Clostridioides difficile Infection: Developing Drugs for Treatment, Reduction of Recurrence, and Prevention

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clostridioides difficile Infection: Developing Drugs for Treatment, Reduction of Recurrence, and Prevention Guidance for Industry[1]

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I. INTRODUCTION

This guidance outlines the Food and Drug Administration's (FDA's) current thinking regarding the clinical development of drugs[2] to support an indication of treatment,[3] reduction of recurrence,[4] or prevention[5] of *Clostridioides difficile* infection (CDI).[6]

CDI is a toxin-mediated disease caused by *Clostridioides difficile* (*C. difficile*), an anaerobic, gram-positive, spore-forming bacterium that produces two pathogenic enterotoxins, Toxin A (TcdA) and Toxin B (TcdB). Some *C. difficile* strains (e.g., 027/BI/NAP1) produce a third toxin called binary toxin, which has been associated with increased production of TcdA and TcdB and more severe CDI.

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] In this guidance, the term *drugs* includes both small molecule drugs and therapeutic biological products regulated by CDER unless otherwise specified. This guidance does not apply to certain biological products such as fecal microbiota transplantation products, probiotics, and vaccines.

[3] In this guidance, treatment of *Clostridioides difficile* (*C. difficile*) infection (CDI) refers to treatment of an acute episode of CDI defined as greater than or equal to three unformed stools or greater than or equal to 200 milliliters (mL) of unformed stool (in subjects with a stool collection device) in a less than or equal to 24-hour period, associated with a stool test positive for *C. difficile* TcdA or TcdB using an accepted and prespecified testing method.

[4] Reduction of recurrence refers to reducing the risk of a subsequent CDI episode in subjects immediately after resolution of an episode of CDI.

[5] In this guidance, prevention refers to prevention of CDI in subjects with or without a history of CDI who are at risk for CDI (e.g., subjects on antibacterial therapy in the context of other predisposing factors such as increased age or immunosuppression). For subjects with a history of CDI, the sponsor should discuss with FDA the time between resolution of the previous episode and enrollment in a prevention trial.

[6] In this guidance, CDI includes symptomatic disease, not asymptomatic carriage. Sponsors that want to include study populations with asymptomatic carriage of *Clostridioides difficile* should consult with FDA.

Clinical manifestations of CDI may range from self-limited to unremitting diarrhea to colitis accompanied by features of systemic inflammatory response (e.g., fever, hypotension, tachycardia) to severe manifestations like toxic megacolon, intestinal perforation, septic shock, and death. Following resolution of the first episode, CDI recurs in 15 to 40 percent of patients with further recurrences occurring in an even higher proportion of those patients.[7]

Because clinical manifestations of CDI may not be limited to diarrhea alone, and in keeping with current terminology in treatment guidelines and literature, the term CDI rather than *Clostridioides difficile*-associated diarrhea is used in this guidance.

Because the design of clinical trials for CDI will depend on the goal of treatment, this guidance addresses the development of small molecule drugs and therapeutic biological products for the following indications:

- Treatment of CDI
- Reduction of recurrence[8] of CDI following resolution[9] of a CDI episode after treatment with a standard of care (SOC) regimen
- Treatment of CDI ***and*** reduction of recurrence
- Prevention of CDI in patients at risk[5]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEVELOPMENT PROGRAM

A. Trial Populations

Sponsors developing drugs for CDI indications should consider enrolling the following clinical trial populations:

- Trials for treatment: Subjects with CDI.[7]

[7] McFarland LV, Elmer GW, and Surawicz CM, 2002, Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent Clostridium Difficile Disease, Am J Gastroenterol, 97(7):1769–75.

[8] See footnote 4. Sponsors that want to include subjects with multiple recurrences following resolution of a CDI episode with SOC treatment should discuss this with FDA before trial enrollment.

[9] In this guidance, resolution of CDI is defined as less than three unformed stools or less than 200 mL of unformed stool (for subjects with a stool collection device) in a 24-hour period.

- Trials for treatment ***and*** reduction of recurrence: Subjects with CDI.

