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002-00

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to C. difficile toxin B), and MK-3415A (Human Monoclonal Antibodies to C. difficile toxin A and B) in Patients Receiving Antibiotic Therapy for C. difficile Infection (MODIFY II)

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

2

Product: MK-3415A**Protocol/Amendment No.:** 002-00

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TITLE:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to *C. difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *C. difficile* toxin A and B) in Patients Receiving Antibiotic Therapy for *C. difficile* Infection (MODIFY II)

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PROTOCOL

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to C. difficile toxin B), and MK-3415A (Human Monoclonal Antibodies to C. difficile toxin A and B) in Patients Receiving Antibiotic Therapy for C. difficile Infection (MODIFY II)

TABLE OF CONTENTS

Contents	Application Starting Page
1. SUMMARY	11
1.1 Title	11
1.2 Indication	11
1.3 Summary of Rationale	11
1.4 Summary of Study Design	12
1.5 Sample	14
1.6 Dosage/Dosage Form, Route, and Dose Regimen	14
1.7 Study Flow Chart - MAIN Study (Day 1 to Week 12)	15
1.8 Study Flow Chart - Extended Follow-Up Period for Subset of Patients (Months 4 to 12)	20
2. CORE PROTOCOL	21
2.1 Objectives and Hypotheses	21
2.1.1 Primary	21
2.1.2 Secondary	21
2.1.3 Exploratory Objectives	23
2.2 Patient Inclusion Criteria	23
2.3 Patient Exclusion Criteria	25
2.4 Study Design and Duration	26
2.4.1 Summary of Study Design	26
2.4.2 Biomarker Assessments	28
2.4.3 Treatment Plan	28

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
2.5 List of Efficacy/Pharmacokinetic/Immunogenicity Measurements	30
2.5.1 Efficacy	30
2.5.1.1 Primary Objective (CDI Recurrence)	30
2.5.1.2 Other Efficacy Measures (Secondary/ Exploratory Objectives)	30
2.5.2 Endogenous Antibody Levels and Pharmacokinetics	30
2.5.3 Immunogenicity	31
2.6 List of Safety Measurements	31
2.7 Statistical Analysis Plan Summary	32
2.7.1 Efficacy Analyses	32
2.7.2 Safety Analyses	33
2.7.3 Power and Sample Size	34
3. PROTOCOL DETAILS	36
3.1 Rationale	36
3.1.1 Rationale for This Study	36
3.1.2 Rationale for Dose Regimen	38
3.1.3 Rationale for Patient Population and Primary Endpoint	39
3.1.4 Rationale for 3-Arm Study Design	39
3.1.5 Rationale for Biomarker Evaluations in This Study	40
3.1.6 Rationale for Future Biomedical Research	40
3.2 Study Procedures	41
3.2.1 Concomitant Medication(s)/Treatment(s)	41
3.2.1.1 Standard of Care (SOC) Therapy for CDI	41
3.2.1.1.1 Metronidazole	42
3.2.1.1.2 Vancomycin	42
3.2.1.1.3 Fidaxomicin	42
3.2.1.2 Other Prior/Concomitant Medication(s)/Treatment(s)	42

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.2 Diet/ Activity/ Other	43
3.2.2.1 Diet	43
3.2.2.2 Pregnancy and Contraception	43
3.2.3 Procedures	43
3.2.3.1 Informed Consent	44
3.2.3.1.1 General Informed Consent	44
3.2.3.1.2 Informed Consent for Additional 9-Month Extended Follow-up	44
3.2.3.1.3 Consent and Collection of Specimens for Future Biomedical Research	45
3.2.3.2 Assignment of Baseline/Screening Number	45
3.2.3.3 Procedures Performed During the Pre-Infusion Phase	45
3.2.3.3.1 General Medical History	46
3.2.3.3.1.1 CDI History	46
3.2.3.3.1.2 Horn's Index	46
3.2.3.3.1.3 Charlson Index	46
3.2.3.3.2 Physical Examination	47
3.2.3.3.3 Vital Signs	47
3.2.3.3.4 Stool Sample Collection	47
3.2.3.3.5 Blood and Urine Sample Collection	47
3.2.3.4 Stratification	48
3.2.3.5 Randomization/Allocation	49
3.2.3.6 Nonrandomized Patients	49
3.2.3.7 Procedures Performed in Conjunction with Treatment Infusion (Day 1)	49
3.2.3.7.1 Vital Signs Pre-Infusion	49
3.2.3.7.2 12-Lead Electrocardiogram Pre-Infusion	50
3.2.3.7.3 Dosage and Administration of Infusion	50

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.3.7.4 Unblinded Preparation of Infusion (Unblinded Pharmacist)	51
3.2.3.7.5 Vital Signs During and Immediately Post-Infusion	51
3.2.3.7.6 Infusion Reactions During and Post-Infusion	52
3.2.3.7.7 Blood Sample Post-Infusion	53
3.2.3.7.8 12-Lead Electrocardiogram Post-Infusion	54
3.2.3.8 Procedures Performed Post-Infusion (Day 1 through Week 12)	54
3.2.3.8.1 Clinical Follow-up	54
3.2.3.8.1.1 Loose Stool Counts and Body Temperature	54
3.2.3.8.1.2 Phone/Visit Contact to Assess and Record Loose Stool Counts and Body Temperature	55
3.2.3.8.1.3 Vital Signs	55
3.2.3.8.1.4 Physical Examination	55
3.2.3.8.2 Laboratory Follow-up	55
3.2.3.8.2.1 Blood and Urine Samples	56
3.2.3.8.3 New Episode of Diarrhea/ Unscheduled Visit	56
3.2.3.8.4 Procedures During the Additional 9-Month Extended Follow-up (Through Month 12)	57
3.2.3.8.4.1 Randomization/ Allocation into Additional 9-Month Extended Follow-up	58
3.2.3.8.4.2 Assessment of CDI recurrence in the Additional 9-Month Extended Follow-up	58
3.2.3.8.4.3 Stool Sample Collection During the Additional 9-Month Extended Follow-up	58
3.2.3.8.4.4 Blood Sample Collection During the Additional 9-Month Extended Follow-up	58
3.2.3.9 Blinding/Unblinding	59
3.2.3.10 Discontinuation/Withdrawal from Study	60
3.2.3.11 Withdrawal From Future Biomedical Research	60

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.3 Efficacy/Pharmacokinetic/Immunogenicity Measurements	61
3.3.1 Clinical Measurements for Efficacy (Assessment of Primary, Secondary, and Exploratory Efficacy Endpoints)	61
3.3.2 Immunologic and Bacteriologic Measurements	63
3.3.2.1 Toxigenic <i>C. difficile</i> Testing in Stool Specimens (Local Assays Specified in Appendix 6.1)	63
3.3.2.2 Anaerobic Stool Culture	63
3.3.2.2.1 Toxigenic Strain Typing	63
3.3.2.2.2 Antibacterial Susceptibility Testing	64
3.3.2.3 Detection of MK-3415 and MK-6072 in Stool Samples	64
3.3.2.4 Detection of MK-3415 and MK-6072 in Blood Samples	64
3.3.2.5 Detection of Endogenous Antibodies to Toxin A and Toxin B in Blood Samples	64
3.3.2.6 Detection of Anti-Drug Antibody (ADA) to MK-3415 or MK-6072	65
3.3.2.7 Neutralizing Antibody in Samples Positive for ADA	65
3.4 Safety Measurements	65
3.4.1 Clinical and Laboratory Measurements for Safety	65
3.4.1.1 Laboratory Safety Tests	66
3.4.2 Recording Adverse Experiences	66
3.4.3 Definition of an Overdose for This Protocol	67
3.4.3.1 Reporting of Overdose to SPONSOR	67
3.4.4 Reporting of Pregnancy to SPONSOR	67
3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR	68
3.4.5.1 Serious Adverse Experiences	68
3.4.5.2 Selected Nonserious Adverse Experiences	68
3.4.6 Evaluating Adverse Experiences	68

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences	71
3.5 Statistical Analysis Plan (SAP)	71
3.5.1 Responsibility for Analyses/ In-House Blinding	71
3.5.2 Hypotheses	71
3.5.3 Analysis Endpoints	72
3.5.3.1 Efficacy Endpoints	72
3.5.3.2 Safety Endpoints	74
3.5.4 Analysis Populations	75
3.5.4.1 Efficacy Analysis Populations	75
3.5.4.2 Safety Analysis Populations	75
3.5.5 Statistical Methods	75
3.5.5.1 Statistical Methods for Efficacy Analyses	76
3.5.5.2 Statistical Methods for Safety Analyses	78
3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses	80
3.5.5.4 Other Analyses	80
3.5.5.4.1 Analysis of High Risk Demographic and Clinical Identifiers	80
3.5.5.4.2 Biomarker Analysis	80
3.5.5.4.3 Pharmacokinetic/ Population Pharmacokinetic Analysis	80
3.5.6 Multiplicity	81
3.5.7 Sample Size and Power Calculations	82
3.5.8 Combined Data (Subgroup Analyses and Effect of Baseline Factors)	83
3.5.9 Interim Analyses	84
3.5.10 Additional 9-Month Extended Follow-up	84
3.6 Labeling, Packaging, Storage, Dispensing, and Return of Clinical Supplies	84
3.6.1 Patient and Replacements Information	84

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.6.2 Product Descriptions	85
3.6.3 Primary Packaging and Labeling Information	85
3.6.4 Secondary Packaging and Labeling Information (kit)	86
3.6.5 Clinical Supplies Disclosure	86
3.6.6 Storage and Handling Requirements	86
3.6.7 Standard Policies / Return of Clinical Supplies	87
3.6.8 Distributing to Sites and Dispensing to Patients	87
3.7 Data Management	87
3.8 Biological Specimens	87
4. ADMINISTRATIVE AND REGULATORY DETAILS	88
4.1 Confidentiality	88
4.1.1 Confidentiality of Data	88
4.1.2 Confidentiality of Subject/Patient Records	88
4.1.3 Confidentiality of Investigator Information	88
4.2 Compliance with Law, Audit, and Debarment	89
4.3 Compliance with Financial Disclosure Requirements	90
4.4 Quality Control and Quality Assurance	91
4.5 Compliance with Information Program on Clinical Trials for Serious or Life Threatening Conditions	91
4.6 Publications	91
5. LIST OF REFERENCES	93
6. APPENDICES	102
6.1 Acceptable C. Difficile Diagnostic Methods	102
6.2 Bristol Stool Chart	103
6.3 Modified Horn's Index	104
6.4 Charlson Index	105
6.5 Laboratory Safety Tests	107

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
6.6 Biomarker Evaluation in This Study	109
6.7 Collection and Management of Specimens for Future Biomedical Research	116
6.7.1 Scope of Future Biomedical Research	116
6.7.2 Definitions	116
6.7.3 Summary of Procedures for Future Biomedical Research	116
6.7.4 Confidential Subject Information for Future Biomedical Research	118
6.7.5 Biorepository Specimen Usage	119
6.7.6 Withdrawal From Future Biomedical Research	119
6.7.7 Retention of Specimens	119
6.7.8 Data Security	120
6.7.9 Reporting of Future Biomedical Research Data to Subjects	120
6.7.10 Gender, Ethnicity, and Minorities	121
6.7.11 Risks Versus Benefits of Future Biomedical Research	121
6.7.12 Self-Reported Ethnicity	121
6.7.13 Questions	121
7. ATTACHMENTS	122
8. SIGNATURES	133
8.1 SPONSOR'S REPRESENTATIVE	133
8.2 INVESTIGATOR	133

Product: MK-3415A

1

Protocol/Amendment No.: 002-00

1. SUMMARY

1.1 TITLE

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-6072 (Human Monoclonal Antibody to *C. difficile* toxin B), and MK-3415A (Human Monoclonal Antibodies to *C. difficile* toxin A and toxin B) in Patients Receiving Antibiotic Therapy for *C. difficile* Infection (MODIFY II)

1.2 INDICATION

Fully human monoclonal antibodies to *C. difficile* toxin A and toxin B are investigational products for intravenous infusion:

- MK-3415 is a fully human monoclonal antibody to *C. difficile* toxin A only.
- MK-6072 is a fully human monoclonal antibody to *C. difficile* toxin B only.
- MK-3415A is the combination of fully human monoclonal antibody to *C. difficile* toxin A (MK-3415) and fully human monoclonal antibody to *C. difficile* toxin B (MK-6072).

