Study Title:	**Prospective, open-label trial to evaluate efficacy of 30-day duration of fidaxomicin in patients with recurrent *Clostridioides (Clostridium) difficile* infection.**
Protocol Version Date/Number	01OCT2020 Version No. 5
ClinicalTrial.gov	NCT02395848
Protocol No:	CDI.FIDAXOMICIN.1
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Safety Reporting:	Vancouver Island Health Authority Clinical Research Ethics Board

1 STUDY RATIONALE/BACKGROUND

Clostridioides difficile (*C. difficile*) infection (CDI) is one of the most frequent causes of healthcare associated infections and its rates are also growing in the community. The case fatality rate associated with CDI is 6%. CDI is also problematic as it can lead to chronic diarrhea and has been the source of outbreaks in many hospitals.[1-6]
The efficacy of standard antibiotics especially for recurrent CDI is limited as oral vancomycin and metronidazole also suppress the growth of anaerobic bacteria such as *Bacteroides fragilis (B. fragilis)* group which protect against proliferation of *C. difficile*. In contrast, in vitro study has shown that fidaxomicin has negligible activity against *B. fragilis*. The persistent disruption of healthy colonic flora may be the reason for recurrences following a course of treatment with metronidazole or vancomycin. Fidaxomicin has shown to reduce recurrences by approximately 50% when compared to oral vancomycin for primary or 1st episode of recurrent CDI.

There is a growing concern regarding failure rates for metronidazole, which is recommended as the first line therapy for uncomplicated CDI; as it has risen from 2.5% to greater than 18% since 2000.[1] Recurrence of CDI following a course of standard antibiotic (metronidazole/oral vancomycin) therapy is high, especially in the elderly patients over 65 years of age, in hospitalized and in the immunocompromised patients. Rates of recurrences are greater than 50% for those over the age 65.[9] The risk of further recurrence is over 60% for patients who have failed 3 or more episodes of standard antimicrobial therapies.[9-12] Fecal microbiota transplantation (FMT) has shown to be very effective for multiple recurrent CDI.[13] Although effective, FMT has limitations as the majority of healthcare facilities, worldwide do not have the infrastructure available to offer the treatment as it requires readily available donors and laboratory capacity to screen donors and manufacture FMT in timely manner. There are also potential risks associated with FMT such as transmission of pathogens, including SARS-CoV-2, antibiotic resistant organism, development of bacteremia especially in immunocompromised hosts, peritonitis and intestinal perforation.[14-16]

Determining the efficacy and safety of 30-day duration of fidaxomicin for recurrent CDI through an open label clinical trial has important implications for policy making related to the drug reimbursement programs. In addition, the results of this study will be instrumental in demonstrating to the scientific and healthcare communities there may be a role for the 30-day

course of fidaxomicin as a treatment modality for recurrent CDI. Curing CDI will restore the health and quality of life not just at the individual patient level but to the healthcare communities as well. Patients with refractory CDI require prolonged hospital admission, which increases the organism burden within the healthcare facilities. This in turn leads to the spread of the infection to other vulnerable patients. If a 30-day course of fidaxomicin proves to be safe and effective in curing patients with recurrent CDI, it will reduce the risk of severe complications in each patient and reduce transmission of CDI to other susceptible patients. All these will also reduce healthcare costs.

2 STUDY HYPOTHESIS

Thirty-day duration of fidaxomicin will be effective in reducing the rates of recurrence of CDI. Fidaxomicin has shown to reduce recurrences by 50% when compared to oral vancomycin for primary or 1st episode of recurrent CDI. In vitro study has shown that fidaxomicin has virtually no activity against *B. fragilis* and may explain the significant reduction in *C. difficile* recurrences.

3 STUDY OBJECTIVE AND ENDPOINTS

3.1 STUDY OBJECTIVE

To study the outcome of patients treated with a 30-day course of fidaxomicin for recurrent CDI

3.2 STUDY ENDPOINTS

3.2.1 *PRIMARY EFFICACY ENDPOINT*

1. Clinical response at study day 30, in this context, clinical response will be defined as those participants who have improvement in the number of bowel movements as determined by ≤ 3 unformed stools in a 24-hour period for 2 consecutive days during treatment and remaining well through study day 30.
2. Sustained clinical response as defined by those participants who achieved clinical response by study day 30 and did not experience a recurrence of CDI at the end of the follow-up period, evaluated at 8 weeks after the completion of treatment.
3. Recurrence of CDI as defined by return of diarrhea (a minimum of 3 unformed bowel movements or ≥ 200 mL of stool for individuals with a stool collection device such as rectal tube or colostomy within a 24-hour period) and positive stool test after a period of symptom resolution within study period and has received at least a 10-day course of standard antibiotic therapy.
4. Treatment failure as defined by patients not meeting the definition of cure and requiring additional treatment(s) for current CDI episode.