- Trials for reduction of recurrence only: Subjects immediately after resolution of a CDI episode with an SOC regimen.

- Trials for prevention: Subjects at risk of developing CDI[5]

- Trials for all CDI indications should include older adults and immunosuppressed subjects and those with varying severity of illness, comorbidities, and concomitant medications, including antibacterial drugs and proton-pump inhibitors, among others. The representation of polymerase chain reaction (PCR) ribotypes in the trial population should reflect current CDI epidemiology.

B. Trial Design

Sponsors developing drugs for CDI indications should consider the following clinical trial designs:

- Trials should be randomized, double-blinded, and controlled.

- Sponsors should use an active control in trials for CDI treatment and treatment ***and*** reduction of recurrence. Sponsors can use a placebo or active control in trials for prevention or reduction of recurrence only.

- In trials for treatment ***and*** reduction of recurrence, the initial CDI episode should be treated with the investigational or comparator drug. In trials for reduction of recurrence only, the investigational and comparator drug (active or placebo) should be started as soon as possible after resolution of the initial CDI episode with an SOC regimen.

- A noninferiority (NI) or superiority finding of the investigational drug to SOC is acceptable to support approval of a drug for treatment of CDI. FDA prefers a showing of superiority for drugs developed for treatment ***and*** reduction of recurrence, and reduction of recurrence only, unless the sponsor can justify an NI margin for these trials. As there are currently no suitable active comparators for CDI prevention trials, superiority trials are most appropriate for drugs developed for prevention of CDI.

- The timing of assessments should be the same for all subjects defined based on a fixed timepoint from randomization. FDA recommends the following time point definitions:

  — **End of treatment (EOT)**: the final day of the planned duration of therapy (or planned duration of the longest therapy if the treatment arms are not of the same

duration) timed from randomization. In general, the duration of therapy should be no more than 14 days.[10]

— **Test of cure (TOC)**: 2 days after the end of the planned duration of therapy (i.e., 2 days after EOT).

— **Late follow-up (LFU)**: a fixed time point at least 4 weeks after the end of the planned duration of treatment (e.g., this would be at least 6 weeks after randomization for a 14-day planned duration of therapy).

C. Efficacy Considerations

1. Efficacy Assessments

Sponsors developing drugs for CDI indications should consider the following regarding a drug's efficacy:

- In general, two adequate and well-controlled trials are needed to support the effectiveness of the investigational drug.[11] One trial demonstrating evidence of efficacy for treatment alone and another trial for reduction of recurrence or for prevention of CDI alone may support two indications. If treatment and reduction of recurrence are evaluated in the same trial, two adequate and well-controlled trials would be needed.

- In trials for treatment of CDI, the primary efficacy endpoint should be survival and resolution of diarrhea while on the randomized study treatment that is sustained after the EOT through the TOC visit without a requirement for additional CDI treatment. Sponsors can also consider sustained clinical response[12] as an important secondary endpoint for trials for CDI treatment only.

- In trials for treatment ***and*** reduction of recurrence, the sponsor should assess two coprimary endpoints that include the efficacy of treatment of CDI at TOC and sustained clinical response as described above.

- In trials for reduction of CDI recurrence only, sponsors should define the primary efficacy endpoint as survival without recurrent CDI or requirement for additional CDI

[10] Sponsors proposing a drug regimen requiring more than 14 days of treatment to resolve CDI should discuss this with FDA before trial enrollment because the proposed NI margin may not be applicable.

[11] See the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and *Integrated Summary of Effectiveness* (October 2015) and the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[12] Sustained clinical response is defined as being a success at TOC and survival without recurrent CDI or additional CDI treatment for at least 4 weeks after the EOT visit.

treatment for at least 4 weeks after the EOT. In trials for CDI prevention, the primary efficacy endpoint should be the occurrence of an episode of CDI within a predefined trial period. The sponsor should discuss with FDA the duration of the prevention trial and approaches to handling deaths in the efficacy analyses (see section II., C., 2. *Statistical Considerations*).

