# Investigator Studies Program (MISP) Protocol Template

## Requirements for Submitting a Full Proposal

### Section #1 - MISP Protocol Identification

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| **Study Title:** | ***A pragmatic trial of secondary prophylaxis with Bezlotoxumab to prevent C. difficile relapse among hospitalized adults receiving antibiotics***. |
| **Request Date:** | August 31,2018 |
| **Institution Name** | Montefiore Medical Center |
| **Investigator Contact Information:**<br>Full address<br>Phone No.<br>Fax No.<br>e-mail address | Paul Riska<br>111 E 210th Street<br>Division of Infectious Disease/AIDS Center<br>Bronx,NY 10467<br><br>718-920-6494<br>Fax 718-231-9187<br>priska@montefiore.org |

| Section #2- Core Protocol | |
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| **2.1 Objectives & Hypotheses** | 2.1 Objectives:<br><br>A. Can monoclonal antibody treatment active against *C. difficile* toxin B (Bezlotoxumab) prevent relapse of CDI (*C. difficle* infection) among patients recently infected with *C difficile*, with resolved CDI after completing standard *C. difficile* therapy, but receiving subsequent antibiotics for other infections?<br>B. Does stool carriage of *C difficile* after end of CDI treatment predict relapse? If so, are failures of CDI prophylaxis due to reinfection or relapse with the same strain?<br><br>2.1.1 List the clinical hypotheses.<br><br>A. Antibody active against *C. difficile* toxinB (Bezlotoxumab) can prevent relapse of *C. difficile* disease (CDI), when patients recently affected by CDI are prescribed antibiotics for other indications.<br>B. Failures of CDI prophylaxis, if found, are due to persistent carriage of *C. difficile*, rather than acquisition of a new strain. |
| **2.2 Background & Rationale, Significance of Selected Topic & Preliminary Data** | *Clostridioides difficile* infection (CDI) is the leading hospital-acquired infection in the US, affecting nearly 500,000 persons annually, and killing 29,000. Of concern, 83,000 patients or ~20% have relapsing disease with an estimated healthcare cost of $13,500 – 18,000 per relapse (Lessa, 2015). Some of these relapses can continue to recur whenever treatment is stopped. The main risk factor for CDI relapse after resolution of symptoms is further antibiotic exposure (Despande, 2015) as this is believed to disrupt the intestinal microbiome favoring regrowth of *C difficile*.<br><br>Attempts to attenuate the risk of CDI relapse include prolonged use of CDI-active therapy, fecal microbiota transplant (FMT) and monoclonal antibodies targeting *C. difficile* toxins. Retrospective studies by Van wise (2016) and Wong (2015) , including nearly 500 patients showed CDI relapse rates in a population of recent CDI patients receiving further antibiotics could be reduced from 20-27% to 4-8% with oral vancomycin and/or metronidazole. Another study showed no benefit of oral vancomycin prophylaxis after a first episode of CDI (Carignan, 2016). Fidaxomicin may be even better in this regard due to its more selective effect on the microbiome leading to fewer relapses after initial treatment (15% relapse with fidaxomicin vs. 25 % for vancomycin)(Louie,2011; Fidaxomicin Package Insert ). In initial CDI therapy where concurrent antibiotics were also used in this trial, Fidaxomicin still demonstrated less relapse than oral vanco,17% vs. 26% [Mullane,2011] Finally, prophylactic fidaxomicin use prevented *C difficile* in high risk oncology patients, all of whom also received other antibiotics(rate of confirmed CDI was 4% vs. 10% with placebo) (Mullane, 2018). Nonetheless, the recent Infectious Disease Society of America statement on CDI (published 3/2018) indicates the following: “There are insufficient data at this time to recommend extending the length of anti–*C. difficile* treatment beyond the recommended treatment course or restarting an anti–*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment, respectively *(no recommendation)”*. FMT has shown promising efficacy in frequent CDI relapsers (Moayyedi, 2017) but is cumbersome, there is no FDA-approved regimen, and there are potential long-term adverse side effects as the intestinal microbiota has been associated with colon cancr, diabetes, obesity, and atopic disorders such as asthma. |