MK-3415 (fully human monoclonal antibody to toxin A only) will not be tested alone in this study but will be used in combination with MK-6072 to make up MK-3415A (the combination of fully human monoclonal antibody to *C. difficile* toxin A [MK-3415] and fully human monoclonal antibody to *C. difficile* toxin B [MK-6072]). A separate Phase III study (Protocol 001, also known as MODIFY I) is evaluating the efficacy and safety of MK-3415.

The primary goal of this clinical program is to show that a single intravenous infusion of MK-3415A (10 mg/kg of each monoclonal antibody to *C. difficile* toxin A [MK-3415] and toxin B [MK-6072]) reduces recurrence of *C. difficile* infection (CDI).

1.3 SUMMARY OF RATIONALE

Epidemiology and Pathophysiology of *C. difficile* Infection

Infection with *C. difficile*, an anaerobic, Gram-positive, spore-forming bacillus, usually occurs as a complication of antibiotic therapy due to the disruption of normal colonic flora caused by an antibacterial agent(s). Almost all antibiotics, including clindamycin, cephalosporins, penicillins and fluoroquinolones, have been associated with *C. difficile* infection [1, 2, 3]. Over the past 2 decades, the incidence of *C. difficile* infection has risen steadily. The number of *C. difficile* cases reported in 1996 in the United States was 31 cases per 100,000 population. In 2005, the number of cases in the United States rose to almost 3 times the 1996 rate (84 cases per 100,000 population) [4]. *C. difficile* is now the most common cause of infectious diarrhea in hospitalized patients in the developed

Product: MK-3415A

2

Protocol/Amendment No.: 002-00

world [5, 6]. Of even greater concern are increases in severe or fatal infections, standard of care therapy failures, emergence of a more virulent, epidemic strain (BI/NAP1/027), and the incidence of recurrent infection [7, 8, 9, 10, 11, 12].

Pathogenic strains of *C. difficile* produce 2 potent protein exotoxins, toxin A and toxin B (some strains only produce toxin B). With the disruption of the normal colonic flora from antibiotic therapy, *C. difficile* is able to flourish and release toxins A and B. The toxins cause the disorganization of the cytoskeleton, disruption of protein synthesis, cell rounding, and cell death in the colonic epithelium. In the lamina propria, an inflammatory response occurs with recruitment of neutrophils and subsequent pseudomembrane formation on the surface of the damaged epithelium. Clinical manifestations of *C. difficile* infection range from asymptomatic carriage to fulminant colitis. Antibiotic therapy (with metronidazole or oral vancomycin) is usually successful in treating the initial episode of *C. difficile* infection; however, approximately 15-30% of these patients will have a recurrent episode [10, 4, 11]. Patients who have experienced at least one episode of recurrent CDI have up to a 33-60% chance of experiencing additional episodes [10, 13, 14].

Use of Monoclonal Antibodies Against Toxin A and B in *C. difficile* Infection

A new adjunctive approach to the treatment of *C. difficile* infection is the use of monoclonal antibodies directed against the exotoxins produced by *C. difficile*. Data from both a primary and relapse hamster disease model support the co-administration of monoclonal antibodies to toxin A (MK-3415) and antibodies to toxin B (MK-6072), with optimal protection in both models provided by the combination therapy.

Recent results from the Phase II clinical study of a single infusion of the combination of monoclonal antibodies directed against toxins A and B (the combination of the 2 monoclonal antibodies hereafter referred to as MK-3415A) demonstrated a significant difference ($p \leq 0.001$) in CDI recurrence between recipients of the monoclonal antibodies (7% [7/101]) and those who received placebo (25% [25/99]) [15]. The safety of MK-3415A was comparable to placebo. There are currently no available clinical data assessing the efficacy of a monoclonal antibody to *C. difficile* toxin B (MK-6072). Please refer to the Investigator's Brochure (IB) for a full assessment of the available preclinical and clinical data for this compound.

1.4 SUMMARY OF STUDY DESIGN

NOTE: See Section 3.5.3 for definition of study endpoints.

This study is a randomized, double-blind, placebo-controlled, multicenter, Phase III study evaluating the efficacy, safety, and tolerability of monoclonal antibodies to *C. difficile* toxin B alone (MK-6072) and toxin A and toxin B together (MK-3415A). Patients with CDI who are receiving standard of care (SOC) therapy (metronidazole, and/ or oral vancomycin, or oral fidaxomicin) (see Section 3.2.1.1) will be randomized in a 1:1:1 ratio into 1 of 3 treatment groups. On Day 1 (day of study therapy infusion), patients will receive MK-6072, MK-3415A, or placebo. Investigators are encouraged to enroll

Product: MK-3415A

3

Protocol/Amendment No.: 002-00

patients and administer the study therapy infusion as soon as possible relative to the initiation of SOC therapy (including the same day as SOC onset). Patients enrolled in this study should receive SOC therapy for a minimum of 10 days and a maximum of 14 days.

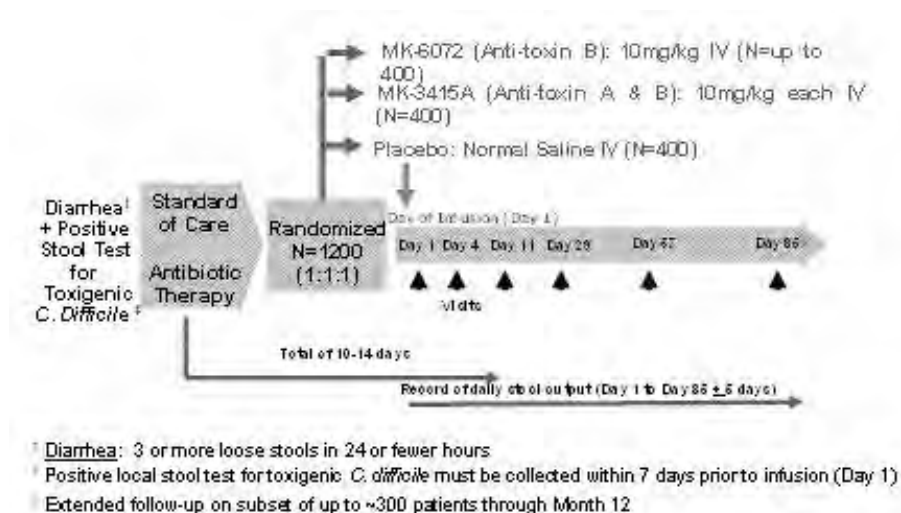
All patients will be followed through Week 12 (Day 85 ± 5 days), hereafter referred to as Week 12. The primary efficacy endpoint is the proportion of patients with CDI recurrence through Week 12. Safety will be assessed by the accumulated data on clinical and laboratory adverse experiences in the 3 treatment groups through Week 4 (Day 29 ± 3 days), hereafter referred to as Week 4.

An extended follow-up period of 9 months will be conducted in a subset of patients to assess for CDI recurrence through Month 12.

A diagram of the study design describing the first 12 weeks of the study is in Figure 1-1.

Figure 1-1

Diagram of Study Design - Base Study (Day 1 to Week 12)



Product: MK-3415A

4

Protocol/Amendment No.: 002-00

1.5 SAMPLE

Adult patients (at least 18 years of age) with CDI are eligible to participate in the study provided they are receiving SOC therapy (or are planning to initiate SOC therapy on the same day as the study therapy infusion) and have provided consent for participation. The study plans to enroll approximately 400 patients in each treatment group (or a sample size of approximately 1,200 patients). Actual enrollment will depend on the results of an interim analysis from an adaptive Phase 3 trial (Protocol 001 [MODIFY I]), as the *individual* monoclonal antibody treatment group (MK-6072) may be dropped at the time of the interim analysis (Section 3.5.9); therefore, enrollment in the MK-6072 treatment arm may be less than 400 patients.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Patients will be randomized at study onset in a 1:1:1 ratio into 1 of 3 treatment groups to receive one of the following:

- A single infusion of MK-6072 (10 mg/kg of monoclonal antibody to *C. difficile* toxin B only), or
- A single infusion of MK-3415A (combination of 10 mg/kg of monoclonal antibody to *C. difficile* toxin A [MK-3415] and 10 mg/kg of monoclonal antibody to *C. difficile* toxin B [MK-6072]), or
- A single infusion of placebo (0.9% sodium chloride)

Hereafter, all study therapy infusions are simply referred to as infusion.

The infusion, which will be prepared by an Unblinded Pharmacist, will be administered as a single 250 mL infusion in 0.9% sodium chloride. The total infusion volume for all patients, regardless of treatment arm (i.e., whether receiving placebo, one monoclonal antibody therapy [MK-6072], or both monoclonal antibody therapies [MK-3415A]) is to be 250 mL. However, if the patient's underlying medical condition warrants caution in the administration of intravenous (IV) fluids (e.g., congestive heart failure [CHF]), the investigator may request the Unblinded Pharmacist to reduce the total infusion volume to 200 mL in an effort to decrease the risk of fluid overload. The infusion is to be administered as soon as possible after preparation. Due to slight differences in appearance for MK-6072 and MK-3415A versus placebo, all study infusion bags will be covered in an opaque sleeve to ensure that blinded study personnel and patients remain blinded to clinical material assignment. Once started, the infusion should be administered over approximately a 1-hour period through a sterile 0.22 micron filter controlled by a volumetric pump. Details regarding dose preparation and administration can be found in the Pharmacy Binder.

Product: MK-3415A
Protocol/Amendment No.: 002-00

5

1.7 STUDY FLOW CHART - MAIN STUDY (DAY 1 TO WEEK 12)

Activity	Time Point						
	#1	#2	#3	#4	#5	#6	Unscheduled
Study Visit							
Relative Day/Week of Study	Day 1	Day 4 (± 1 day)	Day 11 (± 2 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 7 days)	Week 12 (Day 85 ± 5 days)	Day 1 to Week 12 (Day 85 ± 5 days)
CDI Diagnosis, local laboratory (stool test for toxigenic <i>C. difficile</i>) [†]	X						X
Written Informed Consent	X						
Informed Consent for Future Biomedical Research	X						
Medical History/ CDI History/ Assessment by Horn's Index and Charlson Index/ Patient ID card provided [‡]	X						
Inclusion/Exclusion Criteria	X						
Randomization	X						
Infusion (over an ~1-hour period)	X						
CLINICAL SAFETY EVALUATIONS							
Physical Assessment/Exam [§]	X		X			X	X
Vital Signs Assessment [¶]	X (pre- & post-infusion)	X	X	X	X	X	X
Non-serious Adverse Experience Assessment ^{††}	X						X
Serious Adverse Experience Assessment	X						X
Collection of Prior/Concomitant Medication Use [#]	X (All medications)				X (All medications used to treat CDI, other antibiotic therapies, anti-diarrheal medications, and excluded medications only)		X
12-Lead Electrocardiogram ^{†††}	X (pre- & post-infusion)						
LABORATORY SAFETY EVALUATIONS							
Pregnancy Testing ^{‡‡}	X						
Safety Lab Sample ^{§§}	X	X	X	X			X
Blood sample for anti-drug antibody (ADA) levels	X			X	X	X	

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3415A, Protocol 002-00 Issue Date: 09-Aug-2011

15

Product: MK-3415A
Protocol/Amendment No.: 002-00

6

Activity	Time Point						
Study Visit	#1	#2	#3	#4	#5	#6	Unscheduled
Relative Day/Week of Study	Day 1	Day 4 (± 1 day)	Day 11 (± 2 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 7 days)	Week 12 (Day 85 ± 5 days)	Day 1 to Week 12 (Day 85 ± 5 days)
PATIENT REPORTED OUTCOMES							
Daily Loose Stool Count (with stool count log) ^{¶¶}	X						
Daily Body Temperature (with stool count log) ^{¶¶}	X (Days 1 to 14)						
CLINICAL EFFICACY EVALUATIONS							
Stool Sample for Central Laboratory (microbial identification, toxigenic strain typing, & antibacterial susceptibility testing) ^{¶¶¶}	X						X
Daily/Weekly Phone Calls/Contact with Patient ^{¶¶¶}	X (Daily through Day 14)			X Twice weekly during Weeks 3 through Week 12			
Record of Daily Loose Stool Counts on Electronic Case Report Form (eCRF) ^{§§§}	X						
PHARMACOKINETICS (PK)							
Blood sample for MK-3415 & MK-6072 levels ^{¶¶¶}	X (pre- & post-infusion)	X	X	X	X	X	X
CLINICAL SEROLOGY & BIOMARKER SAMPLES							
Blood sample for endogenous anti-toxin A & anti-toxin B antibodies ^{¶¶¶}	X			X		X	X
Blood Sample for Dehydroepiandrosterone (DHEA) ^{¶¶¶}	X						
Blood Sample for Cytomegalovirus (CMV) IgG ^{¶¶¶¶}	X						
Blood Sample for Cytokine Profile ^{¶¶¶¶}	X						
Blood Sample for Immune Profile (Flow Cytometry) ^{§§§§}	X						

