the presence of a healthy and diverse gut microbiome, and 2) the deficiency of microbiome-derived secondary bile acids, which prevent the germination of *C. difficile* spores into toxin-producing vegetative *C. difficile*.

1.2.2.1 Lack of Colonization Resistance Due to Low Microbiome Diversity

The healthy microbiome has high diversity and provides colonization resistance against enteric pathogens including *C. difficile* (Perez-Cobas et al. 2015; Ducarmon et al. 2019). Patients with recurrent CDI have markedly lower microbiome diversity, impairing colonization resistance, compared to healthy controls or patients with primary CDI (Allegretti et al. 2016; Chang et al. 2008). A community-level dysbiosis characterized by low microbiome diversity, increases susceptibility to *C. difficile* colonization and infection (Seekatz and Young 2014; Chang et al. 2008). Both disease severity and the development of CDI recurrence is associated with decreased microbiome diversity, suggesting a lack of colonization resistance (Seekatz and Young 2014). Additionally, although CDI antibiotics kill vegetative *C. difficile* capable of producing toxin, they do not address residual *C. difficile* spores, which – in a low microbiome diversity environment –germinate into toxin-producing *C. difficile* following cessation of antibiotics (Seekatz et al. 2015).

1.2.2.2 Impaired Conversion of Primary to Secondary Bile Acids

Patients with recurrent CDI also have depleted secondary bile acids, derived from a healthy microbiome, when compared to patients with primary CDI or healthy controls (Allegretti et al. 2016). The disruption of microbiome-mediated conversion of primary to secondary bile acids is an important pathophysiological mechanism in the development of recurrent *C. difficile* infection (Allegretti et al. 2016). Loss of protective, microbiome-derived secondary bile acids allow for *C. difficile* spore germination, expansion of the vegetative form of *C. difficile* bacteria and subsequent production of cytotoxins which cause tissue damage, diarrhea and C. *difficile*-associated complications (Baktash et al. 2018).

1.3 Clinical Findings

1.3.1 CP101, a Microbiome Therapeutic for Prevention of Recurrent C. difficile Infection

CP101 is an investigational oral microbiome drug designed to deliver a complete and functional microbiome to durably repair intestinal dysbiosis, which is being evaluated for the prevention of recurrent CDI. CP101 contains live microbial communities, derived from rigorously screened human donor stool that is tested, stabilized, characterized, and formulated into capsules [redacted]. CP101 increases microbiome diversity, reestablishing colonization resistance, and increasing the protective, microbiome-derived secondary bile acids, addressing the underlying biology of recurrent CDI.

Improved microbiome diversity: In a Phase 1b trial of CP101, participants with recurrent CDI who were treated with CP101 demonstrated a significant increase in microbiome diversity compared to baseline ($n=49$, $p<0.001$), and thus improved colonization resistance leading to a high efficacy rate (87.8%) (Staley, Hamilton, et al. 2017; Staley, Vaughn, et al. 2017). [redacted]

[redacted]

01.

[redacted]

Figure 2: [redacted]

Figure 3: [redacted]

Increase in beneficial microbiome-derived secondary bile acids: CP101 increases secondary bile acid biosynthesis by restoring gut microbes active in the conversion of primary to secondary bile acids. Secondary bile acids inhibit germination of *C. difficile* and toxin-production (Staley et al. 2018). Data from the Phase 1b trial demonstrated that CP101

increased in the protective, microbiome-derived secondary bile acids in participants with recurrent CDI ($p<0.0001$) (Staley, Vaughn, et al. 2017).

[redacted]

Figure 4: [redacted]

[redacted]

1.4 Summary of Trial Design

This trial is composed of 2 parts: A) Part A is a randomized, double-blind, placebo-controlled trial and B) Part B is an *optional* open-label treatment (OLT) arm for participants who experience an on-trial central laboratory-positive *C. difficile*-related diarrhea through Week 8 (Figure 5).

- **Part A** will evaluate the efficacy, safety and tolerability of CP101 versus placebo for the prevention of recurrent CDI
- **Part B** is an *optional* OLT arm evaluating the efficacy, safety, and tolerability of CP101, in eligible participants from Part A who experience an on-trial central laboratory-positive *C. difficile*-related diarrhea through 8 weeks after receiving CP101 or placebo. See Part B, Section 6 of the protocol for further details regarding the OLT arm. **Participants are not eligible to enter Part B of the trial without having been dosed in Part A first.**

Participants with recurrent CDI who have received SOC CDI antibiotics (vancomycin, fidaxomicin, and/or metronidazole [Section 4]) will be randomized using an interactive response technology (IRT) system in a 2:1 ratio to CP101 or placebo. Participants should have completed a minimum of 10 days and a maximum of 21 days of SOC CDI antibiotics

[redacted] Following randomization on Day 1, participants will receive either CP101 or placebo.

Note: See Section 8.1 for definition of trial endpoints.

All participants will be followed through 8 weeks (Day 57 ± 3 days) for the primary efficacy endpoint (hereafter referred to as Week 8) and to Week 24 (Day 169 ± 14 days) for long-term safety endpoint (hereafter referred to as Week 24). The primary efficacy endpoint is the proportion of participants with CDI recurrence, through Week 8. CDI recurrence will be adjudicated by an independent blinded Adjudication Board (AB). For the primary safety endpoint, the incidence rate of treatment-emergent adverse events (TEAEs) will be presented by treatment group through Week 8. Participants will be followed through 24 weeks for other safety endpoints.

An interim analysis (IA) is planned after primary endpoint data is available for approximately 217 participants from the intent-to-treat (ITT) population (67% information fraction) (see Section 8.8). This IA is intended to evaluate whether the data are sufficient to declare success for efficacy early but not for evaluating futility. [redacted]

A trial diagram outlining Part A and Part B and the trial visits is described in Figure 5.

1.5 Rationale for Trial

1.5.1 Rationale for Use of CP101 for the Prevention of Recurrent CDI

CP101 is an investigational oral microbiome drug designed to deliver a complete and functional microbiome to durably repair intestinal dysbiosis. CP101 increases microbiome diversity, reestablishing colonization resistance, and increasing the protective, microbiome-derived secondary bile acids, addressing the underlying biology of recurrent CDI. CP101 efficacy in recurrent CDI has been demonstrated in Phase 1b and the first adequate and well-controlled trial (PRISM3) studies. PRISM4 is the second adequate and well-controlled pivotal trial in the drug development process for CP101 and will evaluate the efficacy and safety of CP101 in the prevention of recurrent CDI.

1.5.2 Data Supporting the Use of CP101 for the Prevention of Recurrent CDI

Phase 1b trial of CP101: The first clinical trial to evaluate CP101 for the treatment of recurrent CDI was a 49 participant, single-center, open-label Phase 1b clinical trial conducted at the University of Minnesota (Staley, Hamilton, et al. 2017). The trial enrolled participants who had experienced 2 or more recurrences of CDI. The primary endpoint was the safety and tolerability of CP101. Clinical success was defined as absence of CDI recurrence within 2 months post-treatment. No related serious adverse events (SAEs) occurred and there was an efficacy rate of 87.8% after treatment with CP101. Approximately one-third of participants reported mild, transient gastrointestinal symptoms following the treatment.

Multiple doses were evaluated in this first cohort, including a high dose range (1.25 to 2.5×10^{12}) and a low-dose range (2.1 to 2.5×10^{11}), with no meaningful dose-dependency at the dosing levels tested. [redacted]

Adequate and well-controlled trial of CP101: In PRISM3, the first randomized placebo-controlled trial investigating CP101 for prevention of recurrent CDI, topline results demonstrate persuasive evidence of safety and efficacy. PRISM3 was a large multicenter, randomized, blinded, placebo-controlled trial, conducted in 51 centers across the United States and Canada. In PRISM3, CP101 treated trial participants had a significantly lower CDI recurrence rate through 8 weeks compared to placebo (74.5% vs 61.5%, p=0.0488) in the modified intent-to-treat (mITT) population (n=198).

The PRISM3 topline safety results through Week 8 were also compelling. Among the safety population through Week 8 (n=203), one-time oral administration of CP101 following SOC CDI antibiotic was well-tolerated. There were no drug-related treatment-emergent serious adverse events (TESAEs) in the CP101 treated cohort. Drug-related TEAEs were 16.3% in CP101 and 18.2% in placebo. Adverse events (AEs) were similar across both groups, with the most frequent treatment-related AEs being gastrointestinal symptoms (mild to moderate in severity).

1.6 Rationale for Dose and Administration

[redacted]

The choice of CP101 dose was based on safety, tolerability, pharmacodynamic profile, and clinical efficacy data obtained in our Phase 1b and PRISM3 studies.

Phase 1b

In the Phase 1b dose-ranging trial, oral dosing with CP101 was initiated at 1.25 to 2.5 × 10^{12} (high dose range) cells; and 2.1 to 2.5 × 10^{11} (low-dose range) cells.

Pharmacodynamics: Based on analysis of high-throughput sequence data, modest changes in dosing did not significantly affect alpha diversity, a key biomarker associated with efficacy (Staley, Hamilton, et al. 2017). [redacted]

Clinical outcome: Clinical success was defined as no CDI recurrence within a 2-month follow-up period. The success rate was 87.8% (43/49 participants) in the entire cohort. There was no meaningful difference in CP101 efficacy or safety between the high and low-dose groups.

[redacted]

First Adequate and Well-Controlled Trial: PRISM3

In PRISM3, the Sponsor evaluated single administration of CP101 [redacted]

Clinical outcome: As previously described, the topline efficacy results from PRISM3 demonstrate that participants treated with CP101 had a significantly lower CDI recurrence rate through 8 weeks compared to placebo (74.5% vs 61.5%, p=0.0488) in the mITT (n=198). Additionally, the safety profile was favorable with no drug-related SAE in the CP101 arm and no meaningful difference in the proportion of AEs or TEAEs between the CP101 and placebo groups.

[redacted]

1.6.1 Dose for this Clinical Trial

Participants will be randomized in a 2:1 ratio into 1 of 2 treatment groups to receive 1 of the following:

- **CP101**: Single oral dose of CP101 [redacted]

- **Placebo**: Single oral dose of placebo that are identical in size, smell, texture and appearance to those of the CP101 capsules.

Duration of Treatment: The treatment period will be 1 day, and participants will be monitored through Week 24 for long-term safety outcomes following Randomization.

[redacted] Blinded IP will be administered under direct supervision of trial staff.

1.7 Risk-Benefit Analysis

[redacted]

Based on the finding from the Phase 1b and PRISM3 studies of CP101, treatment with CP101 demonstrates a favorable benefit-to-risk ratio and represents a novel therapeutic option in participants with recurrent CDI.

1.8 Trial Population

Population:

This trial is a 2-part trial which will enroll adult participants with recurrent CDI infection.

Part A:

- Participants with recurrent CDI defined as:
  - A history of **≥ 3 episodes of CDI**, with 2 episodes occurring within the previous 6 months (inclusive of the current episode); OR
  - A history of **2 episodes of CDI** occurring within the previous 6 months (inclusive of the current episode) may be eligible if **65 years of age or older**.

Part B:

- Participants who have an on-trial, central laboratory-positive *C. difficile*-related diarrhea within 8 weeks after receiving CP101 or placebo in Part A of the trial, and consent to having open-label administration of CP101.

2 TRIAL OBJECTIVES

The overall objectives of this Phase 3 trial are:

- To evaluate the efficacy of CP101 treatment relative to placebo in adults with previously treated recurrent CDI
- To evaluate the safety and tolerability of CP101 treatment compared to placebo in adults with previously treated recurrent CDI

Full details of the trial objectives are described below.

2.1 Primary Efficacy Objective, Endpoint, and Estimand

Primary Objective	Primary Endpoint
To evaluate the efficacy of a single oral dose of CP101 compared to placebo following SOC CDI antibiotics in preventing CDI recurrence in participants with recurrent CDI	Proportion of participants experiencing a CDI recurrence through Week 8 based on adjudication

The primary clinical question of interest is:

What is the difference in the proportions of participants experiencing CDI recurrence through 8 weeks after randomization to CP101 vs placebo in participants with recurrent CDI regardless of discontinuation of investigational intervention for any reason or change in background medication (dose and product)?