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| | Bezlotoxumab is an FDA-approved monoclonal antibody targeting the pathogenic major toxin B of *C. difficile*, which has been shown in the MODIFY trials to reduce the risk of recurrent CDI from 27 to 16% when used concurrently with primary CDI therapy (Merck, Zinplava Package Insert, Wilcox,2017). In these pivotal studies, 35-42% of subjects (in different treatment groups) had concurrent antibiotics with CDI therapy, and ~35% continued antibiotics beyond their CDI therapy (Wilcox, appendix, 2017). The efficacy of bezlotoxumab in this high-risk group for relapse has not been specifically reported; nonetheless, bezlotoxumab was effective in other high-risk groups including older age (>=65), the immunocompromised, and those with more than 1 prior CDI or severe CDI.<br><br>While Bezlotoxumab was approved for use during an episode of CDI concurrent with standard-of-care CDI-active antibiotics, there is no reason to expect it would not work in the high-risk setting proposed here – inpatient subjects with recently treated CDI (within the past 90days) receiving subsequent courses of antibiotics for non-CDI indications. This cohort of patients at our institution has a 20.8% rate of CDI (Wong, 2015) which is increased to 26.7% if age of >=60 is used as a cutoff (unpublished data). Birch et al (2018) showed that within the MODIFY trials, the timing of Bezlotoxumab use relative to the start of CDI-active antibiotics ( a 10-14day window) had no bearing on its efficacy; its half-life of 19 days means that it provides protection over the course of the 12-week observation period after the start of CDI therapy. This proposal suggests expanding the utilization of bezlotoxumab to a 14-90 day (~2-12 weeks) window after initial CDI therapy, if and when other antibiotics with a propensity for inducing CDI relapse are utilized. A single dose of bezlotoxumab in this setting would not affect the risk for CDI acquisition or relapse, but should attenuate the clinical consequences of this occurring by neutralizing the pathogenic toxin B, to a similar extent as in the MODIFY trials. In fact, it may work more efficiently as the highest levels of antibody will be available during the highest risk period for relapse –concurrently or shortly after use of CDI-inducing antibiotics. |
| **2.3 Study Design** | This proposal uses a prospective cohort of CDI patients, 60 years of age and older, admitted to 2 sites of 1 Medical Center, and receiving “other” antibiotics, within 14-90 days of their CDI diagnosis.<br><br>These patients will be identified by a bioinformatics approach, using Clinical Looking Glass software developed at our medical center. All inpatients 60 years old or above, with a CDI laboratory diagnosis within 14-90 days of the present date will be assessed for use of antibiotics at high-risk for inducing CDI, as well as any concurrent *C difficile* active antibiotics (“prophylaxis”). In addition, all new admissions to our hospital with a CDI diagnosis within 12 months are flagged for infection control purposes, and these patients will also be assessed for qualification into the study. Inclusion criteria are :<br>1. CDI within 90 days<br>2. Use of high-risk antibiotics for inducing CDI within 72 hrs. of enrolment<br>3. No use of CDI active antibiotics within 24 hrs.<br>4. Able to sign consent for the study, or have an identified surrogate.<br><br>As this is a pragmatic study, reflecting mostly standard medical care, there are few exclusion criteria :<br>1. Prior CDI episode was felt to be colonization after chart review;<br>2. Subject not expected to survive 8 weeks (based on PI impression or chart review, considering factors including end-stage cancer, CHF, sepsis with high pressor requirement);<br>3. Documentation of current diarrhea (3 or more unformed stools per day) at time of enrollment, possibly due to CDI.<br>4. Receipt of prior fecal microbiota transplant or prior bezlotoxumab.<br>5. Congestive heart failure, as this diagnosis demonstrated increased mortality in the |