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

Product: MK-3415A
Protocol/Amendment No.: 002-00

7

Activity	Time Point						
	#1	#2	#3	#4	#5	#6	Unscheduled
Study Visit							
Relative Day/Week of Study	Day 1	Day 4 (± 1 day)	Day 11 (± 2 days)	Week 4 (Day 29 ± 3 days)	Week 8 (Day 57 ± 7 days)	Week 12 (Day 85 ± 5 days)	Day 1 to Week 12 (Day 85 ± 5 days)
CLINICAL SEROLOGY & BIOMARKER SAMPLES							
Blood Sample for RNA Profiling ^{††††}	X (All patients)	X (Subset population)	X (Subset population)	X (Subset population)			
Blood Sample for SNP genotyping ^{†††}		X (Subset population)					
Stool Sample for 16s ribosomal RNA (rRNA) PCR deep sequencing of gut flora ^{†††††}	X (All patients)	X (Subset population)	X (Subset population)	X (Subset population)			
Blood for Future Biomedical Research (DNA sample) ^{†††††}		X					
MECHANISM OF ACTION:							
Stool Sample for measurement of MK- 3415 and MK-6072 ^{†††††}	X (All patients)	X (Subset population)	X (Subset population)	X (Subset population)			X (Subset population)
<p>Note: The following approximate blood draw volumes will be collected during the main study (not including the Biomarkers or Future Biomedical Research samples): Visit 1 = 25.5 mL, Visit 2 = 11 mL, Visit 3 = 15 mL, Visit 4 = 19 mL, Visit 5 = 8 mL, Visit 6 = 12 mL, and UNS = 11 mL</p> <p>[†] A stool sample to be tested for toxigenic <i>C. difficile</i> (tested locally as per the methods outlined in Appendix 6.1) must be collected within 7 days prior to administration of the infusion. NOTE: If diarrhea resolves (defined as ≤2 loose stools per day for at least 2 consecutive days, with loose stools defined by Bristol Chart Type 5 through Type 7, as per Appendix 6.2) and subsequently begins again with 3 or more loose stools in 24 or fewer hours (i.e., a new episode of diarrhea), the investigator must send a stool sample for another local stool test for toxigenic <i>C. difficile</i> (tested locally). Samples tested by the local stool test for toxigenic <i>C. difficile</i> for each new episode of diarrhea during the study period should use a method as outlined in Appendix 6.1. Preferably, the testing for toxigenic <i>C. difficile</i> in the setting of new episodes of diarrhea should use the same diagnostic method as used for study entry. A stool sample for toxigenic <i>C. difficile</i> testing must be collected for each separate, new episode of diarrhea during the study period.</p> <p>^{††} Medical history should be reviewed to confirm study eligibility, and all medical conditions present within the last 12 months should be recorded. Each prior CDI episode occurring within the last 6 months should be recorded. The number of prior CDI episodes occurring in the past 2 years will also be recorded. Relative to the presenting case of CDI, hospitalization status, ICU treatment, and endoscopic evidence of pseudomembranous colitis (if performed) should be recorded. An assessment of underlying disease severity by modified Horn's Index (see Appendix 6.3) must be provided. An assessment of comorbidities by Charlson Index (see Appendix 6.4) must also be provided. In addition, all patients will be given a card, after consent is provided and a baseline number assigned, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.</p> <p>^{†††} Physical exam should be performed within 72 hours prior to the infusion, at other prespecified visits, and at each unscheduled visit at the time of a new episode of diarrhea. If a physical exam was previously performed within 72 hours of Visit 1, those results can be recorded and a new physical exam is not required.</p>							

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

Product: MK-3415A
Protocol/Amendment No.: 002-00

8

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

	Vital signs (heart rate, blood pressure, respiration rate, body temperature, height, and weight) should be measured just prior to infusion on Day 1. Vital signs (heart rate, blood pressure, respiration rate, and body temperature) should also be measured in 30 minute increments until the end of the infusion, at the end of the infusion, at other prespecified visits per protocol and at each unscheduled visit at the time of a new episode of diarrhea .
†	Adverse experiences, both non-serious and serious, should be collected from the time a patient is assigned a baseline number through Week 4. Non-serious adverse experiences which occur after Week 4 will <u>not</u> be collected, including at Unscheduled Visits. Serious adverse experiences will be collected through Week 12 and at Unscheduled visits as described in Section 3.4.5.1. In addition, infusion-specific reactions will also be evaluated for 24 hours following the start of infusion †
#	Prior medication use should be recorded for the 14 days prior to study entry. All concomitant medications on Day 1 and following the infusion should be recorded through Week 4. Of note, any medications used to treat CDI, other antibiotic medications, anti-diarrheal medications, and excluded medications/therapies (e.g., cholestyramine, <i>S. boulardii</i> , ribaximin and nitazoxanide) should be recorded for the full 12-Week study period.
††	Electrocardiogram (ECG) should be performed just prior to infusion. A post-infusion ECG should also be completed within 2 hours of the end of the infusion. It is recommended to leave the electrodes in place during the infusion to reduce variability in the post-infusion ECG relative to pre-infusion ECG.
††	A urine pregnancy test is required within 48 hours prior to infusion for pre-menopausal females who are not sterilized and therefore have the potential to bear a child. If results are positive, the patient should be excluded from study participation.
§§	Safety labs include blood and urine samples. The Visit 1 blood and urine sample must be obtained within 24 hours prior to infusion and are for baseline measurements only. Results are not required for patient entry into the study. Safety testing (as outlined in Appendix 6.5) will include blood measurements for CBC with WBC differential [including platelets], blood chemistry (including serum electrolytes and liver-function testing), and urinalysis with possible microscopic evaluation. A limited panel of safety lab tests will be performed on samples obtained at unscheduled visits; these limited safety tests are outlined in Appendix 6.5.
	Anti-drug antibody (ADA) titer samples must be drawn within 24 hours prior to infusion and at other prespecified visits. Samples testing positive for ADA will then be tested for neutralizing antibody (~6 mL blood).
¶¶	The number of loose stools (defined by Bristol Chart Type 5 through Type 7, as per Appendix 6.2) will be recorded daily by the patient or designee through Week 12 (Day 85 ± 5 days) using the stool count log.
##	Body temperature will be recorded daily by the patient or designee from the day of infusion through Day 14 post-infusion.
†††	A stool sample for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) must be collected and sent to a central laboratory. This is an absolute requirement for this study. This sample should be collected after informed consent is obtained and optimally before infusion. However, this stool sample may be collected up to within 72 hours after infusion. NOTE: If diarrhea resolves (defined as ≤2 loose stools per day for at least 2 consecutive days) and subsequently begins again with 3 or more loose stools in 24 or fewer hours (i.e., a new episode of diarrhea), the investigator must send a stool sample for central laboratory testing for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing). The stool sample for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) must be collected for each new episode of diarrhea during the study period.
†††	The study personnel will contact the patient every day through Day 14 for loose stool counts and body temperature and to ensure they are being measured. Thereafter, study personnel will contact the patient twice weekly during Week 3 through Week 12.
§§§	Study personnel will record the number of loose stools (defined by Bristol Chart Type 5 through Type 7, as per Appendix 6.2) daily through Week 12 (Day 85 ± 5 days) via the appropriate eCRF.
	Both pre-infusion (within 24 hours prior to infusion) and the post-infusion sample (within 2 hours after the end of the infusion) and other follow-up samples for pharmacokinetic assessments will be completed at scheduled study visits per the protocol (3-5 mL each).
¶¶¶	Anti-toxin A and anti-toxin B antibody samples (4-6 mL each) drawn within 24 hours prior to infusion will be collected for endogenous baseline levels. Similar samples for endogenous antibody levels will be collected from at scheduled study visits per protocol schedule and at unscheduled visits at the time of a new episode of diarrhea .
###	Blood sample (1.0 to 1.5 mL) will be collected within 24 hours prior to infusion (Day 1) for dehydroepiandrosterone (DHEA) levels.
††††	Blood sample (1.0 to 1.5 mL) will be collected within 24 hours prior to infusion (Day 1) for CMV IgG titers.

Product: MK-3415A
Protocol/Amendment No.: 002-00

9

++++	Blood samples (0.25 mL) will be collected within 24 hours prior to infusion (Day 1) to measure a panel of serum cytokine levels from approximately 170 subjects per treatment arm
8888	Blood sample (3 mL) will be collected within 24 hours prior to infusion (Day 1) for T-cell and B-cell subsets (measured via flow cytometry) from approximately 170 subjects per treatment arm
	Blood samples (2.5 mL into a PAXGENE tube) will be collected within 24 hours prior to infusion for messenger RNA (mRNA) expression profiling from <u>all patients</u> . A <u>subset of patients (optional enrollment)</u> <u>enrolled</u> will be asked to provide samples at subsequent study visits (Visit 2 [Day 4 ± 1 day], Visit 3 [Day 11 ± 2 days], and Visit 4 [Week 4, Day 29 ± 3 days]). Any remaining sample will be stored long term as described in the Future Biomedical Research sections and consent.
####	The stool sample for 16s rRNA PCR deep sequencing of gut flora is collected prior to infusion from <u>all patients</u> . A stool sample for 16s rRNA PCR deep sequencing will also be collected at subsequent post-infusion study visits (Visit 2 [Day 4 ± 1 day], Visit 3 [Day 11 ± 2 days], and Visit 4 [Week 4, Day 29 ± 3 days]) from a <u>subset of patients (optional enrollment)</u> . All samples will be sent to a central laboratory for 16s rRNA PCR deep sequencing of gut flora. Any remaining sample will be stored long term as described in the Future Biomedical Research sections and consent.
****	Blood sample will be collected on Day 4 (± 1 day) from a subset of patients (<u>optional collection</u>) for single nucleotide polymorphism [SNP] genotyping. If a sample is not collected at Visit 2, it can be collected at a subsequent visit.
+++++	Informed consent for future biomedical research samples must be obtained before the FBR sample for DNA analysis. The DNA sample for analysis should be obtained pre-dose, at Visit 2, as the last sample drawn, and on randomized subjects only. The sample may be collected with next scheduled blood draw, as soon as the informed consent is obtained.
+++++	Stool testing for the detection of antibodies of toxin A and toxin B (MK-3415 and MK-6072 antibodies) will be performed at baseline on all subjects to assess mechanism of action. All samples will be sent to a central laboratory for detection of these antibodies to toxin A and toxin B.

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

Product: MK-3415A

10

Protocol/Amendment No.: 002-00

1.8 STUDY FLOW CHART - EXTENDED FOLLOW-UP PERIOD FOR SUBSET OF PATIENTS (MONTHS 4 TO 12)

An additional 9-month extended follow-up period will be implemented to assess for CDI recurrence in a subset of patients (~300) who have completed the primary 12-Week study period. Enrollment in the 9-month extension will be conducted at all study sites. In addition, stool carriage of *C. difficile*, endogenous anti-toxin A and anti-toxin B antibody levels, and anti-drug antibody (ADA) levels will be assessed. The number of patients enrolled in the follow-up period may be modified based on the number of patients enrolled in Protocol 001 (MODIFY I).

