NCT03834038

Date of Document: June 12, 2019

Study title: Prospective, open-label trial to evaluate efficacy of lyophilized fecal microbiota transplantation for treatment of recurrent *C. difficile* infection

ABBREVIATIONS

CDI	*Clostridioides difficile* infection
DSMC	Data Safety Monitoring Committee
FMT	Fecal Microbiota Transplantation
IBD	Inflammatory Bowel Disease
LYO-FMT	Lyophilized Fecal Microbiota Transplant

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Introduction and study rationale

Clostridioides (Clostridium) 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 attributable case fatality rate associated with CDI is 6% and there are increasing reports of treatment failures with standard therapy. CDI is also problematic as it can lead to chronic diarrhea and has been the source of outbreaks in many hospitals.

The costs associated with the management of CDI at an individual patient and at the institutional level are significant: a case of hospital-acquired CDI increases the cost of otherwise-matched hospitalization by 4-fold, which translates into annual additional costs of $1 billion in the United States and $100 million in Canada.

One of the major risk factors for developing this infection is taking an oral or intravenous antibiotic. The healthy bacteria, which reside within the colon are the major defense against the growth of *C. difficile* within the large intestine. Antibiotics kill these bacteria and allow *C. difficile* to multiply, produce the toxins and cause disease. The available treatments in Canada for this infection are the antibiotics metronidazole, oral vancomycin and fidaxomicin. The efficacy of these antibiotics is limited as oral vancomycin and metronidazole also suppress the growth of anaerobic bacteria such as *Bacteriodes fragilis* group which protect against proliferation of *C. difficile*. The persistent disruption of healthy colonic flora may in part explain the high frequency of recurrences following a course of treatment with these antibiotics.

Recurrence of CDI following a course of standard antibiotic therapy is high, especially in patients over 65 years of age, in hospitalized and in immunocompromised patients. As CDI and ulcerative colitis (UC) are characterized by intestinal dysbiosis, Fecal Microbiota Transplantation (FMT) has been investigated as an alternative treatment for both of these conditions. The aim of FMT is to correct the compositional and diversity imbalances of the microbial communities of the colon. Stool is collected from healthy, screened donors, and combined with water or saline solution to create a suspension that can be administered in a variety of ways, including colonoscopy, nasogastric tubes, or retention enemas

One of the major challenges of offering FMT is the availability of suitable donors. A donor may no longer be able to continue to donate for a number of reasons and this has led to temporary interruption of FMT in centers which offered the program. In order to continue to offer FMT whenever needed, we will investigate the efficacy of lyophilized FMT. The lyophilization (freeze-drying) process works by dehydrating a frozen donor stool sample to complete dryness, using controlled temperature and pressure gradients. This lyophilized process results in a powdered form of the sample. Studies have shown that lyophilized donor stool samples depict similar microbial compositions as the same fresh sample. The technique of freeze drying has been used for decades for the industrial storage of microbes. Preliminary study of lyophilized stool for FMT has been performed in dogs. Preliminary efficacy data in dogs with inflammatory bowel disease suggest equal efficacy as compared to fresh stool, although a controlled study has yet to be performed.

Should lyophilized FMT (LYO-FMT) demonstrate to be equally or more effective than control (frozen) FMT, there would be significant advantages. As with frozen FMT, LYO-FMT will allow patients to receive FMT immediately as it can take up to two weeks for a donor's screening laboratory testing results to be available. LYO-FMT will also be more cost effective as fewer donors will need to be screened given the prolonged shelf life of LYO-FMT which can be kept at above freezing temperature. This will also allow

wider distribution and accessibility across Canada especially to regions with limited capacity to manufacture FMT.

This study is designed to be open-labeled to evaluate the efficacy of LYO-FMT (versus historical controls) as expeditiously as possible and to minimize the time and cost associated with conducting a two-armed randomized controlled trial given that the efficacy of frozen or fresh FMT is known to be 85%. The result of this trial will be useful to inform policy makers and to assist in formulating practice guidelines. The decision to pursue this open-labeled trial is based on the recent initiatives to optimize the utilization of limited resources available for conducting clinical trials. The US Food and Drug Administration and the United Kingdom's National institute for Health Research Health Technology Assessment Programme launched guidance on adaptive research designs to increase the speed and the efficiency of clinical trials. An open-label clinical trial to add an arm to existing study is an example of such study, which can lead to rapid results with less cost. This in turn will lead to providing the "best" therapies to as many patients as possible.

Study hypothesis

- Administration of 2 enemas of LYO-FMT will have similar efficacy as control (frozen-historical) FMT in reducing the rates of recurrence of CDI.

Study objective

- To study the outcome of participants treated with 2 enemas of LYO-FMT for recurrent CDI

Study outcomes

Primary endpoint

- Evaluate treatment efficacy as determined by no recurrence of CDI-related diarrhea at 13 weeks after receiving up to 2 LYO-FMTs without the need for an intervention (antibiotics or frozen or LYO-FMT as per investigator's decision) specifically for recurrence of CDI.