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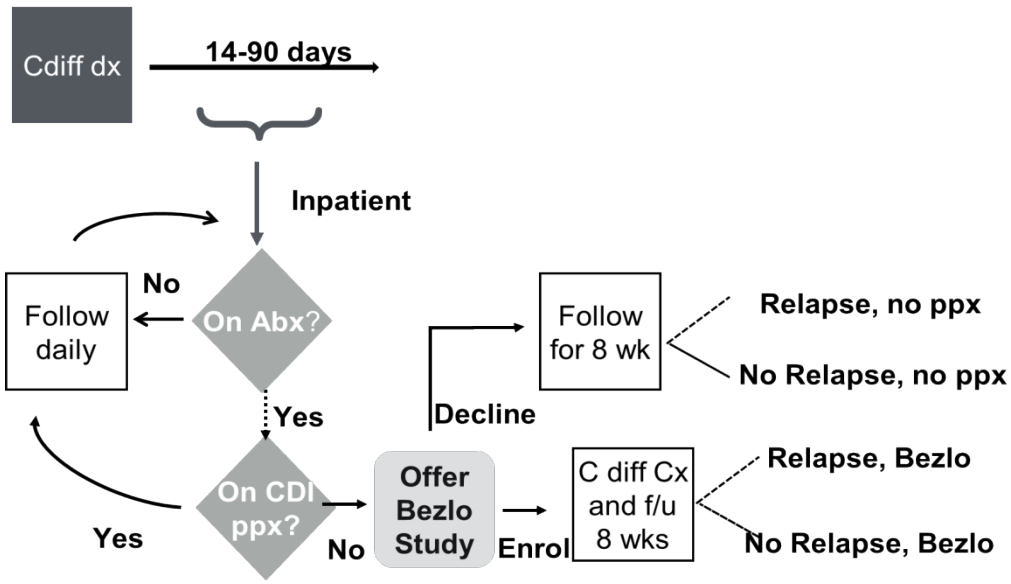
| | MODIFY studies with bezlotoxumab vs. placebo (Zinplava Package insert).<br><br>Those patients meeting the study inclusion/exclusion criteria will be offered open-label Bezlotoxumab infusion. This active intervention arm will have baseline stool samples collected for *C difficile* culture and typing at study entry and upon CDI relapse, if any<br><br>The comparator groups will be<br>1. The historical control group from the Wong study, and<br>2. A concurrent observational arm – consisting of those patients otherwise eligible for the study, but :<br>A. Not consenting to study enrolment, and<br>B. Taking no form of CDI prophylaxis (no oral vancomycin, metronidazole or fidaxomicin use as defined below).<br><br>All cohort members will be subject to standardized chart review for baseline parameters at study entry, and structured followup by chart review every 2 weeks for 8 weeks for CDI relapse (the primary endpoint), tolerability of study drug (if administered) , length of hospitalization/ICU stay or death.<br><br>Use of CDI prophylaxis will be adjudicated to see if it conforms to the standards established in the Wong study – prophylaxis used for at least 50% of the duration of the concomitant antibiotics course and at least up to 72 hrs before the end of the concomitant antibiotics. Patients receiving any such prophylaxis will be excluded from the per-protocol analysis, which will be the primary analysis. Secondary analysis will also be performed on an intent-to-treat basis, where group assignment is determined based on use of prophylaxis at study entry only.<br><br>This design was chosen to parallel that of the retrospective Wong study at our same site – to allow comparisons with the historical treatment groups in that study. |
| **2.4 Study Flowchart** | .<br>  |
| **2.5 Study** | STUDY DESIGN |