Activity	Time Point									
			#7			#8			#9	Unscheduled
Study Visit [†]										
Relative Month of Study	4	5	6	7	8	9	10	11	12	4 to 12
Assessment of CDI Recurrence (including stool samples for local toxigenic <i>C. difficile</i> testing and culture by a central laboratory) [‡]	----- X ----->									
Monthly Phone Call to Patient [§]	X	X	X	X	X	X	X	X	X	
Stool sample (or rectal swab sample) for central laboratory to assess for <i>C. difficile</i> carriage: Anaerobic culture and other ancillary microbiological assessments (microbial identification, toxigenic strain typing, and antibacterial susceptibility testing)			X			X			X	X
Blood sample for endogenous anti-toxin A & anti-toxin B levels [¶]			X			X			X	X
Blood sample for MK-3415 & MK-6072 (PK) levels [¶]			X							X
Blood sample for anti-drug antibody (ADA) levels [¶]			X							
[†] There are 3 defined visits: Visit 7 (Month 6 ± 10 days), Visit 8 (Month 9 ± 10 days), and Visit 9 (Month 12 ± 10 days) [‡] If diarrhea resolves (defined as ≤2 loose stools per day for at least 2 consecutive days) and subsequently begins again with 3 or more loose stools in 24 or fewer hours (i.e., a new episode of diarrhea) at <u>any</u> time during the follow-up period, the investigator must send a stool sample for a test for toxigenic <i>C. difficile</i> (tested locally). Stool samples for local toxigenic <i>C. difficile</i> testing for each new episode of diarrhea during the follow-up period should use a diagnostic method as outlined in Appendix 6.1. Preferably, the stool test for toxigenic <i>C. difficile</i> in the setting of new episodes of diarrhea should use the same diagnostic method as used for study entry. A stool sample for toxigenic <i>C. difficile</i> testing must be collected for each new episode of diarrhea during the follow-up period. In addition, a stool sample for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) must be collected for each new episode of diarrhea during the follow-up period (as per the initial 12-week study period for this study). The sample will be sent to a central laboratory for anaerobic culture and other ancillary assessments. [§] The patient will be contacted every month by phone to assess CDI recurrence. A scheduled visit can take the place of the phone call for that month (for Months 6, 9, and 12). A stool sample to assess for <i>C. difficile</i> carriage is required at Visit 7 (Month 6 ± 10 days), Visit 8 (Month 9 ± 10 days), and Visit 9 (Month 12 ± 10 days). <u>This sample may be collected via a rectal swab unless diarrhea is present at that visit.</u> The sample, which will undergo anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing), must be collected at the visits outlined above. The sample will be sent to a central laboratory for anaerobic culture and other ancillary assessments. [¶] Serum samples to test for endogenous anti-toxin A and anti-toxin B, pharmacokinetic assessment of MK-3415 and MK-6072, and anti-drug antibody (ADA) are from blood drawn at the scheduled visits outlined above. Samples for endogenous anti-toxin A and anti-toxin B antibodies and pharmacokinetic testing will also be drawn at an unscheduled visit at the time of a new episode of diarrhea .										

Product: MK-3415A

11

Protocol/Amendment No.: 002-00

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

Primary Objective #1: To determine if treatment with a single infusion of monoclonal antibody therapy with SOC therapy (*combined* monoclonal antibody therapy [MK-3415A] or the *individual* monoclonal antibody therapy [MK-6072]) decreases the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo with SOC therapy.

Primary Hypothesis #1a: Treatment with a single infusion of MK-3415A given with SOC therapy will decrease the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo given with SOC therapy.

Primary Hypothesis #1b: Treatment with a single infusion of MK-6072 given with SOC therapy will decrease the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo given with SOC therapy.

Primary Objective #2: To evaluate the safety profile in patients receiving a single infusion of monoclonal antibody therapy (MK-6072 or MK-3415A) with SOC therapy for CDI as compared to those patients receiving a single placebo infusion and SOC therapy for CDI.

Primary Hypothesis #2: Administration of a single infusion of monoclonal antibody therapy (MK-6072 or MK-3415A) in patients receiving SOC therapy for CDI will be generally well tolerated with a safety profile comparable to that seen in patients receiving a single placebo infusion with SOC therapy for CDI, as assessed by the accumulated safety data up to Week 4.

2.1.2 Secondary

NOTE: *The various secondary efficacy objectives (objectives 1 to 4) are predominantly focused on the comparison of MK-3415A versus placebo. However, these secondary efficacy objectives may also include the individual monoclonal antibody treatment group (MK-6072) provided this regimen demonstrates superiority versus placebo for the primary hypothesis (1b, as outlined above).*

Secondary Objective #1: To evaluate, in the subset of patients who achieve a clinical cure for the initial CDI episode, if treatment with a single infusion of MK-3415A with SOC therapy decreases the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo and SOC therapy.

Product: MK-3415A

12

Protocol/Amendment No.: 002-00

Secondary Hypothesis #1: In the subset of patients who achieve a clinical cure for the initial CDI episode, treatment with a single infusion of MK-3415A given with SOC therapy will decrease the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo given with SOC therapy.

Secondary Objective #2: To determine the proportion of patients who achieve global cure in the treatment group receiving a single infusion of MK-3415A with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

Secondary Hypothesis #2: The proportion of patients who achieve global cure is greater following treatment with a single infusion of MK-3415A given with SOC therapy than following treatment with a single placebo infusion given with SOC therapy.

Secondary Objective #3: To evaluate if treatment with a single infusion of MK-3415A with SOC therapy decreases the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of placebo and SOC therapy in the following subgroups:

- Patients with or without a history of CDI in the 6 months prior to enrollment
- Patients infected with or without the BI/NAP1/027 strain of *C. difficile* at study entry
- Patients infected with or without an epidemic strain (including but not limited to BI/NAP1/027, 001, 078, and 106) of *C. difficile* at study entry
- Patients with or without a clinically severe *C. difficile* infection at study entry
- Patients <65 years of age or ≥65 years of age at study entry
- Patients with or without compromised immunity at study entry

Secondary Objective #4: To determine if treatment with a single infusion of combined monoclonal antibody therapy (MK-3415A) with SOC therapy decreases the proportion of patients with CDI recurrence over a period of 12 weeks as compared to treatment with a single infusion of individual monoclonal antibody therapy (MK-6072) with SOC therapy.

Secondary Objective #5: To assess infusion-specific reactions occurring within 24 hours of the start of the infusion in the treatment group receiving a single infusion of monoclonal antibody therapy (MK-6072 or MK-3415A) with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

Product: MK-3415A

13

Protocol/Amendment No.: 002-00

2.1.3 Exploratory Objectives

NOTE: The various exploratory efficacy objectives (Exploratory Objectives #1 through #4 below) are focused on the comparison of MK-3415A versus placebo. However, these exploratory efficacy objectives may also include the individual monoclonal antibody treatment group (MK-6072) provided this regimen demonstrates superiority versus placebo for the primary hypothesis (1b, as outlined above).

Exploratory Objective #1: To evaluate the proportion of patients with clinical cure in the treatment group receiving a single infusion of MK-3415A with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

Exploratory Objective #2: To determine if treatment with a single infusion of MK-3415A with SOC therapy reduces the time to resolution of the initial CDI episode as compared to treatment with a single placebo infusion with SOC therapy.

Exploratory Objective #3: To assess the impact of treatment with a single infusion of MK-3415A or placebo with SOC therapy on the median number of loose stools per day for the initial CDI episode (day after infusion [Day 2] through Day 14).

Exploratory Objective #4a: To evaluate the proportion of patients whose elevated baseline WBC ($>10,000$ cells/mm³) decreases to $\leq 10,000$ cells/mm³ by Day 4 or Day 11 in the treatment group receiving a single infusion of MK-3415A with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

Exploratory Objective #4b: To evaluate the proportion of patients whose elevated baseline body temperature ($\geq 101.0^{\circ}\text{F}$ [38.4°C]) decreases to $<101.0^{\circ}\text{F}$ [38.4°C] by Day 4 or Day 11 in the treatment group receiving a single infusion of MK-3415A with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

2.2 PATIENT INCLUSION CRITERIA

1. Patient must be 18 years of age or older.
2. Patient has a diagnosis of *C. difficile* infection (CDI) as defined by:
 - a. Presence of diarrhea, as defined by passage of 3 or more loose stools in 24 or fewer hours [16],

AND

- b. A positive stool test for toxigenic *C. difficile*.

NOTE: Diarrhea is not required to be present on the day of infusion. Toxigenic *C. difficile* positivity should be determined locally by a hospital/clinic/reference microbiology laboratory test using only those methodologies listed in Appendix

Product: MK-3415A

14

Protocol/Amendment No.: 002-00

6.1; the stool sample with the documented positive result for toxigenic *C. difficile* must have been collected within 7 days prior to the infusion.

3. Patient must be receiving or planning to receive a 10- to 14-day course of SOC therapy for CDI. SOC therapy is defined as the receipt of oral metronidazole, oral vancomycin, intravenous metronidazole concurrent with oral vancomycin, oral fidaxomicin, or oral fidaxomicin concurrent with intravenous metronidazole. Oral metronidazole should be administered at a dose of 1200-1500 mg per day (usually 400 to 500 mg every 8 hours [three times a day]). Intravenous metronidazole should be administered at a dose of 1500 mg per day (500 mg every 8 hours [three times a day]). Oral vancomycin should be administered at a dose of 125-500 mg at least every 6 hours (4 times a day). Oral fidaxomicin should be administered at a dose of 200 mg twice daily.

NOTE: A patient who is planning to initiate SOC therapy on the same day as the infusion is eligible for participation. The first dose of SOC therapy must have been administered prior to or within a few hours following the infusion.

4. Patient is highly unlikely to become pregnant or to impregnate a partner since they meet at least one of the following criteria:
 - a. A female patient who is not of reproductive potential is eligible without requiring the use of contraception. A female patient who is not of reproductive potential is defined as: one who has either (1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum FSH levels in the postmenopausal range as determined by the local laboratory, or 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).
 - b. A male or female patient 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 12-Week study period. Acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy and any registered and marketed hormonal contraceptives that contain an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).
5. Patient or legal representative must have voluntarily agreed to participate by providing written informed consent after the nature of the study has been fully explained. The subject may also provide consent for use of a blood sample for Future Biomedical Research. However, the subject may participate in the main trial without agreeing to participate in Future Biomedical Research.

Product: MK-3415A

15

Protocol/Amendment No.: 002-00

2.3 PATIENT EXCLUSION CRITERIA

1. Patient with an active chronic diarrheal illness such as, but not limited to, ulcerative colitis or Crohn's disease or with a condition such that they routinely pass loose stool (e.g., patients with an ostomy).
2. Patient with a planned surgery for CDI within 24 hours.
3. Patient has a positive pregnancy test in the 48 hours before the infusion or is unwilling to undergo pregnancy testing if a pre-menopausal female who is not sterilized and therefore has the potential to bear a child.
4. Patient is breast-feeding or plans to breast-feed prior to the completion of the 12-Week study period.
5. A female patient who plans to donate ova prior to the completion of the 12-Week study period, or a male patient who is planning to impregnate or provide sperm donation prior to the completion of the 12-Week study period.
6. Patient has previously participated in this study or has previously received MK-3415 or MK-6072 (either alone or in combination).
7. Patient plans to donate blood and/or blood products within 6 months following the infusion.
8. Patient has received immune globulin within 6 months prior to receipt of the infusion or is planning to receive immune globulin prior to the completion of the 12-Week study period.
9. Patients for whom treatment with SOC therapy is planned for longer than 14 days (e.g., planned tapered or pulsed regimen of vancomycin).
10. Patient has received cholestyramine, rifaximin, or nitazoxanide within 14 days prior to receipt of the infusion or is planning to receive these medications prior to the completion of the 12-Week study period.
11. Patient plans to take medications to control diarrhea or to decrease peristalsis, such as loperamide (ImodiumTM), or diphenoxylate hydrochloride/atropine sulfate (LomotilTM), at any time during the 14 days following infusion. Patients receiving opioid medications at the onset of diarrhea may be included if they are expected to be on stable doses of these medications, or there is anticipation of a dose decrease or cessation of their use.
12. Patient plans to take the probiotic *Saccharomyces boulardii* at any time following infusion (Day 1) and through the completion of the 12-Week study period.

Product: MK-3415A

16

Protocol/Amendment No.: 002-00

13. Patient has received another investigational study agent within the previous 30 days, or is currently participating in or scheduled to participate in any other clinical trial during the 12-Week study period.
14. Patient is not expected to survive for 72 hours.
15. Patient has any other condition that, in the opinion of the investigator, would jeopardize the safety or rights of the patient participating in the study, would make it unlikely for the patient to complete the study, or would confound the results of the study.

2.4 STUDY DESIGN AND DURATION

NOTE: See Section 3.5.3 for definition of study endpoints. Terms in bold are defined in Section 3.3.1.