- Subjects in CDI prevention, treatment, or treatment ***and*** reduction of recurrence trials should not receive oral or rectal vancomycin, intravenous or oral metronidazole, fidaxomicin, rifaximin, tigecycline, nitazoxanide, or fusidic acid for more than 24 hours before randomization. Sponsors should discuss with FDA the inclusion of subjects with a history of fecal transplantation or bezlotoxumab use.

- Sponsors should discuss with FDA the use of patient-reported outcome measures in clinical trials for CDI.

2. Statistical Considerations

FDA recommends the following statistical considerations for sponsors developing drugs for CDI indications:

- An NI margin of 10 percent for the primary efficacy endpoint for clinical response in trials for CDI treatment with vancomycin as the active comparator is supported by historical evidence (see the Appendix). For CDI treatment trials using an active comparator other than vancomycin, the sponsor should provide additional justification of an NI margin.

- If an NI trial is proposed for drugs developed for reduction of CDI recurrence, the sponsor should provide justification of an NI margin.

- For CDI prevention trials, the statistical analysis plan should specify the approaches for handling deaths, which is considered an intercurrent event. Depending on the trial population (e.g., hematopoietic stem cell recipients), the number of deaths from underlying comorbidities may be greater than the rate of CDI and could complicate the interpretation of trial results, especially if there are differences between treatment groups in occurrence of death unrelated to CDI or death overall.

D. Safety Considerations

Sponsors developing drugs for CDI indications should consider the following:

- For drugs developed for CDI treatment and/or reduction of recurrence, the marketing application (new drug application or biologics license application) safety database should include at least 300 subjects exposed to the proposed investigational drug treatment dose and duration.

- Clinical programs for drugs developed solely for prevention of CDI may require a larger safety database. Sponsors should discuss the appropriate size of the premarket safety database with FDA during clinical development.

E. Other Considerations

FDA recommends the following additional considerations for sponsors developing drugs for the treatment, treatment ***and*** reduction of recurrence, reduction of recurrence only, or prevention of CDI:

Relevant Nonclinical Safety Considerations

- Sponsors of drugs developed for CDI indications should test the investigational drug *in vitro* and in animal models[13] for general toxicity before submitting an initial investigational new drug application (IND). For recommendations on the types, duration, and timing of nonclinical studies needed to support clinical trials, see the International Council for Harmonisation guidance for industry M3(R2) *Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

- Because patients with CDI may have increased oral drug absorption due to disruption of the intestinal barrier, FDA recommends an intravenous toxicology study in at least one mammalian species to identify potential risk associated with enhanced absorption.

- If the drug is to be used as part of a clinical regimen (e.g., in combination with an approved CDI treatment), nonclinical studies to evaluate toxicological effects of the proposed combination may be warranted. Sponsors should contact FDA to determine if nonclinical toxicology studies of the specific investigational drug combination regimen should be conducted.

Pharmacokinetic and Dose Selection Considerations

- Drugs developed for CDI indications can be administered by various routes (e.g., intravenous, oral administration). Some of these drugs can be systemically available although some orally administered drugs may act locally in the gastrointestinal tract (site of action) with minimal systemic absorption.

- During development, sponsors should adequately characterize the pharmacokinetics of the investigational drugs, as appropriate, based on the route of administration. The characterization includes, but is not limited to, assessment of drug-drug interaction potential and the evaluation of the effect of renal and hepatic impairment on the pharmacokinetics of the drug. Of particular relevance for CDI drug development,

[13] We support the principles of the 3Rs (reduce, refine, and replace) for animal use in testing when feasible. We encourage sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

pharmacokinetic assessments for locally acting orally administered drugs should include, but are not to be limited to, systemic absorption in healthy subjects and CDI patients and effect of food on the systemic absorption, drug metabolism and drug-drug interaction potential in the gastrointestinal tract, as well as the extent and duration of drug excretion in stool. Given that CDI is most common in older adults, sponsors should evaluate the pharmacokinetics of the investigational drugs in this population to assist the assessment of safety and efficacy.