The estimand is described by the following attributes:

- Population:

  Adult participants with recurrent CDI who have completed SOC CDI antibiotics for their qualifying episode

- Endpoint:

CDI recurrence through 8 weeks post randomization

- Treatment condition:

  CP101 or placebo on Day 1 with 8 week follow-up for recurrence regardless of discontinuation of investigational intervention for any reason, or change in background medication (treatment policy strategy).

- Remaining intercurrent events:

  The intercurrent events “intervention discontinuation for any reason” and "change in background medication (dose and product)” are addressed by the treatment condition of interest attribute.

The following intercurrent events will result in an outcome of "recurrence" for the primary efficacy analysis:

- Initiation of rescue medication for CDI (fecal microbiota transplantation [FMT] or full course of SOC antibiotics) prior to 8 weeks post randomization
- Occurrence of *C. difficile*-related diarrhea prior to 8 weeks in a participant who does not qualify for Part B of the study, per central lab testing algorithm, and discontinues the study for any reason
- Participants who enter into Part B of the study however, the *C. difficile*-related diarrhea episode is adjudicated as "no recurrence" by the AB
- Participants who die or experience another debilitating event prior to 8 weeks, which precludes continued participation in the study
- Participants who withdraw consent prior to 8 weeks after randomization
- Participants who are lost to follow-up prior to 8 weeks after randomization

There are no other intercurrent events anticipated at this time.

- Population-level summary:

  Difference in the proportion of participants experiencing a CDI recurrence through Week 8 after randomization between CP101 and Placebo

2.2 Secondary Objectives

Key Secondary Objective

- To determine if treatment with a single oral dose of CP101 following SOC CDI antibiotics in participants with recurrent CDI increases microbial diversity at Week 1 as determined by 16S ribosomal ribonucleic acid (rRNA) gene amplicon sequencing compared to placebo.

Other Secondary Objectives

- To determine if treatment with a single oral dose of CP101 following SOC CDI antibiotics in participants with recurrent CDI decreases the proportion of participants with CDI recurrence through 8 weeks, as determined by toxin enzyme immunoassay (EIA)-related diarrhea, as compared to placebo.

- To determine if treatment with a single oral dose of CP101 following SOC CDI antibiotics in participants with recurrent CDI increases the Time-to-first recurrent CDI episode (Day 1 through Week 8), as compared to placebo.
- To determine if treatment with a single oral dose of CP101 following SOC CDI antibiotics in participants with recurrent CDI decreases the proportion of participants with CDI recurrence through a period of 24 weeks, as compared to placebo.
- To determine if treatment with a single oral dose of CP101 following SOC CDI antibiotics in participants with recurrent CDI increases the Time-to-first recurrent CDI episode (Day 1 through Week 24), as compared to placebo.
- [redacted]

Exploratory Objectives

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

Primary Safety Objective

- To evaluate the safety profile in participants with recurrent CDI receiving a single oral dose of CP101 following SOC CDI antibiotics as compared to placebo.

3 TRIAL DESIGN

3.1 Overall Trial Design

This Phase 3 trial will be conducted in 2 parts: a randomized, double-blind, placebo-controlled trial arm (Part A) and an OLT arm (Part B). The trial is designed to

evaluate the efficacy, safety, and tolerability of a single oral administration of CP101 for the prevention of recurrent CDI in adult participants.

- **Part A** will evaluate the efficacy, safety, and tolerability of CP101 versus placebo for the prevention of recurrent CDI.
- **Part B** is an *optional* open-label arm evaluating the efficacy, safety, and tolerability of CP101, in eligible participants from Part A who experience an on-trial central laboratory-positive *C. difficile*-related diarrhea through 8 weeks after receiving CP101 or placebo. See Part B (Section 6) of the protocol for further details regarding the OLT arm. **Participants are not eligible to enter Part B of the trial without having been dosed in Part A first.**

Eligible participants must have a history of recurrent CDI. The Qualifying CDI episode is the most recent diagnosis of recurrent CDI prior to Screening. To be eligible for the trial, participants are required to have a documented toxigenic *C. difficile* stool test that has been reviewed and confirmed by the trial Medical Monitor (Figure 6). Additionally, participants must have received a course of SOC CDI antibiotics for the Qualifying CDI episode (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator) and demonstrated an adequate clinical response defined as ≤ 3 unformed stools in 24 hours for 2 consecutive days.

Participants will be randomized in a 2:1 ratio into 1 of 2 treatment groups to receive 1 of the following:

- **CP101**: Single oral dose of CP101 [redacted] OR
- **Placebo**: Single oral dose of placebo

Randomization will be stratified based on 2 factors present at the time of Randomization: (1) SOC CDI antibiotics (fidaxomicin vs. no fidaxomicin) and (2) age (< 65 years vs. ≥ 65 years) (Table 1). Participants will be randomized in a 2:1 ratio to CP101 or placebo respectively within each stratum. Prior to Randomization, Inclusion Criteria Part A Randomization must be satisfied. Importantly, participants must have completed their course of SOC CDI antibiotic (minimum of 10 days and maximum of 21 days) [redacted] Investigational product will be administered as a single oral dose after Randomization on Day 1.

Participants will be followed through Week 8 after dosing for safety outcomes (all AEs and safety laboratory values), and primary efficacy outcomes. In addition, participants will be followed through Week 24 for long-term safety outcomes. AEs will be recorded from informed consent through Week 24 trial visit. Blood samples for safety laboratory analysis, [redacted] will be collected at scheduled

trial visits per the Schedule of Assessments (Appendix 2; Table 3 [Part A] and Table 4 [Part B]).

The primary clinical outcome is CDI recurrence confirmed by an independent AB. Given that diarrhea is the key initial symptom of CDI recurrence, participants will be required to promptly report any new episode of diarrhea to trial site personnel (defined as > 3 unformed stools in 24 hours for 2 consecutive days). Participants who experience a new episode of diarrhea will undergo stool testing for *C. difficile* by central laboratory and an Investigator evaluation as outlined in Section 7.1.2 and Figure 8 [Investigator Assessment of a New Diarrhea Episode].

[redacted]

The maximum trial sample size is approximately 324 participants. An IA is planned when Week 8 data become available for approximately 217 participants from the ITT population (67% information fraction), including those that discontinued earlier than 8 weeks (e.g., due to a CDI recurrence, lost-to-follow-up, withdrawal of consent). This IA is intended to evaluate whether the data are sufficient to declare success for efficacy early but not for evaluating futility.

3.2 Adjudication Board

The purpose of the independent AB is to adjudicate the primary efficacy outcome of the trial. The diagnosis of recurrent CDI can pose a clinical challenge. To ensure data quality, reliability and consistency, a centralized independent AB examining the totality of the data and in alignment with international CDI clinical guidelines, will confirm recurrent CDI case(s) identified by individual Investigators as described in the AB charter.

[redacted]

3.3 Trial Endpoints

Part A:

Primary Endpoints:

- Proportion of participants experiencing a CDI recurrence through Week 8.
- Incidence of TEAEs through Week 8.

Key Secondary Endpoints

- Improvement in intestinal microbiome diversity at Week 1.

Other Secondary Endpoints:

- Proportion of participants experiencing toxin EIA-positive recurrent CDI through Week 8;
- Proportion of participants experiencing toxin EIA-positive recurrent CDI through Week 24;

- Time-to-first recurrent CDI episode during the trial (Day 1 through Week 8);
- Proportion of participants experiencing CDI recurrence through Week 24;
- Time-to-first recurrent CDI episode during the trial (Day 1 through Week 24);
- [redacted]

Exploratory Endpoints

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

Safety:

- Incidence of TEAEs and TESAEs;
- Clinical safety laboratory tests and vital signs will be summarized.

Part B:

Efficacy and Safety Endpoints

- Proportion of participants experiencing CDI recurrence through Week 8 and Week 24;
- Incidence of TEAEs and TESAEs through Week 8 and Week 24.

Other Endpoints

The remaining secondary and exploratory endpoints are identical to Part A and will be described in further detail in the statistical analysis plan (SAP).

3.4 Randomization and Blinding

3.4.1 Randomization/Allocation

The unblinded trial biostatistician will create the randomization schedule which will be uploaded in the IRT for implementation. Participants who satisfy the randomization eligibility criteria outlined in the protocol will be randomized in a 2:1 ratio to receive CP101 or placebo via the IRT. The Investigator will enter all Screening information, including demographics, and will confirm inclusion/exclusion criteria to obtain the participant identification number and a corresponding bottle number for treatment assignment. [redacted]

Table 1: Treatment Plan

3.4.2 Investigational Product Blinding

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

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

3.4.3 Investigational Product Unblinding

Part A:

Part A of the trial will be performed in a double-blind manner. All drugs will be supplied in identical packages and IP kits. The IP capsules will be identical in color, smell, taste, and appearance, thereby maintaining double-blind conditions.

Eligible participants will be randomly assigned to treatment in a 2:1 ratio to receive either active drug (CP101) or placebo. Participant will not be aware of their treatment allocation, and all trial staff involved in efficacy and safety assessments will be blinded to treatment assignments until after database lock and release of unblinding randomization codes.

In case of a medical emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's medication assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding unless this could delay emergency intervention of the participant. The

date and reason that the blind was broken must be recorded. The site will be provided with trial-specific instructions on unblinding procedures.

If necessary, the Sponsor may be required to unblind a participant if an AE meets criteria of a Suspected Unexpected Serious Adverse Reaction in order to fulfill expedited regulatory reporting requirements. In this event, the Sponsor will not divulge the treatment code to any other personnel involved in reporting, obtaining, and/or reviewing the clinical evaluations. This level of blinding will be maintained throughout the conduct of the trial.

Part B:

The Part B trial is an open-label trial.

3.5 Trial Treatment

3.5.1 Investigational Products

3.5.1.1 CP101

CP101 is an investigational oral microbiome drug designed to deliver a complete and functional microbiome to durably repair intestinal dysbiosis, which is being evaluated for the prevention of recurrent CDI.

CP101 contains live microbial communities, derived from rigorously screened human donor stool that is tested, stabilized, characterized, and formulated into capsules [redacted]

3.5.1.2 Placebo

Because this is a double-blind, placebo-controlled trial (Part A), placebo will be presented in capsules that are identical in size, smell, texture, and appearance to those of the CP101 capsules.

3.5.2 Investigational Product Administration

In Part A, IP (either CP101 [redacted] or matching placebo) will be administered after Randomization on Day 1 (single administration) as an oral dose [redacted]

In Part B, all participants will be treated with a single dose of CP101 administered orally by capsules [redacted]

3.5.3 Investigational Product Packaging and Labeling

The IP will be packaged and labeled by the Sponsor in accordance with applicable Good Manufacturing Practice and local regulatory requirements.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.

Refer to the Pharmacy Manual for additional information.

3.5.4 Storage of Investigational Product

All IP bottles are to be stored accordance with the storage requirements outlined in the Pharmacy Manual.

All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Refer to the Pharmacy Manual for additional information.

3.6 Trial Duration

Following a 6-week Screening period, the trial duration will be approximately 24 weeks after the IP administration for participants in Part A who do not experience an on-trial, central laboratory-positive *C. difficile*-related diarrhea through Week 8. This includes an 8-week efficacy and safety assessment and an additional safety and CDI recurrence follow-up through Week 24.

Participants who enter Part B of the trial will be followed through Week 24 following OLT. This includes an 8-week efficacy and safety assessment and an additional safety and CDI recurrence follow-up through Week 24.

3.7 Discontinuation Criteria

3.7.1 Criteria for Trial Termination

The Sponsor may terminate this trial at any time. Reasons for termination may include but are not limited to, the following:

- New information regarding the safety or efficacy of the IP that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the trial, as assessed by the Sponsor;
- [redacted]
- Significant violation of International Council for Harmonization (ICH) Good Clinical Practice (GCP) that compromises the ability to achieve the trial objectives or compromises participant safety;
- Insufficient participant enrollment; and
- Sponsor decision.

3.7.2 Participant Withdrawal

A trial participant (or legal guardian acting on behalf of the participant) is free to withdraw consent and discontinue participation in the trial at any time, without prejudice to further treatment according to standard clinical practice. A participant's participation in the trial may be discontinued at any time at the discretion of the Investigator or Sponsor if, for example:

- The participant is noncompliant with the trial responsibilities.
- Participant withdraws consent and refuses to continue procedures/assessments.
- The Sponsor terminates the trial.
- The Investigator determines it is no longer in the participant's best interest to participate in the trial.
- After at least 3 reasonable attempts to make contact, including final contact via certified mail, the participant is lost to follow-up.