3.2.2 *SECONDARY ENDPOINT(S):*

- The evaluation of safety of 30-day duration of fidaxomicin (200mg twice daily x 10 days and 200mg once daily x 20 days).
    - Assessment for adverse reactions by history, complete blood count and chemistry panel at day 10 (-3, +1d), followed by history on day 30 (+/-3d) and week 8 post treatment (week 12) of the study period.
- Any serious adverse events up to and including week 12 for any of the following:
    - Death or a life-threatening event
    - New hospitalization or prolongation of current hospitalization
    - A significant new incapacity to conduct normal life functions

4 STUDY DESIGN

4.1 SITES

Vancouver Island Health Authority

4.2 INCLUSION/EXCLUSION CRITERIA

4.2.1 *INCLUSION CRITERIA*

1. Age 18 years or older.
2. Able to provide informed consent.
3. Willing and able to comply with all the required study procedures.
4. A positive stool test for *C. difficile* toxin/gene using either PCR or enzyme immunoassay within 3 months of recruitment.
5. History of at least ≥ 2 recurrent CDI within 6 months where recurrence is defined as return of diarrhea consistent with CDI within 8 weeks following CDI symptom resolution for at least 24 hours after a minimum of 10-day course of standard antibiotic therapy and positive stool test for *C. difficile* toxin or toxin gene and/or ongoing symptoms consistent with CDI despite at least 5 days of treatment using oral vancomycin.
6. Has more than three unformed bowel movements or ≥ 200 mL of stool for individuals with a stool collection device such as rectal tube or colostomy during a 24-hour period at the time of initiation of fidaxomicin. Participants will be enrolled when they meet inclusion criteria 1 – 5; will be initiated on fidaxomicin when they have CDI symptoms and stool will be tested for *C. difficile* toxin/gene. Only those with positive stool for *C. difficile* toxin/gene with current episode of CDI will continue with the study
7. Females of child bearing potential must be willing to use acceptable birth control as per the Health Canada Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences.

4.2.2 *EXCLUSION CRITERIA*

1. Planned or actively taking an investigational product for another study.
2. Prior fidaxomicin use.
3. Hypersensitivity to fidaxomicin or to any ingredient in the formulation or component of the container.
4. Evidence of toxic megacolon or gastrointestinal perforation or life expectancy of less than 72 hours.
5. Active gastroenteritis due to *Salmonella, Shigella, E. coli* 0157H7, *Yersinia* or Campylobacter.
6. Anticipated requirement for systemic antibiotic therapy for more than 7 days during the study period.
7. Actively taking *Saccharomyces boulardii* or other probiotics other than yogurt.
8. Any condition that, in the opinion of the investigator, that the treatment may pose a health risk to the subject.
9. Pregnant or lactating.

4.3 SAMPLE SIZE

4.3.1 NUMBER OF SUBJECTS TO BE ENROLLED

A sample size of 50 is planned.

4.4 SCREENING, RANDOMIZATION, BLINDING

4.4.1 *SCREENING PROCEDURE*

Potential participants will be screened for eligibility based on the inclusion and exclusion criteria when the PI receives consultation request for recurrent CDI.Patients will be recruited to participate in the trial when they meet the inclusion criteria (1 to 5) and do not have any exclusion ones. The eligible participants with active diarrhea with clinical criteria for CDI will be initiated on fidaxomicin. For those without diarrhea at baseline will be instructed to phone the research office when they experience recurrent symptoms consistent with their previous episodes of CDI. They will be assessed within 48 hours of symptom onset and will be started on fidaxomicin if they continue to meet the inclusion criteria and do not have any exclusion ones. The stool sample collected during the onset of this particular CDI episode will be tested for *C. difficile* toxin. If positive then they will complete the 30-day course of fidaxomicin. If the stool tested negative for *C. difficile* toxin then they will be excluded from further participation of this study and standard of care for this particular episode of diarrhea will be provided based on the most likely etiology.

Females of child bearing potential must be willing to use contraception methods of birth control to participate in the study. Highly effective methods may include: hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy and tubal ligation. Highly effective methods of contraception might not always be achievable in the clinical trial setting and, therefore, the most effective alternative can be achieved using methods in combination. Effective methods may include: barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge).

Use of therapeutic products where the risk of fetal abnormality is not known or is unclear (e.g. lack of adequate reproduction toxicity data), animal studies have failed to reveal evidence of fetal harm and use of fidaxomicin, however there are no controlled data in human pregnancy: therefore at least one highly effective method of contraception or two forms of effective contraception methods need to be used.
The half-life of fidaxomicin is 11.7 +/- 4.8 hours therefore will specify to continue with contraception for 48 hours after the last dose of fidaxomicin.

4.5 REGULATORY AND ETHICS

4.5.1 INFORMED CONSENT

Informed consent will be obtained from each participant.