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| **Procedures** | This prospective cohort study will be conducted using inpatients at the 1044 adult medical/surgical-beds on 2 campuses of the Montefiore Medical Center in the Bronx, New York. No work on this study will proceed until it is approved by our local Institutional Review Board.<br><br>SUBJECT IDENTIFICATION –INCLUSION CRITERIA<br>All patients with a laboratory diagnosis of CDI initially diagnosed within 3 months of screening, who are getting an order placed for inpatient antibiotics will be identified by bioinformatics–and will be eligible for study entry. They will be screened for concurrent use of metronidazole, oral vancomycin or fidaxomicin –if present; they will be rescreened for inclusion if further antibiotics are given without concurrent prophylaxis. If no prophylaxis is identified, then their providers will be approached to consider enrolling the patient into the current active arm for open-label Bezlotoxumab.<br><br>Inclusion criteria are :<br>1. CDI within 90 days<br>2. Use of high-risk antibiotics for inducing CDI within 72 hrs of enrolment<br>3. No use of CDI active antibiotics within 24 hrs<br>4. Able to sign consent for the study, or have an identified surrogate.<br><br>EXCLUSION CRITERIA<br>As this is a pragmatic study, reflecting mostly standard medical care, there are few exclusion criteria :<br>1. Prior CDI episode was felt to be colonization after chart review(any physician-identified diarrhea is allowed, but not testing of asymptomatic patients such as test-of-cure testing or admission screening);<br>2. Subject not expected to survive 8 weeks;<br>3. Documentation of current diarrhea (3 or more unformed stools per day) at time of enrollment, possibly due to CDI.<br>4. Receipt of prior fecal microbiota transplant since the last CDI episode, or planned at time of screening or prior bezlotoxumab.<br>5. Congestive heart failure, as this diagnosis demonstrated increased mortality in the MODIFY studies with bezlotoxumab vs. placebo (Zinplava Package insert).<br><br>CLINICAL DATA COLLECTION<br>Data on included patients will be collected by medical record review both manually and by using Clinical Looking Glass (CLG) software. Clinical data collected consists of patient demographics, comorbidities by ICD10 codes, length of hospital stay, nursing home residence, all antimicrobial agents received, use of proton pump inhibitors or histamine-2 blockers, all prior *C. difficile* assays, and severity of CDI markers on the date of CDI diagnosis – maximum temperature, maximum WBC, maximum creatinine, serum albumin –in order to calculate a Zar severity score (Zar, 2007). Manual chart reviews will be performed of all antibiotic courses for 8 weeks from enrollment and to assess for signs of CDI relapse, including symptoms such as abdominal pain or diarrhea as well as physical findings, vital signs, white blood cell, microbiologic data including both positive and negative *C. difficile* assays, and radiographic data. Particular weight will be given to assessment by infectious disease specialists, if consultation is performed.<br><br>DEFINITIONS<br>A valid high risk antibiotic course is defined as:<br>1. Consisting of a beta lactam, carbapenem, quinolone, clindamycin, macrolide, or polymyxin, AND<br><br>2. Starting as early as 14days after the index CDI date, avoiding courses that |

overlap with extended initial CDI treatment regimens, AND.

3. Encompassing all antibiotics separated by up to 72 hrs linked into the same course, AND

4. Ending with the first episode of CDI relapse, as all concurrent (started within 48HR of recurring *C. difficile* symptoms) and subsequent antibiotic courses are excluded from further analysis

A course with CDI prophylaxis is defined as:

1. Having concurrent use of either metronidazole (intravenous or oral) or oral vancomycin or fidaxomicin therapy for at least 50-percent of the duration of the high risk antibiotic course, AND

2. Having prophylaxis to within 72 hours of the last dose of the high-risk antibiotic agent; thus an extended high risk antibiotic course may have a segment covered by prophylaxis, but if the last 3 days are no longer receiving the potential benefit of prophylaxis, the course is considered to be unprophylaxed.

A CDI relapse is defined as:

1. Attributable to a high risk antibiotic exposure if clinical symptoms and/or positive stool assay developed greater than 48-hours after antibiotic exposure, AND

2. Occurring within 8 weeks of completion of the high risk antibiotic course, AND

3. Compatible with clinical evidence suggestive of CDI disease during chart review; including a leukocytosis without alternative etiology and responding to CDI treatment, new onset of diarrhea, presence of radiographic or if relevant autopsy evidence of colitis, and/or repeat positive stool assay with appropriate clinical symptoms. If these indicators of CDI were present at the time of antibiotic onset, or within 48hrs, this was deemed a recurrence of infection NOT attributable to the high risk antibiotic course and was omitted from the relapse population.