Participants who have discontinued IP by receiving a partial dose (as applicable) are encouraged to remain in the trial and to continue to complete trial assessments to the extent possible. If a participant or the participant's legal guardian, acting on behalf of the participant, discontinues participation in the trial, or the participant is discontinued by the Investigator or Sponsor, the Early Termination Case Report Form (CRF) describing the reason for discontinuation must be completed.

3.7.2.1 Collection of Data from Withdrawn Participants

Whenever possible, Investigators should attempt to obtain information about participants in the case of withdrawal from the trial. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the trial, must be recorded in the source documents. The CRF must document the primary reason for withdrawal from the trial.

If the reason for withdrawal from the trial is an AE and/or clinically significant abnormal laboratory test result, the Investigator will continue to monitor the event until the event has resolved or stabilized, until the participant is referred to the care of a health care professional, or until a determination of a cause unrelated to the IP or trial procedure is made. The specific event or test result (including repeated test results, as applicable) must be recorded both on the source documentation and in the CRF; both the AE page and the relevant page of the CRF will be completed at that time. As soon as possible, the Investigator must inform the Sponsor about each participant who is being considered for withdrawal due to AEs. Additional reports must be provided when requested.

If a participant is withdrawn from the trial for multiple reasons that include AEs, the relevant page of the CRF should indicate the withdrawal was related to an AE.

In the case of participants lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records.

An early termination visit should be conducted for all participants who were randomized but do not complete the trial according to the trial protocol.

3.7.3 Participant Replacement

There is no provision for replacing participants.

3.7.4 Participant Follow-Up

Follow-up within 4 weeks from the date of withdrawal will be conducted for all participants who receive the IP but do not complete the trial according to the trial protocol.

3.8 Trial Material Accountability

The Investigator will ensure that adequate records showing the receipt, dispensing, return, or other disposition of the IP, including the date, quantity, batch or code number, and identification of trial participants who receive the IP are maintained. The Investigator will not supply the IP to any person except Sub-Investigators (as submitted to the local regulatory authority), designated staff, and participants in this trial. The Investigator will not dispense the IP from any sites other than those submitted to the local regulatory authority. The IP will not be relabeled or reassigned for use by other participants.

Each IP shipment will include a packing slip listing the contents of the shipment, return instructions, and any applicable forms.

The Investigator is responsible for ensuring deliveries of the IP and other trial materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with applicable regulatory requirement, and used in accordance with this protocol.

Only participants enrolled in the trial may receive the IP and only authorized staff at the investigational center may supply or administer the IP, which must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the Investigator and authorized staff at the investigational center.

A record of IP accountability (i.e., IP and other trial materials received, used, retained, returned, or destroyed) must be prepared and signed by the principal Investigator or designee with an account given for any discrepancies. Upon completion of the trial, unused IP will be returned to the Sponsor's designee or destroyed locally per the Pharmacy Manual.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

The trial will include approximately 324 participants from approximately 100 centers.

Inclusion Criteria <u>Part A</u> (Screening):

1. Participant or legal representative voluntarily agreed to participate by signing and dating the written informed consent form after trial has been fully explained.
2. Participant 18 years of age or older.
3. History of recurrent CDI defined as:
    - 3.1 ≥ 3 episodes of CDI, with 2 episodes occurring within the previous 6 months (inclusive of the current episode); OR

3.2 Participants with a history of 2 episodes of CDI occurring within the previous 6 months (inclusive of the current episode) may be eligible if 65 years of age or older.

4. For the qualifying CDI episode, the following criteria (4.1-4.4) must be satisfied:
   - 4.1 History of diarrhea (> 3 unformed stools per day) for 2 or more consecutive days that is clinically consistent with CDI.

   AND

   - 4.2 Documented positive stool test by local laboratory for toxigenic *C. difficile* (toxin EIA or polymerase chain reaction [PCR]-based testing) for the current CDI episode and within 45 days prior to Randomization.

   AND

   - 4.3 Received a course of SOC CDI antibiotics for the most recent CDI episode (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator);

   AND

   - 4.4 Demonstrated an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to Randomization.

***NOTE**: ALL Qualifying CDI episode requires CLINICAL and LABORATORY CONFIRMATION of eligibility by Medical Monitor.*

5. Females (assigned at birth) must fulfill at least 1 of the following criteria:
   - 5.1 Postmenopausal, defined as amenorrhea ≥ 1 year; or
   - 5.2 Surgically sterile: hysterectomy, bilateral oophorectomy, or tubal ligation; or
   - 5.3 Abstinent or willing to use adequate contraception from Screening through the Week 24 visit per Section 7.2.9.1.
6. Males (as assigned at birth) must fulfill the following criteria: Abstinent or willing to use adequate contraception from Screening through the Week 24 visit per Section 7.2.9.1.

Exclusion Criteria Part A (Screening):

1. Known stool samples testing positive for enteric pathogens (e.g., *Salmonella*, *Shigella*, diarrhoeagenic *E. coli*, *Campylobacter*, *Giardia*) within 28 days prior to Screening.
2. Inability to ingest capsules (e.g., severe nausea, vomiting, gastroparesis, gastric outlet obstruction, dysphagia and/or history of chronic aspiration).
3. Active or suspected ileus, toxic megacolon, or bowel obstruction.
4. Historical or current diagnosis of inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, indeterminate colitis, or microscopic colitis).
5. Recent diagnosis (< 6 months prior to Screening) of diarrhea-predominant irritable bowel syndrome (post-infection or not related to an enteric infection). Participants with diarrhea-predominant irritable bowel syndrome ≥ 6 months prior to Screening may be randomized following confirmation of eligibility.

6. Current diagnosis of chronic diarrheal illness with pre-CDI baseline diarrhea. This includes but is not limited to celiac disease, bile salt diarrhea, chronic pancreatitis, and short gut syndrome.
7. Past administration of bezlotoxumab (Zinplava™), or past enrollment in a *C. difficile* vaccine trial where participant received active investigational product (IP) within 12 months prior to Randomization. Participants blinded to treatment assignment or with unknown status are excluded. Participants who only received placebo would not be excluded.
8. Participation in PRISM3 (CDI-001) or PRISM-EXT (CP101-CDI-E02) where participant received active IP or received CP101 at any time in the past. Participants who only received placebo would not be excluded.
9. Fecal transplant or other live microbiome therapeutics for any condition, regardless of route of administration within 12 months prior to Randomization.
10. Initiation of any systemic cancer treatment (e.g., chemotherapy, radiotherapy, biologic, immunotherapy, others) for active malignancy that is planned 8 weeks prior to Randomization or during the 8 weeks following Randomization. Participants on maintenance treatment for malignancy may be randomized following confirmation of eligibility. NOTE: Participants on hormone therapy alone are eligible.
11. Known primary or secondary immunodeficiency, including but not limited to, IgA deficiency, common variable immunodeficiency, severe combined immunodeficiency, or human immunodeficiency virus/acquired immune deficiency syndrome.
12. History of solid organ transplantation or stem cell transplant.
13. Initiation or dose escalation of systemic immunosuppressive agents, at the discretion of the Investigator, for any condition during the 8 weeks prior to Randomization or planned during the 8 weeks following Randomization. Examples may include but are not limited to corticosteroid agents given orally or intravenously, cyclosporine, tacrolimus, or tumor necrosis factor inhibitors. Participants on stable low dose of systemic immunosuppressive agents or short courses (< 2 weeks) may be randomized following confirmation of eligibility.
14. Major intra-abdominal surgery (e.g., bowel resection) within the past 60 days prior to Screening (excluding appendectomy or cholecystectomy) and/or planned invasive surgery/hospitalization during the trial.
15. History of total colectomy or ileostomy.
16. Use of a systemic antibiotic for any condition (other than CDI) during the Screening period, or any anticipated use of a systemic antibiotic for any condition other than CDI during the trial for 8 weeks after Randomization. This includes participants who have a known medical procedure that requires antibiotic prophylaxis (e.g., elective surgical procedure or dental procedure requiring prophylactic antibiotics) scheduled during the trial.
17. Active drug, chemical, or alcohol dependency as determined by the Investigator through history or optional toxicology screen.

18. Enrollment in any other investigational drug, device, or observational trial within 30 days or 5 half-lives of the last dose, prior to Randomization (Day 1) or at any time during this trial.
19. Pregnant, breast-feeding, or planning to become pregnant during the trial.
20. Clinically significant abnormal laboratory values including, but not limited to, white blood cell count $\geq 15 \times 10^9$/L, absolute neutrophil count of $< 1 \times 10^9$ neutrophils/L, or laboratory evidence of acute kidney injury at Investigators discretion, at Screening.
21. Screening nasal PCR test is positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
22. Any acute, chronic, or unstable medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety. Examples include but not limited to acute myocardial infarction, acute stroke, uncompensated congestive heart failure, or decompensated liver disease.

    ***NOTE*:** Trial participants may be screened while an inpatient in an acute care facility/hospital but must be discharged from inpatient medical admission prior to Randomization.
23. Life expectancy < 24 weeks.
24. Known hypersensitivity to CP101 or any component of its formulation or history of severe adverse reactions or other common drug class effects during prior exposure to similar compounds per the judgment of the Investigator.

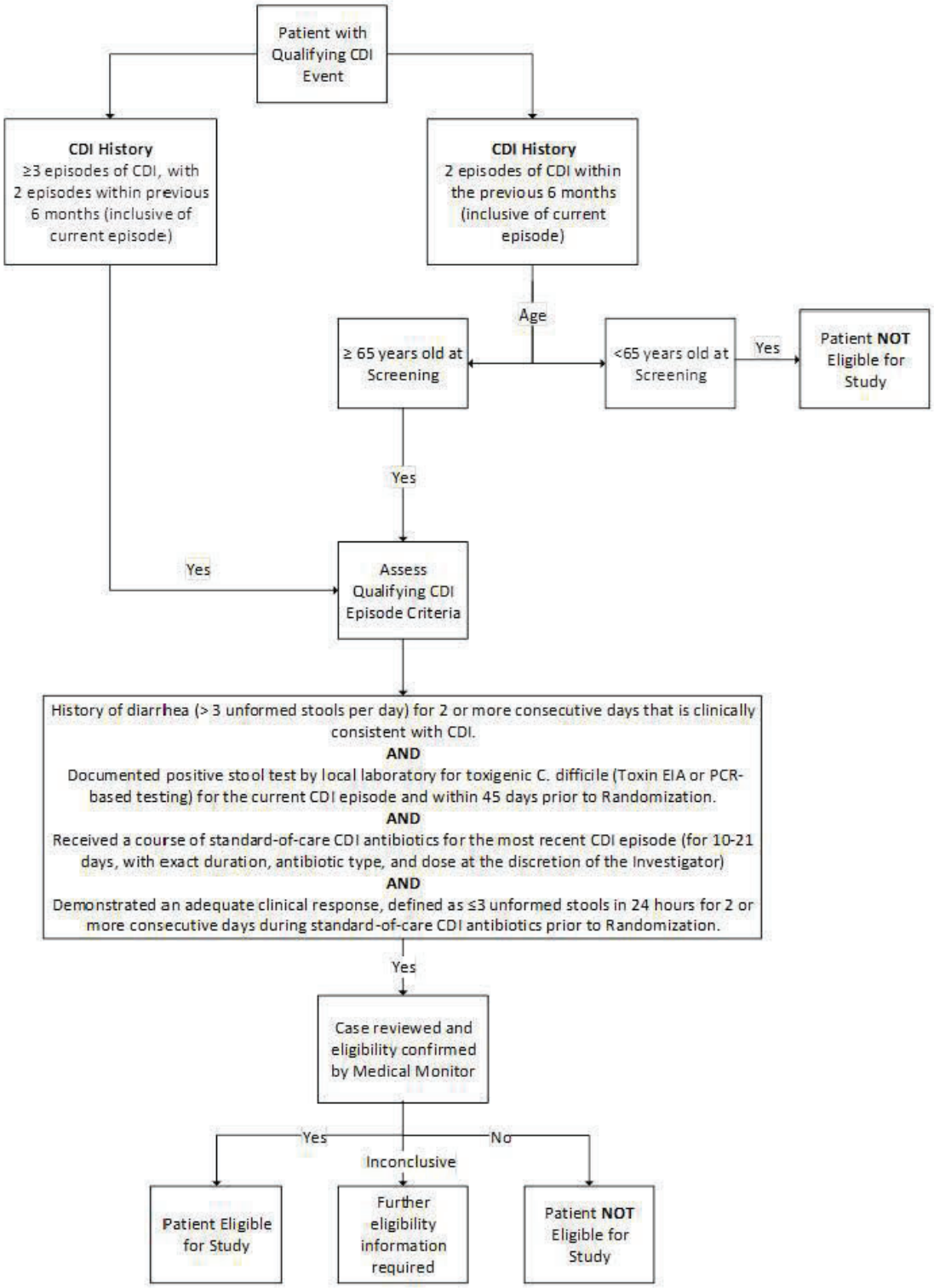
To be eligible for Randomization, the above listed Inclusion/Exclusion Criteria as well as the following <u>additional</u> Inclusion Criteria Part A - Randomization (Day 1) must be satisfied:

Inclusion Criteria <u>Part A</u> Randomization (Day 1):

1. An outpatient prior to Randomization.

   NOTE: Participant may be screened while an inpatient in an acute care facility/hospital but must be discharged from inpatient medical admission prior to Randomization. Participants residing in an assisted living center, long-term care facility, or rehabilitation ward/center may be randomized.
2. Has received a course of SOC CDI antibiotics for the Qualifying CDI episode (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator).
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to Randomization.
4. [redacted]
5. [redacted]

Figure 6: Assessment of Inclusion Criteria



Abbreviations: CDI = *Clostridioides difficile* infection; EIA=enzyme immunoassay; PCR=polymerase chain reaction.