- Appropriate dose-ranging studies should be conducted to aid dose selection. For systemically available drugs, sponsors can use assessment of blood/plasma concentrations in dose-ranging studies to explore the exposure-response relationships for safety and/or efficacy.

APPENDIX

Justification for a Noninferiority Margin for Trials for Treatment of *Clostridioides difficile* Infection[1]

Sponsors can estimate the treatment effect of an active control (M_1) in the treatment of *Clostridioides difficile* (*C. difficile*) infection (CDI) using the results of two identical phase 3 three-arm trials comparing vancomycin, metronidazole, and tolevamer for treatment of CDI.[2] Tolevamer is a polymer that was hypothesized to bind and neutralize *C. difficile* toxins. The trials demonstrated superiority of both vancomycin and metronidazole over tolevamer. Therefore, tolevamer may be considered a putative placebo for the purposes of estimating the treatment effects of potential active controls. Given that in a prior phase 2 trial tolevamer demonstrated dose-response efficacy in resolution of CDI, it can be assumed that tolevamer is not worse than placebo.[3]

The phase 3 trials of tolevamer had a similar design and were randomized, double-blind, and active-controlled trials conducted between 2005 and 2007. One trial enrolled subjects in the United States and Canada (Study 301, NCT00106509) and another trial enrolled subjects in Europe, Australia, and Canada (Study 302, NCT00196794). Subjects 18 years of age and older were randomly assigned in a 2:1:1 ratio to receive tolevamer liquid every 8 hours for 14 days, vancomycin 125 milligram (mg) capsule every 6 hours for 10 days, or metronidazole 375 mg capsule every 6 hours for 10 days.

CDI was defined as three or more bowel movements in a 24-hour period with a loose or watery consistency, a positive *C. difficile* toxin assay result (enzyme immunoassay or cellular cytotoxicity assay) or pseudomembranes on endoscopy.

Subjects with fulminant CDI, intestinal ileus, continued exposure to CDI-inducing antibacterial drugs for more than 7 days, receipt of more than 48 hours of oral vancomycin or intravenous or oral metronidazole, or other effective alternate treatment for CDI within 5 days of enrollment were excluded.

The primary efficacy endpoint was clinical success, defined as resolution of diarrhea and absence of severe abdominal discomfort due to CDI for more than 2 consecutive days including Day 10.

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[1] For prevention of *Clostridioides difficile* infection (CDI), FDA recommends a superiority design. For reduction of CDI recurrence, FDA recommends a superiority design, but if the sponsor decides to conduct a noninferiority (NI) trial for this indication, the sponsor will need to provide a justification for an NI margin. See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[2] Johnson S et al., 2014, Vancomycin, Metronidazole, or Tolevamer for *Clostridium difficile* Infection: Results From Two Multinational, Randomized, Controlled Trials, Clin Infect Dis, 59(3):345–54.

[3] Louie TJ et al., 2006, Tolevamer, a Novel Nonantibiotic Polymer, Compared With Vancomycin in the Treatment of Mild to Moderately Severe *Clostridium difficile*-Associated Diarrhea, Clin Infect Dis, 43(4): 411–20.

Resolution of diarrhea was defined as attainment of bowel movements with a hard or formed consistency or two or fewer watery bowel movements in a 24-hour period.

Key demographics of the trial populations are presented in Table 1. As subjects were similarly matched across the three treatment arms within each trial, the combined data for the trials are presented. Overall, the subject populations in the trials reflect subjects that are expected to enroll in modern CDI trials.

Table 1: Key Demographics in Phase 3 Historical Trials (Full Analysis Set)[*]

Key Demographics	Study 301 N=543	Study 302 N=528
Age, mean and range	62 (18-99)	68 (18-97)
> 65	252 (46%)	323 (61%)
Female	285 (52%)	284 (54%)
Inpatient	306 (56%)	482 (91%)
First episode of CDI	384 (71%)	436 (83%)
CDI severity[**]		
Mild	136 (25%)	172 (33%)
Moderate	221 (41%)	228 (43%)
Severe	185 (34%)	128 (24%)
Missing	1	0
Binary toxin *C. difficile* strain	136 (25%)	40 (8%)

Johnson S et al., 2014, Vancomycin, Metronidazole, or Tolevamer for *Clostridium difficile* Infection: Results From Two Multinational, Randomized, Controlled Trials, Clin Infect Dis, 59(3):345–54.