The beneficial effects of Bezlotoxumab will be considered to last for the entire 8 week observation period, regardless of the number or timing of antibiotic courses within that period. Analysis of the effects of cumulative exposure to high-risk antibiotics or exposure late in this period will be assessed separately. The effect of subsequent CDI-active antibiotics, while excluded within 24 hrs of Bezlotoxumab dosing but potentially used within the Bezlotoxumab therapeutic window, will also be considered in secondary analyses (intent-to-treat).

LABORATORY INVESTIGATION

Using a *C. difficile* toxigenic culture well-established in the laboratory of the PI (referenced in Boyanton, 2012), stool will be collected by rectal swab from consented subjects in the Bezlotoxumab arm. If subsequent stool samples are sent to our clinical microbiology laboratory for any reason, they are routinely held for 5 days and would be available for *C difficile* toxigenic culture. Isolated organisms can be comparatively typed by the multi-locus variable number tandem repeat methodology (Marsh, 2007 ) with great variability in the 3 amplified PCR product sizes. Common letters (below) reflect isolates from neighbor pairs (same ward, same week) albeit each column is a unique patient.

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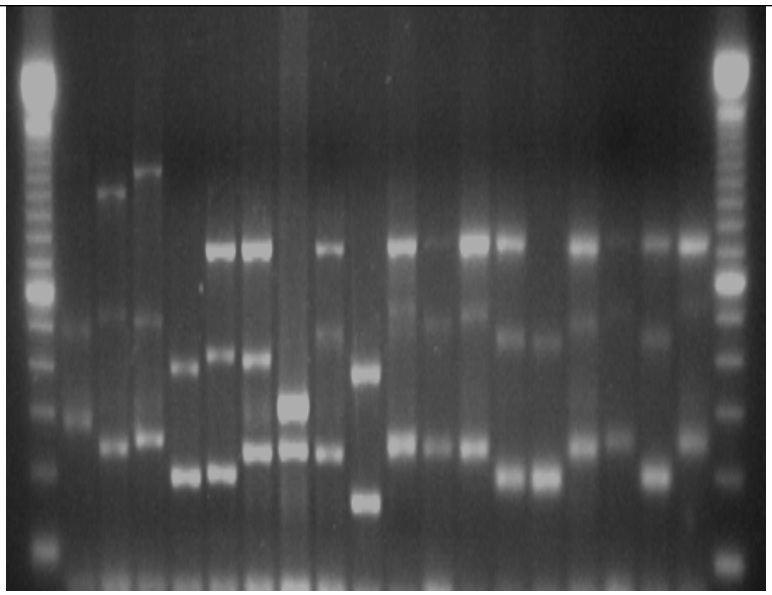
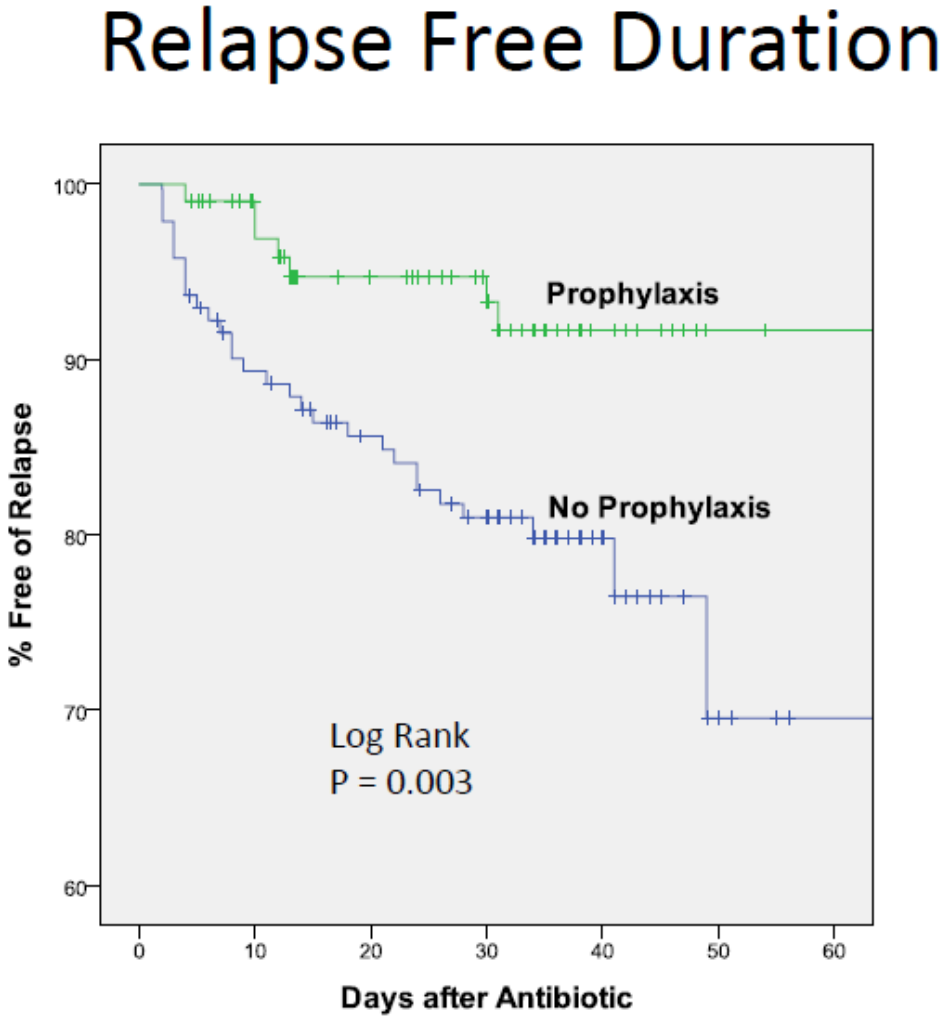
| |  <br>L A A B B C C D D E E E F F G G H H H L |
| **2.6 Study Duration** | Estimate of 1 year required to recruit 50 patients (from an estimated 150 eligible) and another 6 months to complete the study analysis. A computer simulation indicates there should be 150 eligible subjects in 1 year. Of these, ~50 will be on prophylaxis and ~50 will decline participation and will be followed as no prophylaxis controls. |