Secondary endpoints

1. Evaluate treatment failure rate as defined by persistence of diarrhea and a positive *C. difficile* toxin assay or *tcdB* PCR within 5 days of the last LYO-FMT, or the need for additional intervention for CDI, colectomy or death directly due to CDI at 13 weeks following the last LYO-FMT.

2. Evaluate safety of LYO-FMT
    - Assessment for adverse reactions by history, complete blood count and chemistry panel at day 7 (+/- 3d), day 30 (+/-3d) of the study period.
    - Any serious adverse events up to and including week 13 from the 2nd FMT for any of the following:
        - Death or a life-threatening event
        - Hospitalization or prolongation of current hospitalization
        - A significant new incapacity to conduct normal life functions

Study Design

The design of this research is a multi-centre, prospective open-label (single arm) trial using LYO- FMT (treatment) to prevent recurrence of CDI in patients with history of recurrent CDI or to control diarrhea in patients with refractory CDI.

The study participants, individuals over the age of 11 years able to consent and comply with treatment. Participants required to have laboratory or pathology-confirmed diagnosis of recurrent CDI based on the Society for Healthcare Epidemiology of America (SHEA) definition, where recurrence is defined as return of diarrhea and positive stool test after a period of symptom resolution within 8 weeks of the first episode and has received at least a 10-day course of oral vancomycin.

Thirty grams of fresh stool collected within 5 hours from a healthy screened donor to be placed in a 60mL sterile container. Stool be frozen at -80^{o}C and undergo lyophilization. Lyophilized products to be stored at 2 to 8^{o}C for up to 112 weeks inside a box to avoid light exposure. Reconstitute LYO-FMT using 30mL normal saline. The participants received 30mL of the reconstituted lyophilized product as a retention enema using a syringe with a catheter tip. Discontinue the antibiotic 24 - 48 hours prior to the scheduled FMT. Participants to receive LYO-FMT via retention enema(s) on day 1 and the second LYO-FMT between day 5 and day 8 following the first LYO-FMT.

Participant eligibility criteria

Participant inclusion criteria

- Age ≥ 12 years or older.
- Able to provide informed consent.
- Willing and able to comply with all the required study procedures.
- A positive stool test for *C. difficile* toxin/gene using either PCR or enzyme immunoassay within 3 months of recruitment unless patient taking treatment specifically for CDI for more than 3 months.
- History of at least ≥ 2 recurrent CDI 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 for each episode and/or ongoing symptoms consistent with CDI* (defined below) despite at least 7 days of treatment using oral vancomycin at a minimum dose of 250 mg four times daily.
  *Symptoms of CDI include: diarrhea defined as: 3 or more unformed bowel movements in 24 hours for a minimum of 2 days with no other causes for diarrhea

Participant exclusion criteria

- Planned or actively taking another investigational product
- CDI symptom-free for 3 or more weeks following completion of CDI treatment
- Patients with neutropenia with absolute neutrophil count $<0.5 \times 10^9/L$
- Evidence of toxic megacolon or gastrointestinal perforation on abdominal x-ray
- Active gastroenteritis due to *Salmonella*, *Shigella*, shiga-toxin producing *E. coli*, *Yersinia* or *Campylobacter*.
- Presence of colostomy
- Unable to tolerate FMT or enema for any reason.
- Requiring systemic antibiotic therapy for more than 7 days.
- Actively taking *Saccharomyces boulardii* or other probiotic; yogurt is allowed
- Severe underlying disease such that the patient is not expected to survive for at least 30 days.

The duration of treatment and study period

Participants received LYO-FMT via retention enema(s) on day 1 and repeat on day 5 through day 8 following the first LYO-FMT.

Assess the participants at day 1 and with medical history (including concurrent medications and recent antibiotic use), clinical assessment. Reassessment, blood work, and a repeat LYO-FMT on day 5 (+3: between day 5 and 8 from the first). At study visits, assess for clinical response, treatment failure and adverse reactions by clinical assessment and laboratory test. Follow the participants at day-10,week 5 and week-13 and yearly for 2 years subsequent to the completion of treatment for any evidence of relapse, adverse event and overall health. With ongoing or recurrence of diarrhea, the participant(s) undergo medical history, physical examination, complete blood count, chemistry panel and stool for *C. difficile* toxin by EIA or PCR for *tcdB* gene. For treatment failures or relapse during the study period, participants receive repeat lyophilized or frozen FMT(s), based on the investigator's decision and availability of type of FMT or standard antibiotic therapy.

CDI. LYO.FMT.1

Sample size and the justification for the assumptions

158 participants based on the sample size and efficacy result of the trial comparing frozen versus fresh FMT. The control (frozen) FMT efficacy was 85% and the lowest acceptable response rate for LYO-FMT is set at 70%. Based on a one-sided hypothesis test, the sample size is 152, accounting for 10% attrition with 5% significance and 85% power.

Type of statistical analyses

The clinical response rate is to be determined using standard binary outcome protocols.