2.4.1 Summary of Study Design

This study is a randomized, double-blind, placebo-controlled, multicenter Phase III study evaluating the efficacy, safety, and tolerability of monoclonal antibodies to *C. difficile* toxin B alone (MK-6072) or toxin A and toxin B together (MK-3415A) as compared to placebo in adult patients (≥ 18 years of age). Eligible patients must have **a diagnosis of *C. difficile* infection. In addition, patients must have a stool sample collected to be sent to a central laboratory for anaerobic culture and other ancillary microbiological assessments (See Sections 1.7 and 3.2.3.3.4).**

This study will compare 3 treatment groups for the reduction of CDI recurrence:

- A single infusion of MK-6072 (10 mg/kg of monoclonal antibody to *C. difficile* toxin B only)
- A single infusion of MK-3415A (combination of 10 mg/kg of monoclonal antibody to *C. difficile* toxin A [MK-3415] and 10 mg/kg of monoclonal antibody to *C. difficile* toxin B [MK-6072])
- A single infusion of placebo (0.9% sodium chloride)

Patients will be stratified based on 2 factors as present at the time of randomization: (1) SOC therapy (metronidazole vs. vancomycin vs. fidaxomicin, as prescribed by the attending physician) and (2) hospitalization status (inpatient vs. outpatient). A minimum of one fifth (20%) of the enrolled patients in the total study population must be from the vancomycin stratum. Following stratification (see Section 2.4.3), patients will be randomized in a 1:1:1 ratio into 1 of 3 treatment groups. An Unblinded Pharmacist will prepare the infusion (see Sections 3.2.3.7.3 and 3.2.3.7.4). The Unblinded Pharmacist will not be involved in any evaluations of the patients.

In addition to monoclonal antibodies or placebo, all patients must be receiving SOC therapy (oral vancomycin, oral metronidazole, or intravenous metronidazole concurrent with oral vancomycin, oral fidaxomicin, or oral fidaxomicin concurrent with intravenous metronidazole). Investigators are encouraged to enroll patients and administer the

Product: MK-3415A

17

Protocol/Amendment No.: 002-00

infusion as soon as possible relative to the initiation of SOC therapy (including the same day as SOC therapy onset). Patients enrolled in this study should receive SOC therapy for a minimum of 10 days and a maximum of 14 days. After randomization, SOC therapy may only be switched if the patient has received at least 3 days of the current SOC therapy and meets at least one of the 3 following conditions: (1) **diarrhea**, (2) presence of ileus, or (3) a body temperature $>38.3^{\circ}\text{C}$ ($>100.9^{\circ}\text{F}$) and peripheral WBC count $>15,000$ cells/mm³. Emergence of an adverse experience due to the inability of a patient to tolerate their current SOC therapy also warrants an SOC switch. Additionally, hospitalized patients receiving intravenous metronidazole concurrently with oral vancomycin or oral fidaxomicin may be switched to the respective oral SOC therapy alone upon discharge (see Section 3.2.1.1 for more details). The criteria justifying the switch should be included in the appropriate electronic case report form (eCRF). Even if SOC therapy is switched, patients should receive a minimum of 10 days and a maximum of 14 days of total SOC therapy.

Patients will be evaluated during the infusion, through Week 4 after receipt of infusion for safety outcomes (all adverse experiences and safety laboratory values), and through Week 12 for efficacy outcomes and serious adverse experiences. The primary efficacy endpoint is the proportion of patients with CDI recurrence. Study visits will occur at Day 1, Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days). Blood samples for safety laboratory analysis, endogenous anti-toxin A and anti-toxin B levels, pharmacokinetics of MK-3415 and MK-6072, anti-drug antibody (ADA) measurements, and biomarkers will be collected at scheduled study visits as per the Study Chart (Section 1.7). The number of **loose stools** (defined as Type 5 through Type 7 on the Bristol Stool Chart, as outlined in Appendix 6.2) will be recorded daily by the patient or designee (using a stool count log) through Week 12 (Day 85 ± 5 days) days following the infusion. Body temperature will be recorded daily by the patient or designee (in the stool count log) during the first 14 days of the study period. In an effort to determine if there is a new episode of **diarrhea**, study personnel will make contact with each patient to ascertain and record **loose stool** counts (see Section 1.7 and 3.2.3.8.1.1). The stool count log will also serve as a reminder for patients to contact study personnel if they have **loose stools** during the 12-Week study period.

If there is a new episode of **diarrhea** (see Section 3.2.3.8.3), after resolution of the initial CDI episode, an unscheduled visit should be conducted and patients will be instructed to provide a stool sample, which will be used for toxigenic *C. difficile* testing, performed locally using one of the methods listed in Appendix 6.1, and for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) provided for Future Biomedical Research. Stool culture and other ancillary microbiological assessments will be performed at a designated central laboratory. Blood samples for endogenous anti-toxin A and anti-toxin B levels, pharmacokinetic assessment for MK-3415 and MK-6072, and limited safety laboratory tests (as outlined in Appendix 6.5) should be collected at this unscheduled visit.

Product: MK-3415A

18

Protocol/Amendment No.: 002-00

An extended follow-up period of 9 months to assess for CDI recurrence, carriage in stool of *C. difficile*, endogenous anti-toxin A and anti-toxin B antibody levels, pharmacokinetics of MK-3415 and MK-6072, and anti-drug antibody (ADA) levels (see Section 1.8) will be conducted in a subset of ~300 patients who have completed the primary 12-Week study period.

2.4.2 Biomarker Assessments

Biomarker assessments will be conducted as part of this trial. The aim of these assessments is to explore associations among biologically-based baseline factors and CDI recurrence and to help elucidate the mechanism of action (MOA) of MK-3415 and MK-6072. Certain biomarker samples will be collected in all patients. However, in a subset of patients, more intensive biomarker assessment will be performed. This includes approximately 170 patients per group (total 510 patients) who will be asked to provide a blood sample for both a cytokine profile and an immune profile at baseline. Approximately 100 patients per group (total of 300 patients) will be asked to provide post-baseline blood and stool samples. The post-baseline blood samples will be used for RNA profiling and single nucleotide polymorphism (SNP) genotyping; tests of the post-baseline stool samples will include 16s ribosomal (rRNA) PCR deep sequencing of gut flora, and measurement of MK-3415 and MK-6072. Each subject will be asked to provide samples for the intensive biomarker assessments up until the time when sufficient samples for each type of analysis have been obtained. After this point, these additional samples will no longer be collected. Please refer to Appendix 6.6 for additional information.

2.4.3 Treatment Plan

Overall, the study plans to enroll approximately 400 adult patients (at least 18 years of age) with CDI who are receiving SOC therapy (or are planning to initiate SOC therapy on the same day as the infusion) in each of the 3 treatment groups. A total of approximately 1200 patients will be enrolled in this study.

Table 2-1 describes the treatment plan.

Product: MK-3415A

19

Protocol/Amendment No.: 002-00

Table 2-1

Treatment Plan

Stratification Variable #1 (SOC therapy)	Stratification Variable #2 (Hospitalization Status)	Treatment Group	Infusion	Potency
Vancomycin[†] (includes patients receiving both oral vancomycin and intravenous metronidazole concurrently)	Inpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Metronidazole	Inpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Fidaxomicin (includes patients receiving both oral fidaxomicin and intravenous metronidazole concurrently)	Inpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 and 10 mg/kg of MK-6072
		Placebo	Placebo	N/A

[†] A minimum of 20% of the total patient population should be from the vancomycin stratum.
MAB = Monoclonal antibodies administered in a total volume of 250 mL (or 200 mL at the discretion of the investigator judging the needs of the patient)
Placebo = 0.9% Sodium chloride infusion administered in a total volume of 250 mL (or 200 mL at the discretion of the investigator judging the needs of the patient)
N/A = Not applicable

Product: MK-3415A

20

Protocol/Amendment No.: 002-00

2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS

2.5.1 Efficacy

NOTE: See Section 3.5.3 for definition of study endpoints. Terms in bold are defined in Section 3.3.1.

2.5.1.1 Primary Objective (CDI Recurrence)

The primary endpoint is the proportion of patients with CDI recurrence at Week 12. To assess for CDI recurrence, 3 clinical variables will be measured: (1) **diarrhea**, (2) stool test for toxigenic *C. difficile*, and (3) the type and duration of SOC therapy. The daily count of **loose stools**, as recorded by the patient in the stool count log, will be monitored following the infusion through Week 12 (Day 85 \pm 5 days) in order to identify a new episode of **diarrhea**. All new episodes of **diarrhea** will be tested for toxigenic *C. difficile* (see Section 3.2.3.8.3) to confirm CDI recurrence. The type and duration of SOC therapy as well as the reason for any change in SOC therapy will be recorded in the appropriate eCRF.

2.5.1.2 Other Efficacy Measures (Secondary/ Exploratory Objectives)

To assess the various secondary efficacy objectives, the same 3 clinical variables will be measured as planned for the primary efficacy endpoint: (1) **diarrhea** (via **loose stool** counts through Week 12 [Day 85 \pm 5 days]), (2) stool test for toxigenic *C. difficile*, and (3) the type and duration of SOC therapy. Determination of the key subgroups for the secondary efficacy objectives will be assessed by review of eCRFs (medical history, demographics, and vital signs) and/or appropriate laboratory results. Additional details are included in Section 3.3.1.

To assess the exploratory objective for the proportion of patients with clinical cure, 2 clinical variables will be measured: (1) **diarrhea** (via **loose stool** counts through Week 12 [Day 85 \pm 5 days]) and (2) the type and duration of SOC therapy. The remaining exploratory objectives will be measured by assessment of **loose stool** counts (through Week 12 [Day 85 \pm 5 days]), WBC results from Day 1 and Day 4 (or Day 11), and review of eCRFs for body temperature from Day 1 and Day 4 (or Day 11). Additional details regarding these exploratory efficacy endpoints are included in Section 3.3.1.

2.5.2 Endogenous Antibody Levels and Pharmacokinetics

The blood sample collected within 24 hours prior to infusion will be assessed for endogenous anti-toxin A and anti-toxin B antibody levels. Serum will be separated from blood samples and sent to the central laboratory for testing. Levels of anti-toxin A and anti-toxin B antibody will also be assessed at Week 4 (Day 29 \pm 3 days), Week 12 (Day 85 \pm 5 days) (See Section 3.3.2.4), at the time of a new episode of **diarrhea** at an Unscheduled visit (see Section 3.2.3.8.3), and during the additional 9-month extended follow-up period (Months 6, 9, and 12, and new episode of **diarrhea** at an Unscheduled visit, see Section 3.2.3.8.4.4).

Product: MK-3415A

21

Protocol/Amendment No.: 002-00

Blood samples will be collected within 24 hours prior to infusion and within 2 hours after the end of the infusion on Day 1 to assess for the pharmacokinetics of MK-3415 and MK-6072 (see Section 3.3.2.3). Serum will be separated from blood samples and sent to the central laboratory for testing. Samples for pharmacokinetic testing of MK-3415 and MK-6072 will also be collected at Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), Week 12 (Day 85 ± 5 days), and at an unscheduled visit for a new episode of **diarrhea**. For patients in the additional 9-month extended follow-up period, a sample will also be collected at Month 6 and at an unscheduled visit for a new episode of **diarrhea** to assess the pharmacokinetics of MK-3415 and MK-6072.

2.5.3 Immunogenicity

A blood sample collected within 24 hours prior to infusion and at Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days) and Month 6 (for patients included in the 9-month extension) will be tested for human anti-drug antibody (ADA). Serum will be separated from blood samples and sent to the central laboratory for testing. See Section 3.3.2.5 and 3.3.2.6 for specific assay details.

2.6 LIST OF SAFETY MEASUREMENTS

Safety will be assessed through an evaluation of clinical and/or laboratory adverse experiences. All non-serious and serious clinical and laboratory adverse experiences will be collected from the time the informed consent is signed through Week 4 post-infusion. Serious clinical and laboratory adverse experiences will also be collected from Week 4 through Week 12. These adverse experiences will be identified based on careful assessment or measurement of patient symptoms, vital signs and/or physical examination findings, and other laboratory measures. Vital signs will be monitored just prior to infusion, approximately 30-minutes after the start of the infusion, at the end of the infusion, and on Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), Week 12 (Day 85 ± 5 days), and at an unscheduled visit for a new episode of **diarrhea**. Laboratory tests, including hematology, chemistry, and urinalysis (as outlined in Appendix 6.5), will be performed pre-study (within 24 hours prior to infusion), and at scheduled post-infusion study visits at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days). Visit 1 laboratory safety assessments are for baseline values only and results are not required for patient entry into the study. An electrocardiogram (ECG) will also be conducted just prior to the infusion and within 2 hours after the completion of the infusion.