| **2.7 Statistical Analysis and Sample Size Justification** | The PI and local statistician will be responsible for analyzing the study data.<br><br><u>Variables/Time Points of Interest</u><br><br>The primary outcome variable is relapse of CDI within 8 weeks of study entry. Secondary outcomes are relapse of CDI within 4 weeks of study entry (the interval with highest protective antibody levels), all-cause mortality, time to relapse and duration of hospitalization.<br><br>Baseline variables collected for each subject include :<br>age, gender, number/dates/treatment of prior CDI episodes, current PPI use and H2-blocker use, Charlson score, immunosuppression, Inflammatory Bowel Disease of Irritable Bowel Syndrome, use of cathartics/lactulose, and indication for current antibiotics.<br><br>Variables related to the past CDI episode include markers of disease severity : WBC, fever >100.5$^{o}$F, creatinine, albumin – to generate a Zar score (Zar,2007)<br><br><u>Statistical Methods</u><br>The analysis population is the per-protocol population, with 2 major comparator groups – those receiving Bezlotoxumab and those with no prophylaxis. The latter will be comprised of 3 subgroups – the control group from the Wong study and 2 concurrent observation groups- a PASSIVE followup group of subjects undergoing chart review , and an ACTIVE followup group of subjects declining study drug but agreeing to phone followup at 8 weeks. All groups will be compared across baseline parameters cited above. Risk factors pre-specified for recurrent CDI include age, immunocompromise, and severe CDI will be compared across groups, and tested for associations for the major outcomes of CDI relapse and mortality at 4 weeks and 8 weeks.<br><br>In the Wong study, there was a remarkably equal distribution of variables among the |

antibiotic prophylaxis and no prophylaxis groups. We similarly expect no imbalance between our current study and observation groups in terms of risk factor distribution, though self-selection bias will be considered at the interim analysis after 30 intervention patients are enrolled.