4.1 Participant Recruitment and Screening

Written informed consent will be obtained by the Investigator or a qualified person designated by the Investigator from each participant before any trial-specific procedures or assessments are performed. After informed consent has been obtained and within a period of 45 days before IP administration, all Screening procedures will be performed to check eligibility criteria (see Table 4 for more details).

The Investigator will check that all inclusion/exclusion criteria have been documented completely, and the trial Medical Monitor will be required to confirm final eligibility. Once trial eligibility is confirmed, participants will be enrolled. The participant will be assigned a unique participant identification number by the IRT at Screening.

[redacted]

5 PARTICIPANT TREATMENT

5.1 Prior and Concomitant Therapy

5.1.1 SOC Antibiotics for CDI

To be enrolled in the trial, recurrent CDI participants must meet eligibility criteria as they pertain to SOC CDI antibiotics (Section 4).

Acceptable SOC CDI antibiotics include the following (alone or in combination) at the discretion of the Investigator:

- Vancomycin
- Fidaxomicin
- Metronidazole

[redacted]

[redacted]

5.1.2 Concomitant Therapy and Restricted Medications

[redacted]

5.2 Diet

[redacted]

5.3 Participant Compliance

Investigational product will be administered as a single oral dose under the direct supervision of trial staff on Day 1.

Investigational product accountability must be performed by the trial staff on the day of the visit and recorded on the accountability log, in order to ensure that the participant is compliant with trial requirements. Investigational product accountability is also recorded in the CRF and checked by the Monitor during site visits.

[redacted] Deviation(s) from the prescribed dosage regimen should be recorded.

6 PART B *OPTIONAL* OPEN-LABEL TREATMENT FOR RECURRENCE

6.1 Summary

Part B (OLT) is the *optional* OLT arm of the trial and will similarly evaluate the efficacy, safety, and tolerability of CP101, in eligible participants from Part A. Participants in Part A, who experienced an on-trial central laboratory-positive *C. difficile*-related diarrhea within 8 weeks after receiving CP101 or placebo may be eligible.

Participants in Part A who experience a new episode of diarrhea within 8 weeks after Randomization (> 3 unformed stools in 24 hours for 2 consecutive days) will undergo central laboratory stool testing for *C. difficile*. The participant will have an Investigator evaluation (Figure 8) which will include a) review of diarrhea data; b) assessment of stool *C. difficile* testing by central laboratory testing algorithm (Figure 7); and c) the clinical decision to start a course of SOC CDI antibiotics. Participants with multistep central laboratory-positive *C. difficile*-related diarrhea will be eligible for Part B. All participants entering Part B will require confirmation of eligibility by the Medical Monitor.

Under extenuating circumstances and with approval of Medical Monitor, participants who experience *C. difficile*-related diarrhea in Part A may be allowed into Part B, provided there is positive multistep local laboratory *C. difficile*-related diarrhea AND the symptoms are clinically consistent with CDI recurrence.

Participants who meet eligibility criteria will be enrolled into Part B once eligibility has been confirmed. This participant cohort must have received SOC CDI antibiotics (vancomycin, fidaxomicin, and/or metronidazole [Section 4]) over a 10- to 21-day treatment period [redacted]

All participants in the Part B cohort will be followed from the time of OLT administration of CP101 through their Week 8 trial visit (Day 57 ± 3 days) for the assessment of the primary efficacy endpoint as well as safety follow-up and to Week 24 (Day 169 ± 14 days) for other safety endpoints. Additional trial visits will occur as summarized in the Schedule of Assessments (Table 4). Blood and urine samples for safety laboratory analysis, [redacted] will be collected at scheduled trial visits per the Schedule of Assessments.

Part B will be independent of the participant's blinded trial group allocation in Part A (i.e., participants entering Part B may have received either CP101 or placebo in Part A). The participant-level blinding of initial trial group allocation will be maintained throughout the course of Part B for the participants, and Investigators. The Schedule of Assessment timelines will restart at Screening for participants who enter trial Part B. Visits are labeled by adding 'OLT-' in front of the visit number in the Schedule of Assessments (Table 4) to distinguish Part B trial visits from Part A trial visits. The secondary efficacy endpoint is the proportion of participants with CDI recurrence through Week 8 and Week 24 of Part B. For the secondary safety endpoint, the incidence rate of TEAEs will be presented by treatment group through Week 8 for Part B. Participants will be followed through 24 weeks for other safety endpoints. On-trial *C. difficile*-related diarrhea will undergo Investigator evaluation as outlined in Section 7.1.2.1. Surveillance for new episodes of diarrhea will be conducted as outlined in in Part A (Section 7.1.2.1) and in the Schedule of Assessments (Table 4).

The Investigator will check that all inclusion/exclusion criteria have been documented completely and the trial Medical Monitor will be required to confirm final eligibility for Part B. Screening for Part B (Section 6.2) may be combined with the relevant scheduled or unscheduled visit during Part A if feasible.

6.2 Part B: Inclusion Criteria (Screening)

The following criteria must be satisfied for entry into Part B of the trial:

Inclusion Criteria Part B of the trial:

1. Previously enrolled in Part A: Participants who have an on-trial, central laboratory-positive *C. difficile*-related diarrhea within 8 weeks after receiving CP101 or placebo in Part A defined as:

   a) Diarrhea (> 3 unformed stools in 24 hours for 2 or more consecutive days) or diarrhea that does not meet the definition, but the Investigator has a strong clinical suspicion of *C. difficile*-related diarrhea and Medical Monitor has confirmed per study Figure 8;

   AND

   b) A stool specimen testing positive for *C. difficile* by central laboratory testing algorithm (or local laboratory-positive under extenuating circumstances such as central lab closure);

   AND

   c) Participant has received a course of SOC CDI antibiotics for the most recent CDI event (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator);

   AND

   d) Participant has had an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to IP administration.

NOTE: *Confirmation of eligibility by Medical Monitor is required before entry into Part B.*

Exclusion Criteria Part B (Screening):

1. New onset of any acute, chronic, or unstable medical comorbidity, psychiatric, social, or other circumstances that, in the opinion of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety. Examples include but not limited to acute myocardial infarction, acute stroke, uncompensated congestive heart failure, and decompensated liver disease.
2. Pregnant, breast-feeding, or planning to become pregnant during the trial.
3. Screening nasal PCR test is positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and participant exhibits symptoms that in the opinion

of the Investigator, may interfere with trial compliance, completion, or accurate assessment of trial outcomes/safety.

Inclusion Criteria Part B Open-Label Treatment (Day 1):

The following criteria must be satisfied prior to OLT in Part B of the trial:

1. An outpatient prior to OLT;

   NOTE: Participant may be screened while an inpatient in an acute care facility but must be discharged from inpatient medical admission prior to IP administration. Participants residing in an assisted living center, long-term care facility, or rehabilitation ward/center are eligible for Part B.
2. Has received a course of SOC CDI antibiotics for the on-trial, central laboratory-positive *C. difficile*-related diarrhea (for 10 to 21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator);
3. Has an adequate clinical response, defined as ≤ 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to IP administration;
4. [redacted]
5. [redacted]

7 TRIAL ASSESSMENTS

7.1 Assessment of Efficacy

7.1.1 Efficacy Parameters

The primary clinical outcome is CDI recurrence confirmed by an independent AB. The primary efficacy endpoint is the proportion of participants with CDI recurrence through Week 8 based on adjudication. Primary, Secondary and Exploratory endpoints are provided in Section 3.3.

7.1.2 Analysis Methods

7.1.2.1 Primary Efficacy Outcome

Determination of the primary efficacy outcome described in Section 7.1.1 utilizes a 3-step process:

1. **A new episode of diarrhea**: Participants are required to promptly report a new episode of diarrhea to trial site personnel (defined as > 3 unformed stools in 24 hours for 2 consecutive days). Additionally, surveillance for a new episode of diarrhea will include daily prompts to participants via a diary to record either the presence or absence of any unformed stool from Screening through Week 8. Thereafter participants will be required to contact the trial site if they experience a new episode of diarrhea between Week 8 and Week 24. At any time during the trial, if the number of unformed stools recorded in the diary by the participant meet the definition of a new episode of diarrhea, the trial site will be notified.

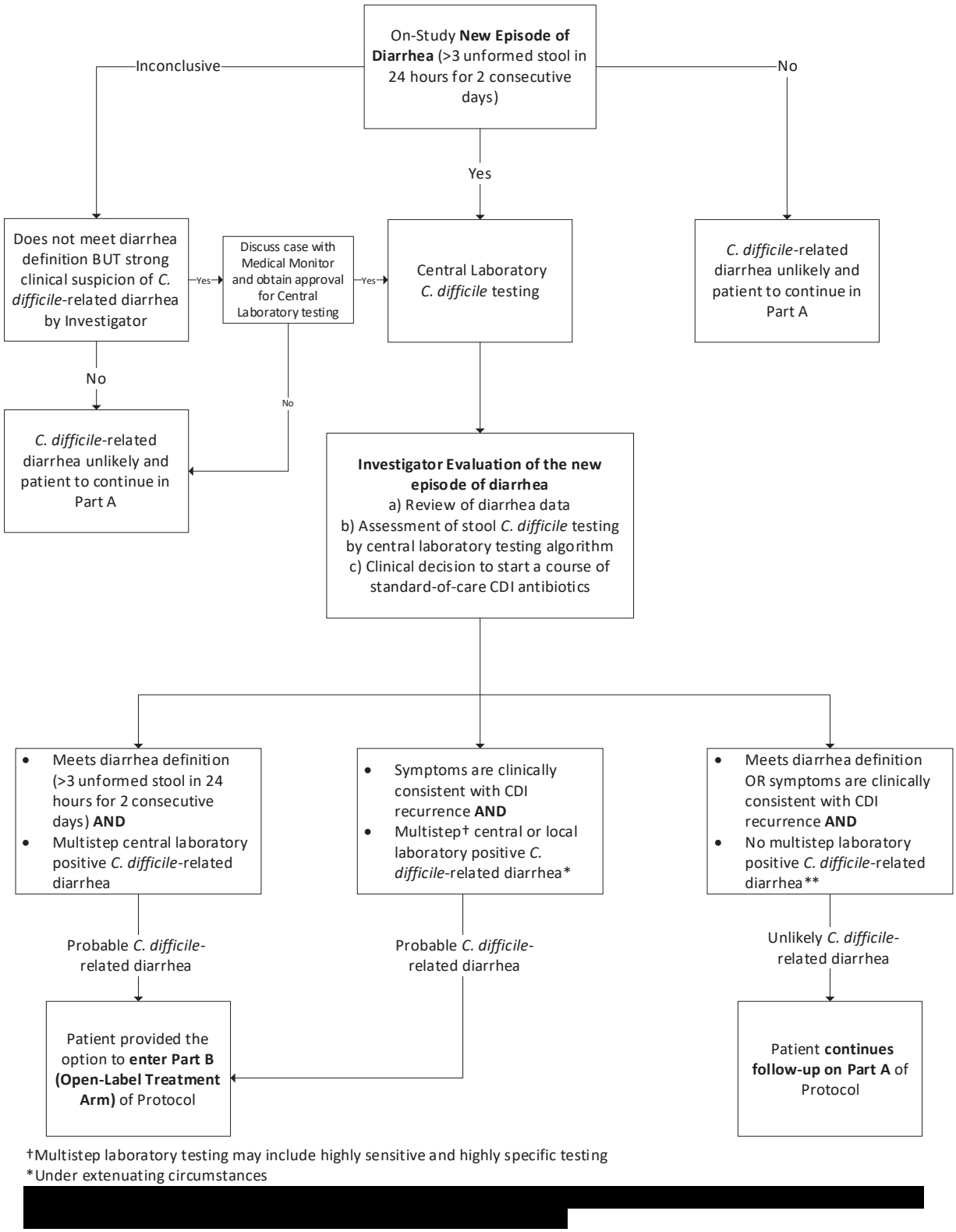
For each new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) during the trial period, a stool sample for central laboratory testing must be collected.