In addition, the presence of infusion-specific reactions will also be evaluated for 24 hours following the start of infusion. These include any of the following: infusion-site adverse experiences, pyrexia, chills, rash, arthralgia, myalgia, joint swelling, obstructive airways disorder, bronchospasm, stridor, dysphonia, headache, fatigue, pruritus, urticaria, hypotension, hypertension, nasal congestion, nausea, vomiting, flushing, angioedema, dyspnea, and dizziness/lightheadedness.

Product: MK-3415A

22

Protocol/Amendment No.: 002-00

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below. Comprehensive descriptions regarding the endpoints, statistical methods, analysis populations, multiplicity adjustments, and other statistical issues are provided in Section 3.5 of the protocol details.

2.7.1 Efficacy Analyses

The primary and secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 2-2 below.

Efficacy Endpoints

CDI Recurrence: Defined as the development of a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode. The primary efficacy endpoint will be the proportion of patients with CDI recurrence assessed through the Week 12 (Day 85 \pm 5 days) primary study period using the Full Analysis Set (FAS) population (see below and Section 3.5.4.1 for definition of the FAS population).

Global Cure: Defined as clinical cure of the initial CDI episode AND no CDI recurrence through Week 12. The proportion of patients with global cure will be assessed as a secondary efficacy endpoint.

Clinical Cure: Defined as patient received ≤ 14 days of SOC therapy AND the patient has no **diarrhea** (≤ 2 **loose stools** per 24 hours) for two consecutive days following completion of SOC therapy for the initial CDI episode. Patients requiring > 14 days of SOC therapy for the initial CDI episode will be considered a failure for the clinical cure endpoint. The proportion of patients with clinical cure will be assessed as an exploratory efficacy endpoint.

Primary Efficacy Analysis

For the primary endpoint of CDI recurrence, Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with CDI recurrence between the treatment groups. The strata will be the same as those used for the randomization: SOC antibiotic therapy at the time of randomization (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (in-patient vs. out-patient). See Section 3.2.3.4 for more details regarding stratification.

The proportion of patients with CDI recurrence will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who develop a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) [16] associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode. The denominator will be the number of patients in the FAS population.

If MK-3415A is found to be superior to placebo (Primary Hypothesis #1a), the individual monoclonal antibody therapy (MK-6072) will then be compared separately to placebo

Product: MK-3415A

23

Protocol/Amendment No.: 002-00

(Primary Hypothesis #1b) in a sequential manner. Under the global null hypothesis that the three therapies (two active treatments and placebo) are equal, the overall probability of making a false claim of superiority for any of the experimental treatment groups is controlled at level 0.025, one-sided.

Secondary Efficacy Analysis of Global Cure

Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with global cure between the treatment groups. The proportion of patients with global cure will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who achieve clinical cure of the initial CDI episode AND have no CDI recurrence through Week 12. The denominator will be the number of patients in the FAS population.

Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as basis for the efficacy analyses unless otherwise indicated in Section 3.5.3.1. The FAS population is a subset of all randomized patients with patients excluded for the following reasons:

- Failure to receive infusion of study medication
- Lack of a positive local stool test for toxigenic *C. difficile* (as per Appendix 6.1)

Table 2-2

Summary of Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
CDI Recurrence	Stratified Miettinen and Nurminen method [17] [†]	FAS [‡]	Last available stool records [§]
Secondary:			
Global Cure	Stratified Miettinen and Nurminen method [17] [†]	FAS [‡]	Last available stool records [§]
[†] Stratified by SOC therapy and hospitalization status. [‡] FAS = Full Analysis Set [§] See Section 3.5.5.1 for more details regarding missing data approaches (for example, how to treat patients lacking any post-randomization endpoint data subsequent to infusion of study medication)			

2.7.2 Safety Analyses

The All-Patients-as-Treated population will be employed for safety analyses. The analysis of safety results will follow a tiered approach (see Section 3.5.5.2 for further details). For this protocol, the broad clinical and laboratory adverse experience categories consisting of the percentage of patients with any adverse experience, a drug related adverse experience, a serious adverse experience, an adverse experience which is

Product: MK-3415A

24

Protocol/Amendment No.: 002-00

both drug-related and serious, and patients who discontinued due to an adverse experience will be considered Tier 1 endpoints. Infusion-specific reactions, as previously defined in Section 2.6, will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with Tier 1 and Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method.

2.7.3 Power and Sample Size

This study has a planned sample size of 1200 patients to be randomized in a 1:1:1 ratio to each of the three treatment groups (MK-6072, MK-3415A, and placebo). The following power calculations are based on a two group chi-square test for comparing independent proportions.

Primary Endpoint - CDI Recurrence

It is anticipated that 400 patients per group will be in the analysis population for the CDI recurrence endpoint. Comparisons between monoclonal antibody therapy groups and placebo will be performed in a sequential fashion (i.e. with MK-3415A vs. placebo tested first, and then MK-6072 tested vs. placebo). These tests will be performed at a 1-sided alpha level of 0.025. This will provide approximately 95% power to detect the following differences in the incidence of CDI recurrence between monoclonal antibody therapy, π_1 , and placebo, π_2 :

π_1	π_2	Difference	Power
.08	.163	.083	95%
.09	.176	.086	95%
.10	.189	.089	95%

Secondary Endpoint - Global Cure

It is anticipated that 400 patients per group will be in the analysis population for the global cure endpoint. Comparisons between monoclonal antibody therapy groups and placebo will be performed at a 1-sided alpha level of 0.025. This will provide approximately 90% power to detect a 10 percentage point difference in the proportion of patients achieving global cure (80% for monoclonal antibody therapy versus 70% for placebo).

Product: MK-3415A

25

Protocol/Amendment No.: 002-00*Secondary Endpoint - CDI Recurrence in Subset of Patients with Clinical Cure*

It is anticipated that 85 to 90% of all randomized patients, regardless of treatment group, will achieve a clinical cure of the initial CDI episode. The following power calculations are based on an anticipated 350 patients per treatment group in the subset of all randomized patients who achieve a clinical cure of the initial CDI episode. Comparisons between monoclonal antibody therapy groups and placebo will be performed at a 1-sided alpha level of 0.025. This will provide approximately 95% power to detect the following differences in the incidence of CDI recurrence between monoclonal antibody therapy, π_1 , and placebo, π_2 :

π_1	π_2	Difference	Power
.08	.172	.092	95%
.09	.185	.095	95%
.10	.197	.097	95%

Product: MK-3415A

1

Protocol/Amendment No.: 002-00

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 Rationale for This Study

Epidemiology and Pathophysiology of *C. difficile* Infection

C. difficile infections are caused by the proliferation of vegetative *C. difficile* cells from toxigenic strains in the gastrointestinal tract. The disease presentation is characterized by gross alteration of the gastrointestinal tract in the affected region, with evidence of pro-inflammatory processes (infiltration of pro-inflammatory effector cells). Lesions to the colon are usually caused by the expression of two potent toxins, produced late in the growth cycle of the organism: toxin A and/or toxin B. Toxin A is generally produced in larger quantities (3-4 fold greater) than toxin B in vitro [18] and has been shown to have direct toxic effects on the lining of the intestinal epithelium in a rabbit ileal-loop model. It has therefore often been referred to as an "enterotoxin." By contrast, toxin B is incapable of inducing permeability changes in the rabbit ileal loop model. Toxin B however is about 100-1,000 fold more toxic in cell culture compared to toxin A [19] and hence is called a "cytotoxin." The spectrum of illness caused by toxigenic *C. difficile* includes abdominal pain and mild diarrhea, a more profuse watery diarrhea and pseudomembranous colitis. The incidence of life-threatening *C. difficile* infection complications such as ileus, perforation, fulminant colitis, toxic megacolon, and death has been increasing in recent years [9, 7, 20].

Transmission of *C. difficile* occurs through fecal-oral route, typically after transient contamination of the healthcare environment or healthcare providers. Although *C. difficile* infection is thought to be mainly hospital-acquired, increasing numbers of community-acquired cases of *C. difficile* infection are being reported [21]. Risk factors for developing *C. difficile* infection fall into three categories: factors that disrupt the protective colonic microflora layer (antimicrobials, other medications, or procedures); increased exposure to *C. difficile* spores (hospital/facility environment, increased length of hospital stay, infected roommates or hand carriage through infected healthcare personnel); and host factors (advanced age, impaired immune status, co-morbid conditions) [22, 23].

The changing epidemiology of *C. difficile* infection has been characterized by a rise in the overall incidence, outbreaks of disease involving epidemic and hypervirulent strains of *C. difficile*, and an increasing risk of treatment failure and recurrent infection. The emergence of an epidemic strain of *C. difficile*, NAP1/BI/027, has been responsible for several notable outbreaks of disease in the U.S. and Canada [8, 12] as well as being problematic in Europe and Japan. These outbreaks have been associated with an increased risk of severity and mortality. The increased virulence of the NAP1/BI/027 strain might be due to increased secretion of toxin A and toxin B and/or increased toxicity of these toxin variants [18]. Adding to the virulence of the NAP1/BI/027 strain is its apparent enhanced sporulation capacity. Hypersporulation may give the strain an

Product: MK-3415A

2

Protocol/Amendment No.: 002-00

added survival advantage against commonly used disinfectants and increase the risk of transmission. More recently, a new emerging strain of *C. difficile*, PCR ribotype 078, has been implicated in community acquired cases of *C. difficile* infection in Europe [24].

The medical implications and cost of *C. difficile* infection are substantial. Patients with mild infection are likely to have prolonged hospital stays as are severely ill patients, whose probability of intensive care unit (ICU) admission, prolonged therapy, or surgery is even greater [25, 26, 27, 28, 29, 30, 31].

Current Treatment Options for *C. difficile* Infection

Historic therapeutic options for the treatment of *C. difficile* infection were limited to two antimicrobial agents, namely metronidazole and vancomycin. Metronidazole has been recommended as the first-line agent for non-severe cases of *C. difficile* infection as standard of care (perhaps to limit the use of vancomycin in hospital settings due to concerns about potential for selection of vancomycin resistance among nosocomial bacteria). Vancomycin is recommended as the first-line agent for severe *C. difficile* infection. Recently, fidaxomicin (a narrow spectrum macrocyclic antibiotic) has been approved for use in the United States by the FDA for the treatment of CDI.

While most cases of *C. difficile* infection resolve after withdrawal of the offending systemic antibiotic and treatment with either oral vancomycin, metronidazole, or fidaxomicin, 15-30% of patients will experience recurrent disease. Recurrence rates appear to be similar after treatment with metronidazole or vancomycin, and are at the lower end of this range following treatment with fidaxomicin [10, 4, 11, 44]. Risk factors for recurrent *C. difficile* infection include advanced age, severe disease, and additional systemic antibiotic use after initial *C. difficile* infection therapy [32, 7, 33, 34]. Patients with at least one episode of recurrent *C. difficile* infection have a 33-60% chance of experiencing further *C. difficile* infection recurrence [13]. Currently, there is no consistently effective treatment for recurrent *C. difficile* infection and the management of these patients often poses a difficult challenge.

Use of Monoclonal Antibodies Against Toxin A and B in *C. difficile* Infection

A new adjunctive approach to the treatment of *C. difficile* infection is the use of monoclonal antibodies directed against the exotoxins produced by *C. difficile* (toxin A and/or toxin B). Both animal and human studies indicate that antibodies directed against these toxins protect against disease and recurrence. Data from both a primary and relapse hamster disease model support the administration of monoclonal antibodies to toxin A (MK-3415) and antibodies to toxin B (MK-6072), with optimal protection in both models provided by the combination therapy (MK-3415A). Kyne and colleagues reported that patients who developed diarrhea after becoming colonized with *C. difficile* had significantly lower levels of serum anti-toxin A IgG at the time of colonization compared with subjects who remained asymptomatic [35]. The same authors reported that patients who developed low concentrations of serum anti-toxin A IgG during initial episodes of *C. difficile* infection were more likely to suffer prolonged and relapsing *C. difficile* infection

Product: MK-3415A

3

Protocol/Amendment No.: 002-00

than those who had higher concentrations of anti-toxin A antibody [36]. The results from a small Phase II study of monoclonal antibody to *C. difficile* toxin A (MK-3415) showed that treatment with MK-3415 did not reduce the rate of CDI recurrence during a 56-day follow-up period compared to placebo. Low anti-toxin A and low anti-toxin B neutralizing titers were each found to be significant predictors of CDI recurrence in this study [37].