[*] Full analysis set = All randomized subjects who received any treatment and had any postdose evaluation.
[**] CDI = *Clostridioides difficile* infection; Mild= Three to five bowel movements (BM)/day, white blood cell counts (WBC) less than or equal to 15,000/cubic millimeter (mm^3), mild or absent abdominal pain due to CDI; Moderate = six to nine BM/day, WBC 15,001–20,000/mm^3, mild, moderate, or absent abdominal pain due to CDI; Severe = 10 or more BM/day, WBC greater than or equal to 20,001/mm^3, severe abdominal pain due to CDI; any characteristics could be used to assign a severity category, and the more severe category was used when characteristics overlapped.

The clinical success rates in the phase 3 tolevamer trials are presented in Table 2 (treatment differences and confidence intervals are not provided in the original paper).

Table 2: Clinical Success Rates in Phase 3 Historical Trials (Full Analysis Set)[*]

Study	Drug	Clinical Success Rate		Treatment Difference (95% CI)
301	Tolevamer	124/266	46.6%	
	Vancomycin	109/134	81.3%	35% (25%, 43%)
	Metronidazole	103/143	72.0%	25% (15%, 34%)
302	Tolevamer	112/268	41.8%	
	Vancomycin	101/125	80.8%	39% (29%, 47%)
	Metronidazole	99/135	73.3%	32% (21%, 40%)

Johnson S et al., 2014, Vancomycin, Metronidazole, or Tolevamer for Clostridium difficile Infection: Results From Two Multinational, Randomized, Controlled Trials, Clin Infect Dis, 59(3):345–54.

[*] Full analysis set = All randomized subjects who received any treatment and had any postdose evaluation.
[**] Confidence interval (CI) was derived using method recommended in Newcombe RG, 1998, Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods, Stat Med, 17(8): 873–90.

The two trials provide a reproducible estimation of the treatment effect of oral vancomycin and oral metronidazole for treatment of CDI. However, metronidazole is not currently considered a first-line therapy for CDI whereas oral vancomycin remains the standard of care.[4]

A meta-analysis of the results of the two trials using the DerSimonian and Laird approach (random effect model) gives an estimate of the treatment effect for oral vancomycin of 37 percent with a 95 percent confidence interval (CI) (30 percent, 43 percent).[5] Thus, the treatment effect (M_1) can be conservatively estimated at 30 percent based on the lower bound of the CI for the treatment difference between vancomycin and tolevamer.

These estimations of the treatment effect may be conservative as tolevamer may be more effective than placebo. However, there are uncertainties regarding possible departures from the constancy assumption and generalizability issues (i.e., it should be noted that in the tolevamer trials clinical success was defined as the resolution of diarrhea by the end of treatment (EOT); whereas in the current guidance, clinical success is defined as the resolution of diarrhea at the EOT sustained through 2 days immediately following EOT). To account for these uncertainties, the treatment effect of vancomycin should be somewhat discounted. We propose a 10 percent discounting, which, when applied to the 30 percent lower limit of the 95 percent CI of the M_1 of vancomycin over tolevamer from the meta-analysis of the tolevamer clinical trials, results in M_1 of 27 percent. The derived M_1 supports a noninferiority (NI) margin of 10 percent while still preserving more than 60 percent of the treatment effect based on the endpoint of clinical success

[4] McDonald LC et al., 2018, Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), Clin Infect Dis, 66(7): 987–994.

[5] See the April 5, 2011, FDA briefing document for the Anti-Infective Drugs Advisory Committee meeting entitled Fidaxomicin for the Treatment of Clostridium difficile-Associated Diarrhea (CDAD) available at https://wayback.archive-it.org/7993/20170405204844/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM249353.pdf.

as defined above. If the sponsor uses active comparators other than vancomycin in CDI treatment trials, the sponsor may need to provide additional justification of an NI margin.