An Unscheduled Visit should be conducted with the participant if there is a positive laboratory stool test (Figure 7). A central laboratory test is a requirement for this trial and should not be replaced with a local laboratory test, unless under extenuating circumstances (e.g., central laboratory is closed due to pandemic). This sample should be collected before SOC CDI antibiotics are commenced.

2. **Investigator evaluation**: The onset of a new episode of diarrhea will trigger an Investigator evaluation for CDI. Investigator evaluation will include a) review of diarrhea data (> 3 unformed stools in 24 hours, for 2 or more consecutive days); b) assessment of stool *C. difficile* testing by central laboratory testing algorithm (Figure 7); and c) the clinical decision to start a course of SOC CDI antibiotics. Figure 8 outlines the possible outcomes of the Investigator evaluation process including the steps to be taken for cases where diarrhea does not meet the definition, but the Investigator has a strong clinical suspicion of *C. difficile*-related diarrhea.
3. **Adjudication board:** The determination of the Investigator evaluation prompts review of the event by an independent AB. The purpose of the independent AB is to is to confirm if the event is a CDI recurrence. The AB decision will be included in the dataset for the statistical analysis of the primary efficacy endpoint of the trial.

Figure 7: Central Laboratory Testing Algorithm

Figure 8: Investigator Assessment of a New Diarrhea Episode



Abbreviations: CDI = *Clostridioides difficile* infection; EIA = enzyme immunoassay; PCR = polymerase chain reaction.

7.1.3 Stool Sample Analyses

Stool samples will be collected and analyzed as shown in the Schedule of Assessments (Table 3 and Table 4).

For the Qualifying CDI episode, a documented stool sample positive for toxigenic *C. difficile* is required within 45 days prior to Randomization to be eligible for the trial. Participants will be excluded if there is known testing on stool specimens that is positive for ova and/or parasite(s), or other enteric pathogens within 28 days prior to Screening.

Further stool samples will be collected at Screening while the participant is completing a course of SOC CDI antibiotics for the Qualifying CDI episode [redacted] Stool sample will be used for molecular testing, including but not limited to 16S rRNA gene amplicon sequencing, [redacted] and safety testing.

On-trial stool samples will also be collected at scheduled trial visits. Analysis may also be performed at any other visit or time point (e.g., Unscheduled Visit, if any). On-trial stool samples will be collected before or after each scheduled trial visit. Participants may also be asked to provide a stool sample for unscheduled visits.

For each new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) during the trial period, a stool sample for central laboratory testing must be collected. A central laboratory test is a requirement for this trial and should not be replaced with a local laboratory test, unless under extenuating circumstances (e.g., central laboratory is closed due to pandemic). This sample should be collected before SOC CDI antibiotics are commenced.

Complete instructions for collection, handling, storage, and transportation/shipping of stool samples will be provided in a separate Laboratory Manual.

7.1.3.1 Stool and Blood Biomarkers

7.1.3.1.1 16S Ribosomal RNA Gene Amplicon Sequencing (Intestinal Microbiome Analysis)

[redacted]

7.1.3.2 Other Biomarkers

Biomarkers are objectively measured indicators of normal biological process, pathogenic, or pharmacologic response to a therapeutic intervention (FDA 2020; FDA-NIH Biomarker Working Group 2020).

[redacted]

[redacted]

7.1.4 Patient-Reported Outcomes

7.1.4.1 Participant Diary

[redacted]

7.2 Assessment of Safety and Adverse Events

7.2.1 Adverse Events

The AE reporting period will begin at informed consent and will continue through the final follow-up visit or, in the case of withdrawal, until the outcome is determined. AEs will be assessed at each visit and through telephone contact with the participant. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs should be recorded on the CRF.

The primary clinical efficacy endpoint is CDI recurrence as defined by the independent AB. If during the Investigator Evaluation, the participant is suspected to have a *C. difficile*-related diarrhea in the trial, then CDI will not be recorded as an AE (unless this meets the criteria of a SAE); instead, it will be considered an on-trial *C. difficile*-related diarrhea and will be

included in the determination of efficacy. If the on-trial *C. difficile*-related diarrhea results in hospitalization of the participant, requiring an overnight stay, this will be recorded as an SAE and reported per the criteria for safety reporting.

7.2.2 Definition of Adverse Events

An AE is an untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Findings at physical examinations.
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the IP are not considered AEs after treatment unless they reoccur after the participant has recovered from the pre-existing condition, or in the opinion of the Investigator, they represent a clinically significant exacerbation in intensity or frequency.

If clinically significant worsening from baseline is noted, the changes will be documented as AEs on the AE page of the CRF. Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the participant until the assessment returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

Investigators should inform the Sponsor regarding any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

7.2.3 Adverse Event Reporting

7.2.3.1 Recording Adverse and Serious Adverse Events

The collection of AEs will begin from the time of informed consent of through the final trial visit. All AEs (serious and non-serious) should be recorded on the CRF.

Refer to Section 7.2.7 for definition and reporting requirement of SAEs. SAEs related to trial procedures after signing informed consent and before the first dose of CP101 shall also be reported.

7.2.3.1.1 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is

known to have resulted in dehydration, it is sufficient to record only what is considered the primary diagnosis, diarrhea, as the AE on the CRF and, if also serious, on the SAE form. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage subsequently leads to renal failure, both events should be recorded separately on the CRF.

7.2.3.1.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between participant evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the AE CRF.

A recurrent AE is one that occurs and resolves between participant evaluation time points and subsequently recurs. All recurrent AEs should be recorded individually on the AE CRF.

7.2.3.1.3 Abnormal Laboratory Values

Clinically significant laboratory abnormalities will be recorded as AEs on the CRF and SAE form (if applicable).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the AE CRF and the SAE form (if applicable).

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs on the CRF and SAE form (if applicable), unless their severity, seriousness, or etiology changes.

7.2.4 Solicitation of Specific Adverse Events

In addition to the collection of all AEs, the following AEs will be specifically solicited using a daily participant diary for 7 days following IP administration (Day 1 to Day 7): abdominal distention or bloating, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, nausea, vomiting, and fever. The diary will be reviewed at the Week 1 visit, and any AEs captured in the diary and confirmed by the Investigator will also be documented on the AE CRF page.

7.2.5 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the participant’s daily activities. The severity of an AE will be evaluated according to the

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The clinical significance of an AE is determined by the Investigator.

Changes in the severity of an AE should be documented in the CRF.

7.2.6 Assessment of Causality

The relationship of each AE to IP or trial intervention will be defined using the terms below.

Not Related (unrelated, not related, no relation) – The biology, time course between the administration of IP and the occurrence or worsening of the AE, or other factors rules out a causal relationship and/or another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Related – The time course between the administration of IP and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified. The definition implies a reasonable possibility of a causal relationship between the event and the IP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from IP administration:
  - The event should occur after the IP is given. The length of time from IP exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases:
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.
- Concomitant drug:
  - The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of IP:
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology of the IP
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the IP should be considered.

Note: The Investigator’s assessment of causality for individual AE reports is part of the trial documentation process and will be recorded in the participant's medical record, AE CRF, and on the SAE form if applicable. AEs recorded without the Investigator’s assessment of the relationship to IP will be followed up until causality is assigned.

7.2.7 Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect not present at Screening
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm)

7.2.7.1 Definition of Terms

Life-threatening: An AE is life-threatening if the participant was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Hospitalization: is defined by the Sponsor as an admission to hospital for diagnosis and treatment requiring an overnight stay. Prolongation of an existing inpatient hospitalization due to an event also meets the regulatory criteria of an SAE.

Examples of visits to a hospital facility that do not meet the serious criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Preplanned or elective procedures prior to trial enrollment (e.g., outpatient surgery)
- Protocol procedures

Hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization planned prior to trial enrollment (e.g., for elective surgery or routine clinical procedures) that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported

during the procedure, that occurrence must be reported as an AE, either serious or non-serious according to seriousness criteria described in Section 7.2.7.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the participant's ability to carry out normal life functions.

Severity is not the same as seriousness. Severity, or intensity, refers to the extent to which an AE or SAE affects a participant's daily activities. Seriousness must be equal to at least one of the criteria listed in Section 7.2.7 above.

7.2.7.2 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 7.2.7) must be reported via EDC immediately (within 24 hours of knowledge by the Investigator). Regardless of causality, severity, and whether the participant has undergone any trial-related procedures, all SAEs must be reported and will be collected and recorded from the time the participant signs the consent form until 30 days following the final follow-up visit.

The initial report in the EDC should include at least the following information:

- Trial number
- Participant’s identification number
- Description of the event
- Date and time of onset of the event
- Seriousness criteria
- Severity
- Investigator’s assessment of Causality to the IP
- Participant’s event outcome, as currently known

When additional information regarding an SAE is brought to the attention of the Investigator, this information should be entered into EDC. Examples would include but are not limited to the following:

- Signs and symptoms initially reported for which there is now a diagnosis leading to a change in the reported term
- Laboratory test results
- Outcome of the SAE
- Change in Investigator causality assessment due to results of further investigations

The Sponsor or designee will be responsible for ensuring Suspected Unexpected Serious Adverse Reaction are reported to IRBs/IEC per local requirements. These activities may be delegated by the Sponsor to their vendor and will be documented in the Safety Monitoring Plan.

Pregnancy in and of itself is not an SAE but all pregnancies should be reported in the same manner and timeframe as SAEs as described in Section 7.2.7. Complications of the pregnancy should be reported within 24 hours of knowledge by the Investigator (e.g., if the mother is hospitalized for dehydration) as an SAE. Pregnancies will be followed by the Sponsor to full term and beyond. Pregnancy terminations/abortions must be reported as an SAE.

7.2.8 Overdose

In the event of overdose, the participant should be observed, and any needed treatment required will be at the discretion of the Investigator. There is no known specific treatment in case of overdose.

Any instance of overdose must be communicated to the Sponsor or Medical Monitor within 24 hours and should be reported as an SAE. Details of any signs or symptoms and their management should be recorded including details of any treatments administered.

7.2.9 Contraception Requirements and Pregnancy

7.2.9.1 Contraception Requirements

Females (assigned at birth) must agree to use an acceptable form of contraception from the time of signing informed consent and through 24 weeks after the last dose of IP. Males (assigned at birth) must agree to use (or have their partner use) an acceptable form of contraception from the time of signing informed consent and through 24 weeks.

Acceptable methods of contraception (as applicable per local practices and regulations) are intrauterine device, diaphragm with spermicide, contraceptive sponge, condom, vasectomy (that takes place at least 12 weeks prior to Screening, with documentation of azoospermia), and any registered and marketed hormonal contraceptives that contain an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Participants do not require contraception if they are highly unlikely to become pregnant or to impregnate a partner since they meet at least 1 of the following criteria:

- A female (as assigned at birth) participant who is not of reproductive potential is eligible without requiring the use of contraception. A female participant who is not of reproductive potential is defined as: one who has either (1) reached natural menopause (defined as 12 months of spontaneous amenorrhea); (2) 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or (3) bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (e.g., anorexia nervosa).
- A male (as assigned at birth) or female (as assigned at birth) participant who is of reproductive potential agrees to remain abstinent or use (or have their partner use) 2 acceptable methods of birth control starting at enrollment and through the 24-week trial period.