4.5.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

The study protocol and informed consent form and amendments will be submitted to the Vancouver Island Health Authority Clinical Research Ethics Board.

4.5.3 INVESTIGATIONAL NEW DRUG (IND) FILING

No Objection Letter will be obtained from Health Canada.

5 STUDY PROCEDURES

5.1 TREATMENT

Participants will take fidaxomicin 200 mg by mouth (PO) twice daily for 10 days, followed by 200 mg PO once daily for 20 days.

5.2 STUDY PROCEDURES SCHEDULE

	Baseline/Day 1	Unscheduled visit	Day 10 (-3 to +1d)	Week 3 to 12
Procedure	Eligibility screen Obtain consent Medical and CDI history Physical examination Laboratory testing if active diarrhea	Active diarrhea consistent with CDI, collect stool sample and bring to clinic		Weekly phone call
Laboratory Testing	CBC, chemistry, creatinine, albumin, sodium, potassium, chloride, alanine transaminase, alkaline phosphatase, bilirubin Stool testing for CD toxin Pregnancy test for females of child bearing potential	CBC, chemistry, creatinine, albumin, sodium, potassium, chloride, alanine transaminase, alkaline phosphatase, bilirubin Stool testing for CD toxin, only if active diarrhea	CBC, chemistry, creatinine, albumin, sodium, potassium, chloride, alanine transaminase, alkaline phosphatase, bilirubin	

5.3 STUDY TREATMENT SCHEDULE

	Day 1 to 10	Day 11 to 30
Treatment	Fidaxomicin 200mg by mouth twice daily for 10 days	Fidaxomicin 200mg by mouth once daily for 20 days

6 SERIOUS ADVERSE DRUG REACTIONS

6.1.1 DEFINITONS

Each serious adverse drug reaction (SADR) which is subject to expedited reporting to Health Canada should be reported individually in accordance with the data element(s) specified in the Health Canada/ICH Guidance Document E2A: "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting". Expedited reports are required for events that meet all of these three criteria: serious, unexpected and a suspected causal relationship.

Serious: Any untoward medical occurrence that at any dose:

- Results in death
- Life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect.

6.1.2 RELATIONSHIP TO STUDY MEDICATION

Event reaction causality scoring system will be used to determine the probability of relationship to study medication

6.1.3 EXPECTEDNESS OF ADR

An "unexpected" adverse reaction is one in which the nature or severity is not consistent with information in the relevant source document(s), such as the IB or Product Monograph.

6.1.4 RECORDING AND REPORTING SADR

SADRs which are unexpected, serious AND suspected causal relationship to the study medication will be reported to the research ethics board within 24 hours of the PI being aware of the event. This information will also be reported to Health Canada:

Health Canada
Office of Clinical Trials

Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
A/L 3015A
1600 Scott Street
Ottawa, Ontario
Canada K1A 0K9
Fax: 613-941-2121

7 DATA COLLECTION AND ANALYSIS

7.1 DATA COLLECTION

Data will be collected at baseline, at initiation of fidaxomicin, on day 10, day 30 and 8 weeks post treatment (week 12 of study) using source documents

7.2 DATA VALIDATION

All data collected during the study will be validated by a second research staff using the investigator's clinical notes, electronic medical records, and laboratory results comparing to the source documents

7.3 DATA / STATISTICAL ANALYSIS

The clinical cure rate will be determined using standard binary outcome protocols. Also, logistic regression and survival analysis methods will be performed. The primary endpoints of clinical response, sustained clinical response, time to resolution of diarrhea (TTROD), recurrence of CDI, and treatment failure will be analyzed by logistical regression.

8 PUBLICATION

The abstract will be submitted for presentation at Infectious Diseases Society of America or Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). The manuscript will be submitted to a medical journal.

9 REFERENCES

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Appendix A: Telephone Script

PHONE CONTACT SCHEDULE AND SCRIPT
Weekly contact by phone –Week 3 to 8

Participant phone follow-up script:

Participant ID: __ __ __ - __ __ __

Date: _____ / _____ / _____ Time: __ __ : __ __

Hi, my name is _____ from Vancouver Island Health Authority. I would like to speak to Mr./Mrs./Ms._____ in regards to his/her participation in the research study for the treatment of *Clostridioides difficile* infection. Mr./Mrs./Ms._____, May I ask you a couple of questions in follow-up to your participation in this study? All of the information that you share with me will remain strictly confidential.

Daily contact in person or by phone:

1. How has your overall health been since we last spoke?
2. Have you experienced any unformed bowel movement since we last spoke? Yes/No

If yes, have you had three or more unformed bowel movements in any 24 hour period during the follow-up? If yes, you will need to return for assessment, bloodwork and stool collection.

Thank you for your time and your participation in this important research project.