Recent results from the Phase II clinical study of a single infusion of the combination of monoclonal antibodies directed against toxins A and B (the combination of the 2 monoclonal antibodies [MK-3415A]) demonstrated a significant difference ($p < 0.001$) in CDI recurrence between recipients of the monoclonal antibodies (7% [7/101]) and those who received placebo (25% [25/99]) [15]. Additional analyses indicated that treatment reduced the recurrence rates in the subpopulations of patients with CDI due to the epidemic BI/NAP1/027 strain and those with a prior history of CDI. In an exploratory analysis, fewer patients were newly hospitalized after infusion during the 12-Week study period in the monoclonal antibodies treatment group (9% vs. 20%). The safety of the combined antibody treatment was comparable to placebo. Eighteen (18) patients in the monoclonal antibodies treatment group and 28 patients in the placebo group reported at least one serious adverse event ($p = 0.09$) [15].

Please refer to the IB for a full assessment of the available preclinical and clinical data for this compound.

3.1.2 Rationale for Dose Regimen

Phase I data support that a 10 mg/kg dose of each monoclonal antibody (MK-3415 and MK-6072) will result in serum concentrations in humans which were commensurate with efficacy seen in preclinical hamster models. When 10 mg/kg of each monoclonal antibody was subsequently evaluated in Phase II (as MK-3415A), there was a robust effect in the reduction of CDI recurrence (~70% reduction compared to placebo) and no safety signals were identified [15]. Notably, there were several adverse experiences reported at a significantly higher rate in the placebo group. Therefore, the SPONSOR believes that 10 mg/kg of each monoclonal antibody (i.e., 10 mg/kg of monoclonal antibody against toxin A [MK-3415] and 10 mg/kg of monoclonal antibody against toxin B [MK-6072]) is an appropriate dosage to provide the proper benefit: risk ratio evaluation in this study.

Furthermore, results from the recent Phase I study (Protocol 005) suggest that the pharmacokinetics of MK-3415 and MK-6072 administered in a 250mL volume rather than 200 mL are broadly similar after 1-hour and 2-hour infusions. The 1-hour infusion was generally well tolerated and the safety profile was comparable to that of the 2-hour infusion; thereby supporting the reduction of infusion time from 2 hours to 1 hour. Thus, a 1-hour infusion of MK-6072 or MK-3415A (MK-3415 and MK-6072) is planned for this study.

Product: MK-3415A

4

Protocol/Amendment No.: 002-00

3.1.3 Rationale for Patient Population and Primary Endpoint

The selection of patient population and primary efficacy endpoint of CDI recurrence were based on the results of the Phase II study of MK-3415A [15]. In this Phase II study, 200 adult patients with CDI were randomized and treated with MK-3415A or placebo. Study assessments were made through Day 84 (± 10 days). The maximum study duration for all subjects was 94 days, except for the first 20 patients enrolled who had a subsequent visit on Day 168 (± 14 days) for an additional blood collection for immunogenicity analysis. CDI recurrence was defined as a new episode of diarrhea associated with a new positive stool test for toxigenic *C. difficile* after resolution of the initial CDI diarrheal episode and after discontinuation of SOC therapy [15].

In this Phase II study, the primary efficacy endpoint pertaining to the proportion of patients with CDI recurrence was significant favoring MK-3415A as compared to placebo at $p < 0.001$ (Intent-to-Treat [ITT]), as calculated by Fisher's exact test. There was no significant difference in the median number of days for resolution of the initial episode of CDI between both treatment groups. Post hoc exploratory analyses examined the effects of prior history of CDI episodes on the treatment effect for reduction in CDI recurrence. For patients with a prior history of CDI episode(s) at enrollment, the recurrence rate following treatment was statistically lower ($p = 0.006$) in the MK-3415A group (7% [2/29 subjects]) than in the placebo group (38% [12/32 subjects]) [15]. Most patients enrolled had no prior history of CDI, but of those who did they were distributed equally between treatment groups and the reduction in CDI recurrence was comparable whether or not the patient had prior CDI. As a result, the results of the Phase II study support administering MK-3415A to a broad population of patients with CDI [15].

CDI recurrence typically occurs within 8 to 10 weeks following an initial CDI episode. Therefore, the follow-up period of 12 weeks for this study was specifically chosen to ensure that CDI recurrences will not be missed, since several months can pass until a CDI recurrence occurs. In fact, in the recent Phase II study, 5 of 32 cases of CDI recurrence were seen in the Day 50 to Day 84 timeframe. Based on data from this Phase II study, the half life of MK-3415 is ~26 days and the half-life of MK-6072 is ~22 days, so the interval of follow-up was chosen with consideration of the half-lives of the monoclonal antibody products.

3.1.4 Rationale for 3-Arm Study Design

As summarized in Section 3.1.1, the results from a small Phase II study of monoclonal antibody to *C. difficile* toxin A (MK-3415) showed that treatment with MK-3415 did not reduce the rate of CDI recurrence during a 56-day follow-up period compared to placebo. However, results from the Phase II clinical study of a single infusion of the combination of monoclonal antibodies directed against toxins A and B (the combination of the 2 monoclonal antibodies hereafter referred to as MK-3415A) demonstrated a significant difference ($p \leq 0.001$) in CDI recurrence between recipients of the monoclonal antibodies (7% [7/101]) and those who received placebo (25% [25/99]) [15]. Importantly, there are

Product: MK-3415A

5

Protocol/Amendment No.: 002-00

currently no available clinical data assessing the efficacy of a monoclonal antibody to *C. difficile* toxin B (MK-6072).

Thus, the current study will only include treatment groups for which there are no available clinical data (MK-6072, monoclonal antibody to *C. difficile* toxin B) or for which there is already demonstrated efficacy (MK-3415A, combined monoclonal antibody to *C. difficile* toxin A and B). As a result, MK-3415 (monoclonal antibody to *C. difficile* toxin A) is not being evaluated alone in this protocol; however, this individual monoclonal antibody therapy will be further evaluated in a separate Phase III study (Protocol 001 [MODIFY I]). Taken together, the current study (Protocol 002 [MODIFY II]) and the separate Phase III study (Protocol 001 [MODIFY I]) should determine the optimal therapeutic approach to address the unmet medical need of the growing *C. difficile* epidemic.

3.1.5 Rationale for Biomarker Evaluations in This Study

In general, those at risk for CDI recurrence are the same individuals who are at risk for developing CDI at all. Although it is possible that a risk assessment score based on standard demographic and clinical factors (e.g., age, co-morbidities, inpatient status) might be helpful in assessing a patient's risk for CDI recurrence, the addition of laboratory biomarkers to a demographic/clinical prediction algorithm or as stand-alone classifiers may be of added value. Several assays will be employed to examine predictors of CDI recurrence in this study. Certain assays will be performed on blood and stool samples collected at study entry (Day 1) in all patients. In addition, more intensive analyses will be performed on blood samples collected at baseline (Day 1) in a subset of ~510 patients (~170 patients per treatment group). Finally, blood and stool samples will also be collected and analyzed for certain assays on an optional basis at various follow-up visits. Please refer to Appendix 6.6 for additional information.

3.1.6 Rationale for Future Biomedical Research

Merck will conduct Future Biomedical Research on specimens routinely and specifically collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), and/or the measurement of other analytes.

Such research is to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6.7: Collection and Management of Specimens for Future Biomedical Research.

Product: MK-3415A

6

Protocol/Amendment No.: 002-00

3.2 STUDY PROCEDURES

NOTE: See Section 3.5.3 for definition of study endpoints.

3.2.1 Concomitant Medication(s)/Treatment(s)

3.2.1.1 Standard of Care (SOC) Therapy for CDI

SOC therapy (oral vancomycin, oral metronidazole, intravenous metronidazole concurrently with oral vancomycin, oral fidaxomicin, or oral fidaxomicin concurrent with intravenous metronidazole) will be prescribed/administered by the attending physician. Investigators are encouraged to enroll patients and administer the infusion as soon as possible relative to the initiation of SOC therapy. SOC therapy can begin on the same day as the infusion, but the first dose of SOC therapy must have been administered prior to or within a few hours following the infusion.

Patients enrolled in this study should complete a minimum of 10 days and a maximum of 14 days of SOC therapy. Even if SOC therapy is switched, patients should still receive a minimum of 10 days and a maximum of 14 days of total SOC therapy (e.g., if metronidazole is given as the primary agent initially, but then switched to vancomycin, the duration of both therapies together would total no more than 14 days).

As noted above, switches in SOC therapy are allowed. After randomization, SOC therapy may only be switched if the patient has received at least 3 days of the current SOC therapy and meets at least one of the 3 following conditions: (1) **diarrhea**, (2) presence of ileus, or (3) a body temperature $>38.3^{\circ}\text{C}$ ($>100.9^{\circ}\text{F}$) and peripheral WBC count $>15,000$ cells/ mm^3 . Emergence of an adverse experience due to the inability of a patient to tolerate their current SOC therapy also warrants an SOC switch. Additionally, hospitalized patients receiving intravenous metronidazole concurrently with oral vancomycin or oral fidaxomicin may be switched to the respective oral SOC therapy alone (i.e., vancomycin or fidaxomicin) upon discharge. SOC therapy may be switched more than once if the above criteria are met on separate occasions.

The first through the last day of each SOC therapy will be recorded via the appropriate eCRF for instances when administered in the 14 days prior to infusion and through the duration of the study (i.e., Week 12). All changes in SOC therapy (including changes in dosages) should be recorded. The reason for any SOC therapy switch must be documented on the appropriate eCRF. Duration of all SOC therapy regimens will be calculated based on the dates provided.

NOTE: SOC medication will NOT be provided by the SPONSOR. Additionally, the defined agents, dosages and treatment durations for SOC medication are required for the treatment of the presenting/initial episode of CDI at the time the patient is randomized in the study. However, the choice of medication, the dosage, and the duration to treat a suspected or confirmed recurrence of CDI following the initial episode is at the discretion of the investigator.

Product: MK-3415A

7

Protocol/Amendment No.: 002-00**3.2.1.1.1 Metronidazole**

Metronidazole will be administered orally as 500 mg every 8 hours (3 times per day) or 400 mg every 8 hours (3 times a day) to achieve at least 1200 mg to 1500 mg in a 24 hour period [16].

Metronidazole may also be administered intravenously as 500 mg at least 3 times per day (i.e., every 8 hours) concurrently with oral vancomycin [16] or oral fidaxomicin.

Metronidazole may not be administered rectally.

3.2.1.1.2 Vancomycin

Vancomycin will be administered orally as 125 mg to 500 mg every 6 hours (4 times per day) [16].

Oral vancomycin may also be administered concurrently with intravenous metronidazole as noted above in Section 3.2.1.1.1 [16]. Oral vancomycin may not be administered concurrently with oral fidaxomicin and/or oral metronidazole.

Vancomycin may not be administered rectally or intravenously.

3.2.1.1.3 Fidaxomicin

Fidaxomicin will be administered orally as 200 mg twice daily.

Fidaxomicin may also be administered concurrently with intravenous metronidazole as noted above in Section 3.2.1.1.1. Fidaxomicin may not be administered concurrently with oral vancomycin and/or oral metronidazole.

Fidaxomicin may not be administered rectally or intravenously.

3.2.1.2 Other Prior/Concomitant Medication(s)/Treatment(s)

The concomitant use of other medication(s)/treatment(s) is allowed except as indicated in Sections 2.2 and 2.3. The following medications are excluded:

- Receipt of immune globulin within 6 months prior to receipt of the infusion or intended receipt of immune globulin prior to the completion of the 12-Week study period.
- Receipt of MK-3415 and/or MK-6072 in prior investigational trials.
- Receipt of cholestyramine, rifaximin, or nitazoxanide, within 14 days prior to receipt of infusion or at any time prior to the completion of the 12-Week study period. The patients must not take these medications during the 12-Week study period and it will result in a protocol violation if they do.
- Receipt of medications to control diarrhea or to decrease peristalsis, such as loperamide (ImodiumTM) or diphenoxylate hydrochloride/atropine sulfate

Product: MK-3415A

8

Protocol/Amendment No.: 002-00

(LomotilTM) at any time during the 14 days following infusion. Patients receiving opioid medications at the onset of diarrhea may be included if they are expected to be on stable doses of these medications, or there is anticipation of a dose decrease or cessation of their use.