7.2.9.2 Pregnancy

Although pregnancy is not always considered an AE or SAE by regulatory definition, for this trial, pregnancies in any participant or in the partner of a male participant receiving at least 1 capsule of IP must be reported in the same manner as SAEs using the Pregnancy Reporting Form.

Any pregnancy complication, or elective termination of a pregnancy for medical reasons, will be recorded as an AE or, if appropriate, an SAE.

The Investigator must submit the Pregnancy Reporting Form immediately (within 24 hours) after the pregnancy is confirmed. If the participant has received the IP prior to becoming pregnant, the participant will continue the efficacy and safety assessment until 6 months after live birth or 24 weeks after the last dose of IP, whichever is longer.

The participant should be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as outcome of the pregnancy must be reported per the SAE Reporting procedures (Section 7.2.7.2).

Should pregnancy occur in a partner, the same SAE pregnancy reporting procedures should be followed. The participant may continue in the trial.

7.2.10 Vital Signs, Height, and Weight

Vital signs (temperature, heart rate, respiratory rate, blood pressure, and pulse oximetry) will be assessed per SOC as listed in the Schedule of Assessments (Table 3 and Table 4). Vital signs will be measured before IP administration when applicable. Vital sign measurement at Week 24 is at the discretion of the Investigator.

Body weight and height will be measured per SOC. Height and weight will be used to calculate body mass index (BMI). Height and weight for wheelchair-bound participants is optional. Height is only required at Day 1.

Pre-CDI BMI will be collected as part of the participant's medical history.

Any vital sign abnormality that is judged by the Investigator as clinically significant (except at the Screening visit) will be considered an AE, recorded on the CRF, and monitored as described in Section 7.2.3.

7.2.11 Physical Examinations

A 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 Assessments (Table 3 and Table 4).

Any physical examination finding that is judged by the Investigator as clinically significant (except at the Screening visit) will be considered an AE, recorded on the CRF, and monitored as described in Section 7.2.3. Investigators should pay special attention to clinical signs related to previous serious diseases.

7.2.12 Electrocardiograms

Single 12-lead electrocardiograms (ECGs) will be performed per SOC at the time points listed in the Schedule of Assessments (Table 3 and Table 4). Evidence of clinically significant abnormalities during the Screening visit may result in exclusion from the trial. A 12-lead ECG will only be performed at Week 8 and Week 24 if medically indicated and is at the discretion of the Investigator.

Any ECG abnormality that is judged by the Investigator as clinically significant (except at the Screening visit) will be considered an AE, recorded on the CRF, and monitored as described in Section 7.2.3.

7.2.13 Clinical Safety Laboratory Evaluations

Samples of blood and urine (Table 2) are scheduled for collection as shown in Table 3 and Table 4. Repeat clinical safety laboratory evaluations may be conducted at the discretion of the Investigator.

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.

Participants with a white blood cell count $\geq 15 \times 10^9$/L, laboratory evidence of acute kidney injury, or an absolute neutrophil count of $< 1 \times 10^9$/L neutrophils at Screening are to be

excluded from the trial. Screening laboratory assessments may be repeated up to twice at the Investigator's discretion.

All clinical laboratory testing, with the exception of optional drug testing or on-site serum (at Screening only) or urine (during the Treatment Period) pregnancy testing 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 Pregnancy	Serum hCG for women of childbearing potential.

Abbreviations: hCG = human chorionic gonadotropin.

A laboratory test result that is judged by the Investigator as clinically significant will be recorded as an AE and will be monitored as described in Section 7.2.3.1.3. An event may include a laboratory or diagnostic test abnormality that results in the withdrawal of the participant from the trial, the temporary or permanent withdrawal of medical treatment, or further diagnostic work up. (**NOTE**: Abnormal laboratory or diagnostic test results at the Screening visit that preclude a participant from entering the trial or receiving IP are not considered AEs.)

7.3 Unscheduled Visit

7.3.1 Unscheduled Visit for New Diarrhea Episode

Participants are to report diarrhea promptly to the trial site at any time during the trial. For each new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) during the trial period, a stool sample for central laboratory testing must be collected. A central laboratory test is a requirement for this trial and should not be replaced with a local

laboratory test, unless under extenuating circumstances (e.g., central laboratory is closed due to pandemic). This sample should be collected before SOC CDI antibiotics are commenced.

If *C. difficile* testing is positive by central laboratory testing algorithm, an Unscheduled Visit should be arranged for the participant. If *C. difficile* testing is negative by the central laboratory testing algorithm, an Unscheduled Visit may be arranged at the discretion of the Investigator for the participant.

NOTE: Every effort will be made to conduct an on-site assessment/home visit at Unscheduled Visit. However, under extenuating participant circumstances that make an on-site visit/home visit not feasible and after all reasonable measures have been exhausted, a virtual/telephonic trial visit may be conducted.

- [redacted]
- [redacted]
- Perform physical examination (only if medically indicated).
- Inquire about concomitant medications and AEs since the last visit.
- Collect vital signs and weight (if medically indicated).
- Collect stool sample for shipment and processing at central laboratory. Samples will be used for molecular testing, including, but not limited to, 16S rRNA gene amplicon sequencing, [redacted], and safety testing.
- Perform laboratory testing, as clinically indicated, including testing stool for CDI using a *C. difficile* testing algorithm (Figure 8).
- [redacted]

7.3.2 Unscheduled Visit for Adverse Events

Procedures conducted at an Unscheduled Visit for indications other than a new episode of diarrhea are at the discretion of the Investigator. During unscheduled visits for AEs, medically appropriate samples previously obtained or to be collected, including but not limited to stool, urine, blood, bacterial isolate may be requested by the [redacted] Sponsor for additional molecular characterization. Further details are described in the Laboratory Manual. NOTE: Under extenuating circumstances, an Unscheduled Visit may be conducted as a telephonic/virtual visit.

8 STATISTICAL METHODS AND DATA ANALYSIS

8.1 Trial Endpoints

Refer to Sections 2.1 and 3.3.

8.2 Overview of Statistical Analysis

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but prior to any unblinding, changes are made to the primary endpoint definition, or the statistical methods related to the test of the primary hypothesis, then the protocol will be amended (consistent with *ICH Guideline E-9*). A stand-alone SAP will be

written to describe in detail all statistical analyses planned for the trial. It will be accompanied by mock tables, figures, and listings. The SAP will be finalized and approved by signatures and dates prior to database lock for Week 8. The SAP will take precedence over the protocol for details about the statistical analyses for the trial except as noted above. In addition to the SAP, other 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 AEs will be mapped to a system organ class and preferred term using the MedDRA, and all prior and concomitant medications will be coded using the World Health Organization Drug Dictionary.

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

Planned interim analyses are described in Section 8.8. Participant-level unblinding will be restricted to the independent statistician who will be preparing the IA and who will have no other responsibilities associated with the trial.

8.3 Analysis Populations

Four analysis populations are planned for the trial:

Intent-to-treat population (ITT or All Randomized)	All participants randomized into the trial including those who were not exposed to any IP will be included in the ITT population. Participants in the ITT population will be analyzed according to the treatment group to which they were randomized. The ITT population will be the primary analysis population for all efficacy analyses.
The mITT population	All participants in the ITT population who receive at least 1 capsule of IP at Randomization (Day 1).
Per-protocol population (PP population)	All participants in the mITT population who have received at least 80% of trial medication, completed 8 weeks of follow-up or had adjudicated 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 IP.
Safety population	All enrolled participants who received at least 1 capsule of IP. 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 participants were randomized. All safety analyses will be performed on the Safety population.

8.4 Efficacy Analysis

8.4.1 Primary Endpoint

The primary efficacy endpoint is defined as the proportion of participants with CDI recurrence through Week 8 based on adjudication calculated as the number of participants with CDI recurrence through Week 8 divided by the total number of participants in the analysis population. Investigator evaluation of a new episode of diarrhea will be adjudicated by an independent AB to confirm CDI recurrence in a blinded fashion prior to database lock.

[redacted]

For the primary efficacy analysis, the active treatment group will be compared to the placebo group. [redacted]

The primary efficacy endpoint analyses will be repeated using the mITT and PP populations defined in Section 8.3.

8.4.2 Secondary Endpoints

[redacted]

8.5 Safety Analysis

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

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

8.5.1 Clinical Laboratory Evaluations

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

Laboratory abnormalities will be graded according to NCI-CTCAE Version 5.0, (for analytes where Common Terminology Criteria for Adverse Events (CTCAE) grading applies). The number and percentage of participants 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 and high.

8.5.2 Adverse Events

Any AE reported on the CRF that occurs during or post the administration of IP is defined as TEAE. Additionally, it will be assumed that an AE that was reported to have started at Randomization (Day 1) without an associated onset time may have occurred after the administration of IP. Hence, AEs 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 TEAEs and TESAEs 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
- SAEs

The number and percentage of participants who experienced at least 1 TEAE will be presented by MedDRA system organ class and preferred term. Drug-related TEAEs, withdrawals due to TEAEs, and all SAEs will be summarized in the same manner.

8.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Descriptive statistical methods will be used to summarize all trial data. Unless stated otherwise, the term “descriptive statistics” refers to number of participants (n), mean, median, standard deviation, minimum, and maximum for continuous data, and refers to frequencies and percentages for categorical data. 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 trial report. Graphical displays may be presented for selected results.

8.6 Biomarker Analysis

8.7 Subgroup Analyses and Effect of Baseline Factors

Subgroup analysis will include, but is not limited to, the following subgroups based on baseline characteristics and will be used for subgroup analyses for the primary efficacy endpoint in the ITT, mITT, and PP populations. The full details of subgroup analysis will be included in the SAP.

- Age group (< 65 years vs. ≥ 65 years)
- Age group (< 70, 70-79, and ≥ 80 years)
- Gender group (male vs. female)
- Race group (White vs. others)
- Charlson Comorbidity Index (< 3 vs. ≥ 3)
- Previous CDI episodes - total number of CDI episode in previous 12 months
- Recurrent CDI category
- [redacted]
- Geographical region/country

8.8 Interim Analysis

An IA is planned to occur at approximately 67% information fraction, i.e., when data become available for approximately 217 participants from the ITT population, including those that discontinued earlier than 8 weeks. The interim data will not include any participants with partial data to keep the cohorts before and after the IA independent. This IA is intended to evaluate whether the data are sufficient to declare success for efficacy early, but not for evaluating futility. As such, the IA will use an efficacy boundary but will not have a futility boundary specified.

success is 0.007 on the p-value scale; that is if the p-value is smaller than 0.007 at this IA,

[redacted]

8.9 Handling of Missing Data

[redacted]

8.10 Determination of Sample Size

[redacted]

[redacted]

The approximate sample size is 324 with an IA planned when 8-week data are available for approximately 217 participants from the ITT population (67% information fraction), including those that discontinued earlier than 8 weeks (e.g., due to lost-to-follow-up, withdrawal of consent). This IA is intended to evaluate whether the data are sufficient to declare "success" for efficacy early based on primary efficacy endpoint, but not for evaluating "futility." Further information on the definitions of success and futility will be included in the SAP.

[redacted]

8.11 Reporting Deviations

Any deviation(s) from the original statistical plan will be described and justified in protocol and/or SAP and in the final report, as appropriate.

8.12 [redacted]

[redacted]

[redacted]

9 TRIAL MANAGEMENT AND DATA COLLECTION

9.1 Confidentiality Regarding Trial Participants

Each participant will be assigned a unique and anonymized identifier in the IRT. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The participant must be informed that his/her medical records may be examined by quality assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

9.2 Source Documents

An Investigator is required to prepare and maintain adequate and accurate case histories or source documents designed to record all observations and other data pertinent to the investigation for each individual treated or entered as a control in the investigation. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site and must be available for inspection or review throughout the trial by the Sponsor and its designees.