Categorical variables will be compared using chi-square and Fisher's Exact analysis and continuous variables will be compared using Mann-Whitney analysis, with $p < 0.05$ considered to be significant.

In survival analysis (Kaplan-Meier), time to CDI relapse is defined from the date of bezlotoxumab study dosing or study refusal - to the date of relapse and limited by a maximum observable window of 8 weeks from the dose of bezlotoxumab. Subjects are censored on the date of death, if death occurred within the observable window, or at the beginning of a new potential antibiotic prophylaxis course (i.e.. If within the 8 week observation period there is receipt of metronidazole, oral vancomycin or fidaxomicin.) or receipt of fecal microbiota transplant. A Cox proportional hazards model will be used for group comparison when adjusting for covariates.

The survival analysis from the Wong study, demonstrating the benefits of antibiotic prophylaxis on preventing relapsed CDI, is summarized in the following figure:



For the second objective, rates of CDI relapse will be compared among study subjects with or without *C. difficile* colonization at study entry. This is an exploratory study to inform future studies. It is expected that 20% of subjects will be colonized at study entry (based on Sunkesula,2013) –the expected number of these that relapse is unknown, as data is conflicting on whether colonization is protective or predictive of relapse.

Power/Sample Size:

Estimates of group size and expected antibiotic prophylaxis outcomes are derived from the Wong and Van Hise studies which have similar or nearly identical design to the current proposal, albeit retrospective. In the Wong study, of 248 enrolled subjects, 104 received prophylaxis with metronidazole (n=63 total, 19 combined with vancomycin) or vancomycin (n=60) , and 144 did not. In this latter group, 86 were >= 60 yrs old of whom 23 relapsed, for a relapse rate of 26.7%. For the bezlotoxumab arm, the expected benefit is between a 43-54% reduction in relapse incidence (Gerding, 2018), with the variability based on the number of risk factors for CDI relapse in our population – all have at least 1 risk factor : most with age >65 and all with concurrent high-risk antibiotics. The expected CDI relapse rate in the active arm is therefore 12.2-15.2%. Thus

1. We need 62 bezlotoxumab subjects (at 12.2% relapse)) to be 80% powered to detect a difference in outcomes vs. the no prophylaxis control population (with a relapse rate of 26.7%), with a two-tailed alpha=0.05.
2. We need 103 bezlotoxumab subjects (at 15.2% relapse)) to be 80% powered to detect a difference in outcomes vs. the no prophylaxis control population (with a relapse rate of 26.7%), with a two-tailed alpha=0.05.

In 1 year, we expect 50 bezlotoxumab subjects and 50 no-prophylaxis controls in the prospective cohort. The numbers of subjects in the no-prophylaxis observational arms can be supplemented by retrospective chart reviews incorporating the same analysis used in the prospective study, or by merging with the control arm of the Wong study.

Given the prospective design, with more data available regarding relapse than in the Wong study (wherein outpatient records were not yet electronic) and the fact that relapse rates in the control group in the MODIFY studies were 39% in those over 65, its possible that more relapses will occur in the no-prophylaxis group than the 26.7% expected. This would lower the numbers needed to show a significant benefit. An interim analysis is planned after 6 months or 30 subjects enrolled, to re-assess realistic timelines for achieving significant results from this project. Notably, this is a pilot study which if it meets targets, could potentially be extended by 3 to 6 months to achieve statistically significant power. Alternatively, if study effects exceed expectations, a placebo-controlled design could be considered moving forward- for the pilot study, this is precluded by the larger sample size anticipated for such a project.