The Investigator may need to request previous medical records or transfer records, depending on the trial.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

9.3 Case Report Forms

[redacted]

[redacted]

9.4 Records Retention

[redacted]

9.5 Data Management

9.5.1 Data Management Responsibilities

[redacted]

9.5.2 Data Errors

Errors, omissions, or requests for clarification at the trial site will be queried; queries will be entered into the EDC system for resolution by trial sites.

9.5.3 Data Collection and Retrieval

[redacted]

10 TRIAL MONITORING, AUDITING, AND INSPECTING

10.1 Risk-Based Quality Management

The Sponsor will implement a risk-based quality management system as described in ICH E6 (R2) with methods to assure and control the quality of the trial throughout all stages of the trial process that will be proportionate to the risks inherent in the trial and the importance of the information collected. The Sponsor will identify Critical Data and Critical Processes and the respective risks associated, which will be the focus of Sponsor oversight, monitoring, and reporting activities during the conduct of this trial.

10.2 Trial Site Training

Before trial initiation, at site initiation visit conducted on site or virtually or at an Investigator's meeting, a Sponsor representative (CRA) will review the protocol, CRFs, and other trial documents with the Investigators and their staff. Training topics may include (but are not limited to) trial background and rationale, clinical data summary, protocol review, ICH GCP, trial-specific procedures, IP review, AE reporting, CRFs, trial documentation, informed consent process, trial monitoring, etc., as applicable.

CRA will confirm that all study procedures are in compliance with the Study Start-Up Plan prior to site activation.

10.3 Monitoring Procedures

The Sponsor CRA or designee will be in regular contact with the investigational team through telephone calls and regular follow-up visits.

Investigators must allow the CRA to conduct monitoring visits at all the trial site locations (in person and/or virtually) at mutually agreed times during the trial and after the trial has been completed. The Investigator or delegate must be available for these visits and must allow the CRA direct access to source documents, regulatory files, and CRFs.

Monitoring visits will be conducted in accordance with the approved clinical monitoring plan. The purpose of trial monitoring is to verify the following:

- The rights and well-being of participants are protected, including obtaining informed consent;
- The conduct of the trial is in compliance with the currently approved protocol, with ICH GCP E6 (R2) and applicable laws and/or regulations;
- The Investigator's obligations are being fulfilled;
- Ensure the accuracy and integrity of trial data;
- Resolve any inconsistencies in the trial records.

The CRA will evaluate the progress of the trial, including progress of enrollment, and ensure that IP is being stored, dispensed, and accounted for according to this protocol and associated Pharmacy Manual. The CRA will discuss the conduct of the trial with the Investigator and verify that the facilities remain acceptable. The CRA will notify the Sponsor of any issues identified in a timely manner and will work with the site on resolution of issues.

10.4 Audit and Inspection

The Sponsor or its designees may conduct quality assurance audits by the Sponsor's Quality Assurance or independent auditors of clinical trial activities at any time in accordance with Sponsor internal standard operating procedures to evaluate compliance with ICH GCP E6 (R2) and applicable regulations/directives. Sponsor audit reports will be kept confidential as indicated in the ICH E6 (R2) guideline.

The trial may also be evaluated by regulatory agency inspectors who must be allowed access to CRFs, source documents, other trial files, and trial facilities. The Investigator must notify the Sponsor promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to the Sponsor.

11 ETHICAL CONSIDERATIONS

11.1 Ethics and Good Clinical Practice

This trial will be conducted in compliance with the appropriate protocol, and with Consensus ethical principles derived from international guidelines that have their origin in the World Medical Association Declaration of Helsinki (Appendix 1) and have been incorporated into the ICH GCP E6(R2) Guideline and other applicable laws and regulations.

Protocols and any substantial amendments to the protocol will require health authority approval (if required per local regulations) prior to initiation except for changes necessary to eliminate an immediate hazard to trial participants.

Trial personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective tasks. This trial will not use the services of trial personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical license, debarment). The Investigator will be responsible for providing oversight of the conduct of the trial at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.

All potential serious breaches must be reported to the Sponsor immediately. A serious breach is a breach of the conditions and principles of ICH GCP in connection with the trial or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the trial or the scientific value of the trial.

The regulatory files at the trial site should contain all required regulatory documents, trial-specific documents, and important communications. Regulatory files will be checked at each participating trial site for regulatory compliance prior to trial initiation, throughout the trial, as well as at the trial closure.

11.2 [redacted]

[redacted]

[redacted]

11.3 Future Use of Stored Specimens

Participants will be asked to give consent to store blood and stool samples for future testing within the trial, as may be required by emergence of adverse conditions. In addition, participants will be asked to give consent to store sample for future exploratory testing related to CDI. Participants may withdraw their consent for the storage and/or use of their stored samples and any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of the existing analysis.

11.4 Institutional Review Board/Independent Ethics Committee

Before implementing this trial, the protocol, the proposed ICF, and other information provided to participants must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, ICF, participant recruitment materials/process (e.g., advertisements), and any other written information to be provided to participants have been approved by the IRB/IEC must be given to the Sponsor before trial initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to the Sponsor or its designee. This committee, as required by local law or procedure, will approve any amendments to the protocol that need formal approval. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes). The Investigator or Sponsor should also provide the IRB/IEC with a copy of the Investigator's Brochure or product labeling, information to be provided to participants and any updates. The Investigator or Sponsor should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

Trial sites will be responsible for maintaining original signed ICFs as source documents for quality assurance review and regulatory compliance.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

11.5 Informed Consent

Informed consent is a process that is initiated prior to the participant agreeing to participate in the trial and continues throughout trial participation. All pertinent aspects of the trial should be discussed with each participant, including the aims, methods, the procedures involved, the expected duration of participant participation, alternative treatment, anticipated risks or discomforts, and possible benefits of trial participation. A written ICF detailing all aspects of the trial and approved by the IRB/IEC, will be provided to participants or their legally acceptable representatives, if applicable. Participants can discuss the trial with their families and friends if they wish. Participants should have the opportunity to ask questions and receive answers from the Investigator and site personnel to all their questions before signing and dating the ICF.

The participant will be provided with a copy of the signed and dated ICF for their records. No participant can enter the trial and no trial-related procedures can be done before his/her informed consent has been obtained. The consent process will be documented as part of the trial site source documents. Trial sites will be responsible for maintaining original signed ICFs as source documents for quality assurance review and regulatory compliance. The Investigator is responsible for notifying enrolled participants of updated study information in a timely manner and ensure all enrolled participants are given opportunity to re-consented in the event of consent form revisions as applicable.

12 FINANCIAL DISCLOSURE AND INSURANCE

[redacted]

13 PUBLICATION PLAN

[redacted]

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15 APPENDICES

Appendix 1 Declaration of Helsinki

Please refer: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Appendix 2 Trial Procedures Flowchart/Table

Table 3: Schedule of Assessments – Part A

Activity	Time Point							
Trial Visit	**Screening**	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**Un-scheduled[21]**
Relative Day/Week of Trial	**(Day -45 to Day 0)**	**Day 1[1] (Random-ization)**	**Week 1 (Day 8 ± 2 days)**	**Week 4 (Day 29 ± 3 days)**	**Week 8 (Day 57 ± 3 days)**	**Week 12 (Day 85 ± 7 days)**	**Week 24/Early Termination (Day 169 ± 14 days)**	**Day 1 to Week 24**
Type of Trial Visit	**On-site/ Home Visit**	**On-site[2]**	**Telephonic/ Virtual Visit**	**Telephonic/ Virtual Visit**	**On-site/ Home Visit**	**Telephonic/ Virtual Visit**	**On-site/Home Visit**	**On-site/ Home Visit**
Informed Consent	X							
Qualifying CDI Episode: Local Laboratory Stool Test for Toxigenic *C. difficile*[3]	X							
Qualifying CDI Episode: Clinical and Laboratory Confirmation of Eligibility by Medical Monitor[4]	X							
Demographics/Medical History/CDI History/Charlson Comorbidity index[5]	X							
Inclusion/Exclusion Criteria Part A at Screening	X							
Inclusion/Exclusion Criteria Part A at Randomization[6]		X						
Start/Continue Treatment of Standard-of-Care CDI Antibiotics[7]	X							
[redacted]		X						
Investigational Product Administration		X						

Table 3: Schedule of Assessments – Part A (Continued)

Activity	Time Point							
Trial Visit	**Screening**	**#1**	**#2**	**#3**	**#4**	**#5**	**#6**	**Un-scheduled[21]**
Relative Day/Week of Trial	**(Day -45 to Day 0)**	**Day 1[1] (Random-ization)**	**Week 1 (Day 8 ± 2 days)**	**Week 4 (Day 29 ± 3 days)**	**Week 8 (Day 57 ± 3 days)**	**Week 12 (Day 85 ± 7 days)**	**Week 24/Early Termination (Day 169 ± 14 days)**	**Day 1 to Week 24**
Type of Trial Visit	**On-site/ Home Visit**	**On-site[2]**	**Telephonic/ Virtual Visit**	**Telephonic/ Virtual Visit**	**On-site/ Home Visit**	**Telephonic/ Virtual Visit**	**On-site/Home Visit**	**On-site/ Home Visit**
CLINICAL SAFETY EVALUATIONS								
Physical Examination[8]		X						
Vital Signs Assessment[9]		X			X			X
12 Lead Electrocardiogram[10]	X							
Adverse Event Assessment[11]	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment[11]	X	X	X	X	X	X	X	X
Collection of Prior/Concomitant Medications[12]	X	X	X	X	X	X	X	X
LABORATORY SAFETY EVALUATIONS								
Pregnancy Testing[13]	X	X						
Safety Laboratory Samples (Blood, Urine, and Stool)[14]	X	X			X		X	X
SARS-CoV-2 Nasal PCR Testing	X							
QUALITY-OF-LIFE ASSESSMENTS AND PATIENT-REPORTED OUTCOMES								
Distribute Diary	X							
Recording of Unformed Stool by Diary[15]	X	X	X	X	X	X	X	X
[redacted]	X	X[16]	X	X	X		X	X
[redacted]	X	X[16]			X		X	X
[redacted]	X	X[16]			X		X	X
CLINICAL EFFICACY EVALUATIONS								
Assessment of CDI Recurrence[17]	X	X	X	X	X	X	X	X
C. difficile Stool Testing by Central Laboratory[18]								X

Table 3: Schedule of Assessments – Part A (Continued)

Activity	Time Point							
Trial Visit	Screening	#1	#2	#3	#4	#5	#6	Un-scheduled[21]
Relative Day/Week of Trial	(Day -45 to Day 0)	Day 1[1] (Random-ization)	Week 1 (Day 8 ± 2 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 3 days)	Week 12 (Day 85 ± 7 days)	Week 24/Early Termination (Day 169 ± 14 days)	Day 1 to Week 24
Type of Trial Visit	On-site/ Home Visit	On-site[2]	Telephonic/ Virtual Visit	Telephonic/ Virtual Visit	On-site/ Home Visit	Telephonic/ Virtual Visit	On-site/Home Visit	On-site/ Home Visit
[redacted]								
[redacted]	X	X[5]	X		X		X	X
[redacted]	X	X[5]			X			X

Abbreviations: CBC = complete blood count; CDI = *Clostridioides di*[redacted]; EIA = enzyme immunoassay; EQ-5D-5L = [redacted]; hCG = human chorionic gonadotropin; IP = investigational product; PCR = polymerase chain reaction; rRNA = ribosomal ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard-of-care; WBC = white blood count; [redacted]: CDI Associated Diarrhea V2.0.

NOTE:

1. Every effort should be made to complete all trial visit procedures listed for Day 1 in a single visit. Under extenuating circumstances and with written approval from the Sponsor, enrollment via the IRT may occur on the calendar day prior to dosing on Day 1.
2. A home visit may be conducted for some assessments under extenuating circumstances per the judgment of the site staff.
3. For Qualifying CDI episode, a documented stool sample positive for toxigenic *C. difficile* is required within 45 days prior to Randomization to be eligible. Two methods are permitted by local laboratory testing:
   - [redacted]
4. ALL Qualifying CDI episode requires CLINICAL and LABORATORY CONFIRMATION of eligibility by Medical Monitor.
5. Demographics and Medical history should be reviewed by Investigator prior to confirm trial eligibility, and all medical conditions present within the last 12 months should be recorded. The number and onset date of prior CDI episode occurring in the participant's lifetime will also be recorded. An assessment of comorbidities by Charlson Index must be provided. A pre-CDI medically documented weight or body mass index will be obtained. Alcohol consumption in the 12 months preceding the screening visit will be recorded as part of medical history.
6. Inclusion Criteria Part A Randomization must be satisfied prior to IP administration. This includes: 1) an outpatient prior to Randomization, 2) has received a course of SOC CDI antibiotics for the Qualifying CDI episode (for 10-21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator), 3) has an adequate clinical response, defined as < 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to Randomization [redacted]

[redacted] NOTE: Missing stool or blood sample at Randomization visit does not preclude the participant from Randomization.

7. For the Qualifying CDI episode, the participant will have received SOC CDI antibiotics (10-21 days: with exact duration, antibiotic type, and dose at the discretion of the Investigator).
8. Physical examination should be performed at Randomization. Performed at Week 8, Week 24, and also at each Unscheduled Visit, only if medically indicated.
9. Vital signs (body temperature, heart rate, respiration rate, blood pressure, pulse oximetry, height, and weight) should be measured just prior to dosing on Day 1, Week 8, and also at each Unscheduled Visit (if medically indicated). Collection of vital signs at Week 24 should be performed if medically indicated and is at the discretion of the Investigator. Weight for wheelchair-bound participants is optional. Height is only required at Randomization.
10. Electrocardiograms should be performed at Screening in all participants, and at Weeks 8 and 24 if medically indicated and is at the Investigator's discretion.
11. Adverse events and serious adverse events will be collected from the time a participant signs informed consent through Week 24 and at Unscheduled Visits as described in Section 7.3. SAEs reported by participants within 30 days after completing Early Termination or Week 24 visit will be collected. In addition to collection of all AEs, the following AEs will be specifically solicited using a daily participant diary for 7 days following IP administration (Day 1 to Day 7): abdominal distention or bloating, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, nausea, vomiting, and fever. The diary will be reviewed at the Week 1 visit.
12. Prior antibiotic medication use should be recorded for the 28 days prior to Screening and all other medications for the 14 days prior to Screening. All concomitant medications at Screening and following dosing should be recorded through Week 24.
13. Females of childbearing potential enrolled in this trial will have serum hCG pregnancy testing administered during Screening. Additionally, a urine pregnancy test will occur at Randomization. The Investigator may repeat a urine pregnancy testing at any point during the trial as medically indicated. Females who are postmenopausal for ≥ 1 year or surgically sterile will not undergo pregnancy testing.
14. Safety labs include blood, urine, and stool samples. Blood samples will include measurements for CBC with WBC differential [including platelets], blood chemistry (including serum electrolytes and liver-function testing), and urinalysis with microscopic evaluation if indicated. At Week 24/ET every effort will be made to obtain safety laboratory tests. Under extenuating circumstances in which this is not feasible, laboratory tests will not be required, however, all other non-laboratory Week 24/ET activities will be performed.
15. The number of unformed stools (defined by Bristol Stool Scale Type 6 through Type 7, will be recorded daily by the participant or designee through Week 8 (Day 57 ± 3 days) using the diary. Collection will be as needed after Week 8.
16. [redacted]
17. If the participant experiences a new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) at any time during the trial period, an Investigator evaluation will be triggered which includes MANDATORY central laboratory testing for toxigenic *C. difficile*. [redacted]
18. For each new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) during the trial period, a stool sample for central laboratory testing must be collected. A central laboratory test is a requirement for this trial and should not be replaced with a local laboratory test, unless under extenuating circumstances (e.g., central laboratory is closed due to pandemic). This sample should be collected before SOC CDI antibiotics are commenced. NOTE: Under extenuating circumstances, participants who experience *C. difficile*-related diarrhea in Part A may be allowed into Part B, provided there is positive multistep laboratory *C. difficile*-related diarrhea AND the symptoms are clinically consistent with CDI recurrence.
19. [redacted]
20. [redacted]
21. Procedures conducted at an Unscheduled Visit for indications other than a new episode of diarrhea are at the discretion of the Investigator. NOTE: Under extenuating circumstances, an Unscheduled Visit may be conducted as a telephonic/virtual visit, if medically indicated.

Table 4: Schedule of Assessments – Part B

Activity	Time Point							
Trial Visit	**Screening**	**#OLT1**	**#OLT2**	**#OLT3**	**#OLT4**	**#OLT5**	**#OLT6**	**OLT Unscheduled[19]**
Relative Day/Week of Trial		**Day 1[1]**	**Week 1 (Day 8 ±2 days)**	**Week 4 (Day 29 ± 3 days)**	**Week 8 (Day 57 ± 3 days)**	**Week 12 (Day 85 ± 7 days)**	**Week 24 /Early Termination (Day 169 ± 14 days)**	**Day 1 to Week 24**
Type of Trial Visit	**On-site/ Home Visit**	**On-site[2]**	**Telephonic/ Virtual Visit**	**Telephonic/ Virtual Visit**	**On-site/ Home Visit**	**Telephonic/ Virtual Visit**	**On-Site/Home Visit**	**On-site/ Home Visit**
On-Trial, Central Laboratory-Positive *C. difficile*-Related Diarrhea Within 8 weeks After Randomization in Part A[3]	X							
Demographics/Medical History/CDI History [4]	X							
Part B: Inclusion Criteria (Screening)	X							
Part B: Inclusion Criteria Open-Label Treatment (Day 1)[5]		X						
Start/Continue Treatment of Standard-of-Care CDI Antibiotics	X							
CP101 Administration [redacted]		X						
CLINICAL SAFETY EVALUATIONS								
Physical Examination[7]		X						
Vital Signs Assessment[8]		X			X			X
Adverse Event Assessment[9]	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment[9]	X	X	X	X	X	X	X	X
Collection of Prior/Concomitant Medications[10]	X	X	X	X	X	X	X	X
LABORATORY SAFETY EVALUATIONS								
Pregnancy Testing[11]	X	X						
Safety Laboratory Samples (Blood, Urine, and Stool)[12]	X	X			X		X	X
SARS-CoV-2 Nasal PCR Testing	X							
QUALITY-OF-LIFE ASSESSMENTS AND PATIENT-REPORTED OUTCOMES								
Recording of Unformed Stool by Diary[13]	X	X	X	X	X	X	X	X
[redacted]	X	X[14]	X	X	X		X	X
[redacted]	X	X[14]			X		X	X
[redacted]	X	X[14]			X		X	X

Table 4: Schedule of Assessments – Part B (Continued)

Activity	Time Point							
Trial Visit	Screening	#OLT1	#OLT2	#OLT3	#OLT4	#OLT5	#OLT6	OLT Unscheduled[19]
Relative Day/Week of Trial		Day 1[1]	Week 1 (Day 8 ±2 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 3 days)	Week 12 (Day 85 ± 7 days)	Week 24 /Early Termination (Day 169 ± 14 days)	Day 1 to Week 24
Type of Trial Visit	On-site/ Home Visit	On-site[2]	Telephonic/ Virtual Visit	Telephonic/ Virtual Visit	On-site/ Home Visit	Telephonic/ Virtual Visit	On-Site/Home Visit	On-site/ Home Visit
CLINICAL EFFICACY EVALUATIONS								
Assessment of CDI Recurrence[15]	X	X	X	X	X	X	X	X
C. difficile Stool Testing by Central Laboratory[16]								X
[redacted]								
[redacted]	X	X	X		X		X	X
[redacted]	X	X			X			X

Abbreviations: CBC = complete blood count; CDI = *Clostridioides difficile* infection; [redacted]; ET = Early Termination visit; hCG = human chorionic gonadotropin; IP = investigational product; OLT = open-label treatment; PCR = polymerase chain reaction; rRNA = ribosomal ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WBC = white blood count; [redacted]

NOTE:

1. Every effort should be made to complete all trial visit procedures listed for Day 1 in a single visit. Under extenuating circumstances and with written approval from the Sponsor, enrollment via the IRT may occur on the calendar day prior to dosing on Day 1.
2. A home visit may be conducted for some assessments under extenuating circumstances per the judgment of the site staff.
3. Participants must have an on-trial, central laboratory-positive *C. difficile*-related diarrhea within 8 weeks following Randomization in Part A. NOTE: Under extenuating circumstances, participants who experience *C. difficile*-related diarrhea in Part A may be allowed into Part B, provided there is positive multistep laboratory *C. difficile*-related diarrhea AND the symptoms are clinically consistent with CDI recurrence.
4. Medical history should be reviewed by the Investigator and any new medical conditions should be recorded.
5. Inclusion Criteria Part B Open-Label Treatment (Day 1) must be satisfied prior to IP administration. This includes: 1) an outpatient prior to CP101 administration, 2) has received a course of SOC CDI antibiotics for the Qualifying CDI episode (for 10-21 days, with exact duration, antibiotic type, and dose at the discretion of the Investigator), 3) has an adequate clinical response, defined as < 3 unformed stools in 24 hours for 2 or more consecutive days during SOC CDI antibiotics prior to IP administration, and [redacted]
6. Participant [redacted] has satisfied Inclusion Criteria 'Part B Open-Label Treatment (Day 1)', the participant may be administered CP101.
7. Physical examination should be performed at IP administration. Performed at Week 8, Week 24, and also at each Unscheduled Visit, only if medically indicated.
8. Vital signs (body temperature, heart rate, respiration rate, blood pressure, pulse oximetry, height, and weight) should be measured just prior to dosing on Day 1, Week 8, and also at each Unscheduled Visit (if medically indicated). Collection of Vital signs at Week 24 should be performed if medically indicated and is at the discretion of the Investigator. Weight for wheelchair-bound participants is optional.
9. AEs and SAEs will be collected from the time a participant signs the ICF through Week 24 and at Unscheduled Visits as described in Section 7.3. SAEs reported by participants within 30 days after completing Early Termination or Week 24 visit will be collected. In addition to collection of all AEs, the following AEs will be

specifically solicited using a daily participant diary for 7 days following IP administration (Day 1 to Day 7): abdominal distention or bloating, chills/severe shivering, abdominal pain or cramping, increased diarrhea, constipation, nausea, vomiting, and fever. The diary will be reviewed at the Week 1 visit.

10. Any new antibiotic medication use should be recorded prior to Screening and any other new medications. All concomitant medications at Screening and following IP administration should be recorded through Week 24.
11. Females of childbearing potential enrolled in this trial will have serum hCG pregnancy testing administered during Screening. Additionally, a urine pregnancy test will occur prior to IP administration at Day 1. The Investigator may repeat a urine pregnancy testing at any point during the trial as medically indicated. Females who are postmenopausal for ≥ 1 year or surgically sterile will not undergo pregnancy testing.
12. Safety labs include blood, stool, and urine samples. Blood samples will include measurements for CBC with WBC differential (including platelets), blood chemistry (including serum electrolytes and liver-function testing), and urinalysis with microscopic evaluation if indicated. At Week 24/ET every effort will be made to obtain safety laboratory tests. Under extenuating circumstances in which this is not feasible, laboratory tests will not be required, however, all other non-laboratory Week 24/ET activities will be performed. **NOTE**: If safety labs were collected in Part A of the trial within 30 days prior to the Screening visit for Part B and there is no medical concern to repeat the laboratory tests, they do not need to be collected.
13. The number of unformed stools (defined by Bristol Stool Scale Type 6 through Type 7, will be recorded daily by the participant or designee through Week 8 (Day 57 ± 3 days) using the diary. Collection will be as needed after Week 8.
14. [redacted]
15. If the participant experiences a new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) at any time during the trial period, an Investigator evaluation will be triggered which must include MANDATORY central laboratory testing for toxigenic *C. difficile*. [redacted]
16. For each new episode of diarrhea (> 3 unformed stools in 24 hours for 2 consecutive days) during the trial period, a stool sample for central laboratory testing must be collected. A central laboratory test is a requirement for this trial and should not be replaced with a local laboratory test, unless due to extenuating circumstances (e.g., central laboratory is closed due to pandemic). This sample should be collected before SOC CDI antibiotics are commenced.
17. [redacted]
18. [redacted]
19. Procedures conducted at an Unscheduled Visit for indications other than a new diarrheal episode are at the discretion of the Investigator. NOTE: Under extenuating circumstances, an Unscheduled Visit may be conducted as a telephonic/virtual visit if medically indicated.