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| **2.8 Specific Drug Supply Requirements** | The Bezlotoxumab drug supplies will be open label and provided by MSD.<br><br>The institution's research pharmacy will require bulk supplies from MSD (one large container of 10 courses at 1 time). As bulk supplies are provided by MSD, our institution's pharmacy will be responsible for preparing individual patient doses. A description as to how the clinical supplies are to be packaged and labeled for each patient will be added to the protocol.<br><br>Note: At conclusion of the study or upon drug expiration, the MSD GRS will be responsible for issuing a Drug Disposition Letter to the investigator for US based studies.<br><br>The investigator will be responsible for the destruction of the supplies at the study center pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies will be received by a designated person (research pharmacist) at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Clinical supplies are dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study. |
| **2.9 Adverse Experience Reporting** | The study agreement will outline the requirement for adverse experience reporting. The Model Study Agreement will be used. Tolerability of study drug will be assessed with longitudinal assessments/chart reviews. Any adverse events during infusion will be recorded and any deaths or serious events leading to prolonged hospitalization or readmission (potentially ascribed to the study drug) in the subsequent 30 days will be reported to our local IRB and the FDA MedWatch.<br><br>All active study subjects will be queried at 1 day, 4 weeks and 8 weeks after enrollment for any change in their health status reflecting potential safety concerns related to receipt of study drug. Though not a primary focus of this research, any Serious Adverse Events will be tabulated and reported to the IRB, and Suspected Unexpected SAE's (SUSAR) will be reported to the FDA.<br>A Safety Officer will be designated (an ID physician who is not part of the study team) to review all SAE's after 12 and 25 (of 50 planned) subjects have been enrolled, and together with a statistician, determine if there are serious safety concerns related to the study drug requiring modification or termination of the study protocol. |
| **2.10 Itemized Study Budget** | A preliminary study budget is provided with the initial proposal submitted to give guidance to the MISP Review Committee as to the expected study costs. A refined itemized budget detailing the costs associated with the study will be provided with the final protocol or included in the study agreement as Exhibit B. |
| **2.11 References** | **Birch T**, Golan Y, Rizzardini G, Jensen E, Gabryelski L, Guris D, Dorr MB; (2018) Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for Clostridium difficile infection. J Antimicrob Chemother. 2018 Sep 1;73(9):2524-2528.<br><br>**Boyanton, Jr**,. B L, P Sural, CR. Loomis, C Pesta, L Gonzalez-Krellwitz, B Robinson-Dunn and **PF Riska**. (2012) ,Loop-Mediated Isothermal Amplification Compared to Real-time PCR and Enzyme Immunoassay for Toxigenic C. difficile Detection. Journal of Clinical Microbiology, 50(3):640-45 |

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| | Guris D, Kartsonis N, Dorr MB; MODIFY I and MODIFY II Investigators. (2017) N Engl J Med. (2017 Jan 26); 376(4):305-317 Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection.<br><br>**Wong**,D & PF Riska *(* 2015) *"*Secondary Prophylaxis in High Risk Patients Reduces the Risk of Clostridium difficile Recurrence" , , oral presentation at Interscience Conference on Antimicrobial Agents And Chemotherapy, Sept 20,2015 San Diego, CA<br><br>**Zar** FA, Bakkanagari SR, Moorthi KM, Davis MB. (2007) A comparison of vancomycin and metronidazole for the treatment of Clostridium **difficile**-associated diarrhea, stratified by disease severity.Clin Infect Dis. 2007 Aug 1;45(3):302-7. |
| **2.12 Publication Plan** | One major manuscript is expected from this work within 2 years of study startup – probably to a journal like Clinical Infectious Disease.. The clinical microbiology data maybe part of a separate manuscript.<br><br>Preliminary data may be presented in abstract form at ID Week 2019.<br><br>• |
| **2.13 Curriculum Vitae** | Attached. |
| **2.13 Protocol Submission for Investigator-Initiated Studies** | U.S. protocols should be submitted by US investigators directly or through the Global Research Specialist at www.merckiisp.com<br><br>Non U.S. protocols should be submitted to the MSD office by the investigators. |