- Receipt of the probiotic *Saccharomyces boulardii* at any time following infusion (Day 1) and through the completion of the 12-Week study period.
- Receipt of another investigational study agent within the previous 30 days or intended receipt of an investigational agent during the 12-Week study period.

All antibiotic therapies, including those used to treat CDI, all anti-diarrheal medications, and excluded medications/therapies (e.g., cholestyramine, *S.boulardii*, rifaximin, and nitazoxanide (see Section 3.2.1.1), should be recorded on the appropriate eCRF(s) for 14 days prior to infusion and for the full 12-Week study period.

All other medications administered 14 days prior to infusion and all other medications administered through Week 4 (Day 29 \pm 3 days) following the infusion should also be recorded on the appropriate eCRF(s).

3.2.2 Diet/ Activity/ Other

3.2.2.1 Diet

There are no dietary or activity restrictions for patients participating in this study.

3.2.2.2 Pregnancy and Contraception

For female patients of child-bearing potential, a urine pregnancy test will be performed at the study site within 48 hours prior to infusion. If the urine pregnancy test result is positive, the patient must be excluded from the study. Study eligibility criteria regarding pregnancy and contraception are provided in Section 2.2 and Section 3.4.4.

If a patient becomes pregnant while in this study, the treating physician should be informed immediately and the pregnancy reported immediately to the SPONSOR. All pregnancies must be followed to the completion/termination of the pregnancy and the outcome reported to the SPONSOR. The patient should continue the study follow-up if the infusion has already been administered (i.e., pregnancy occurs after Day 1 of the study). Continuation of SOC therapy is at the discretion of the investigator. The use of SOC therapy in these patients must be reported on the appropriate eCRF.

3.2.3 Procedures

Study procedures should be performed as close to the scheduled time as possible. See the Study Flow Chart in Section 1.7 for a complete listing of study procedures required at each visit for all patients.

Product: MK-3415A

9

Protocol/Amendment No.: 002-00

3.2.3.1 Informed Consent

A copy of the below-mentioned signed consent form(s) will be given to each patient for his/her records.

3.2.3.1.1 General Informed Consent

The investigator or their designee shall discuss with each patient the nature of the study and its requirements. To participate in the study, informed consent must be obtained from each potential patient prior to any study activities. The information on the consent form should be translated and communicated to the patient in the language that he/she can understand. The consent form and any subsequent revisions must be reviewed by the Institutional Review Board (IRB) or Ethical Review Committee (ERC) overseeing the study. This form will be used for the main study.

The procedures for the main study include receipt of infusion, completion of the stool count log, pre- and post-infusion ECG measurement, and the collection of several blood, urine, and stool samples at protocol-specified time points. These sample collections include blood for testing of antibodies to *C. difficile* toxin A and toxin B (endogenous and pharmacokinetic measurements), anti-drug antibody (ADA), neutralizing antibody (if positive ADA is detected), blood chemistry and hematology (as part of safety monitoring), and biomarkers (includes serum dehydroepiandrosterone [DHEA] level, and cytomegalovirus [CMV] IgG titer). A blood sample for mRNA profiling will be collected from all subjects on Day 1 and on an optional basis on Visits 2, 3, and 4 (Day 4, [\pm 1 day], Day 11 [\pm 2 days], and Week 4 [Day 29 \pm 3 days], respectively). Blood samples for a cytokine panel and immune profile assessments (flow cytometry of T-cell and B-cell subsets) will also be collected on Day 1 in approximately 170 subjects from each treatment arm. Samples also include urine for urinalysis (as part of safety monitoring) and stool for testing toxigenic *C. difficile*, as the causative agent of the patient's **diarrhea**, as well as anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing and antibacterial susceptibility testing of *C. difficile* isolates). Stool will also be collected for 16s rRNA PCR deep sequencing of gut flora in all patients at Day 1 and on an optional basis on Visits 2, 3, and 4 (Day 4, [\pm 1 day], Day 11 [\pm 2 days], and Week 4 [Day 29 \pm 3 days], respectively). Stool will also be collected pre-infusion on Day 1 in all subjects and on an optional basis at Visits 2, 3, and 4 (Day 4, [\pm 1 day], Day 11 [\pm 2 days], and Week 4 [Day 29 \pm 3 days], respectively) and an unscheduled visit(s) for new episodes of **diarrhea**, for measurement of MK-3415 and MK-6072. Providing consent allows for optional as well as non-optional samples to be obtained from all patients.

3.2.3.1.2 Informed Consent for Additional 9-Month Extended Follow-up

An extended follow-up period of 9 months will be conducted at designated study sites in a subset of ~300 patients who have completed the primary 12-Week study period. The purpose of this extended follow-up period through Month 12 is to assess for CDI recurrence, *C. difficile* carriage in stool, levels of endogenous anti-toxin A and anti-toxin

Product: MK-3415A 10

Protocol/Amendment No.: 002-00

B antibodies, pharmacokinetic assessment of MK-3415 and MK-6072, and presence of anti-drug antibodies (ADA).

Please refer to Section 1.8 and Section 3.2.3.8.4 for details on the procedures to be performed during this extension follow-up period.

Sites will need to be pre-approved by their IRB or ERC in order to enroll patients into this extension.

3.2.3.1.3 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

The following specimens are to be obtained as part of Future Biomedical Research:

- Blood for future use (DNA sample)
- Remaining RNA and stool samples from the main study stored for future use

3.2.3.2 Assignment of Baseline/Screening Number

The study staff will evaluate patients for study eligibility according to the inclusion/exclusion criteria described in Sections 2.2 and 2.3. To enroll in this study, patients must have a local positive stool test for toxigenic *C. difficile* using one of the methods listed in Appendix 6.1 and meet other specified baseline evaluation procedures described in Section 3.2.3.3.

After the consent form(s) is/are signed, each patient will receive a unique baseline/screening number, through the IVRS, for identification purposes during the study. This number identifies the patient for all study procedures that occur prior to randomization and cannot be reassigned for any reason. A patient can only be assigned one baseline/screening number.

3.2.3.3 Procedures Performed During the Pre-Infusion Phase

The eligibility of a patient will be assessed to ensure the patient satisfies the inclusion and exclusion criteria of the study. Once a baseline/screening number has been assigned, collection of biological samples, a medical history (including a review of the patient's history of each occurrence of CDI in the past 6 months, the patient's overall history of CDI, Horn's Index, and Charlson Index), review of prior and current medications, physical examination, and vital signs measurements will be performed, as outlined in the sections that follow. Results will be recorded on the appropriate eCRFs.

In addition, all patients will be given a card, after consent is provided and a baseline/screening number assigned, identifying them as participants in a research study.

Product: MK-3415A

11

Protocol/Amendment No.: 002-00

The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

3.2.3.3.1 General Medical History

In addition to the evaluation of a patient's medical history in terms of study eligibility, all medical conditions present during the 12 months prior to study entry will be documented on the appropriate eCRF.

Immunocompromised patients, including but not limited to patients with congenital or acquired immune deficiency, patients with neoplastic disease, or patients with depressed immunity (resulting from corticosteroid or other immunosuppressive therapy), are not excluded from participation in this study solely due to their immune status. These patients are still eligible for participation, provided all other inclusion/exclusion criteria (as outlined in Sections 2.2 and 2.3) are satisfied.

3.2.3.3.1.1 CDI History

Details of the current CDI episode (including documentation of the local stool test for toxigenic *C. difficile*, as per Appendix 6.1) should be documented separately on the appropriate eCRF. The investigator site personnel will also need to record on the appropriate eCRF the number of **loose stools** that satisfies the inclusion criterion for having **diarrhea** for a diagnosis of CDI. This number of **loose stools** should preferably be from the first day on which the number of loose stools meets the criteria for **diarrhea** as defined by the protocol.

All prior episodes of CDI which occurred in the past 6 months should be documented separately on the appropriate eCRF. Additionally, the overall number of episodes of CDI in the past 2 years and the patient's hospitalization status, treatment in the ICU, and endoscopic evidence of pseudomembranous colitis (if performed) relative to the presenting case of CDI, will be recorded on the appropriate eCRFs.

3.2.3.3.1.2 Horn's Index

A modified Horn's index [38, 39, 40] will be used to assess the severity of underlying disease in the patient. The investigator will assess and rank underlying disease severity using the Horn's index according to Appendix 6.3. This information will be recorded on the appropriate eCRF.

3.2.3.3.1.3 Charlson Index

The Charlson index [41] will be used by the investigator to assess comorbid conditions. The comorbid conditions to be assessed as part of the Charlson Index are listed in Appendix 6.4. In particular, liver and renal disease, if present, should be assessed for their severity as described in Appendix 6.4. This information will be recorded on the appropriate eCRF.

Product: MK-3415A

12

Protocol/Amendment No.: 002-00

3.2.3.3.2 Physical Examination

A physical examination should be performed within 72 hours prior to infusion. If a physical examination was otherwise performed within 72 hours prior to infusion, those results can be recorded and a new physical examination is not required. Any abnormal or clinically significant findings from the physical examinations should be recorded on the appropriate eCRF. See Section 3.2.3.8.1.4 for additional study visits when a physical examination should be performed during the 12-Week study period.

3.2.3.3.3 Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, body temperature (oral or oral equivalent), height, and weight, will be measured just prior to the infusion on Day 1. Results should be recorded on the appropriate eCRF. See Section 3.2.3.7.1 for collection of these vital signs just prior to infusion. The timing for collection of vital signs at other visits during the study is provided in Sections 3.2.3.7.5 and 3.2.3.8.1.3.

3.2.3.3.4 Stool Sample Collection

A positive result from the local stool test for toxigenic *C. difficile* obtained from a stool sample collected within 7 days prior to infusion (using a method listed in Appendix 6.1) is required for enrollment. Record the result of the local stool test for toxigenic *C. difficile* on the appropriate eCRF.

A stool sample for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing) must be collected and sent to a central laboratory. This is an absolute requirement for this study. This sample should be collected after informed consent is obtained and optimally before infusion. However, this stool sample may be collected up to within 72 hours after infusion.

In all patients, the pre-infusion (Day 1) stool sample will also undergo 16s rRNA PCR deep sequencing of gut flora and measurement of MK-3415 and MK-6072. These stool samples will also be sent to the designated central laboratory for testing.

Stool samples should not be collected by rectal swab pre-infusion. Appropriate infection control precautions and universal precautions should be observed for all specimen collection. Please refer to Section 3.2.3.8.2.1 for other protocol-specified time points. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

3.2.3.3.5 Blood and Urine Sample Collection

Blood samples (whole and serum) should be collected within 24 hours prior to infusion for safety laboratory assessment (includes hematology and chemistry panels, as per Appendix 6.5), endogenous antibody levels to *C. difficile* toxin A and toxin B, pharmacokinetics of MK-3415 and MK-6072, presence of ADA (including neutralizing antibody), DHEA levels, CMV IgG titer, and mRNA profiling. Blood samples will also

Product: MK-3415A

13

Protocol/Amendment No.: 002-00

be collected within 24 hours prior to infusion from approximately 170 subjects per treatment arm for a cytokine panel and immune profile assessment (flow cytometry of T-cell and B-cell subsets). All blood samples will be tested by designated central laboratories.

Visit 1 laboratory safety assessments are for baseline values only and results are not required for subject entry into the study.

For obtaining all blood samples, a relatively large vein such as the antecubital vein is preferred. Appropriate infection control precautions and universal precautions should be observed for all specimen collection.

A urine sample (for urinalysis as per Appendix 6.5) should be collected within 24 hours prior to infusion. Urine samples will be tested by a designated central laboratory.

Please refer to Section 3.2.3.8.2.2 for other protocol-specified time points for blood and urine collection. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

3.2.3.4 Stratification

Eligible patients who provide consent for study participation will be stratified according to their SOC therapy as prescribed by the attending physician (oral vancomycin [alone or concurrently with intravenous metronidazole] vs. oral metronidazole [alone] vs. oral fidaxomicin [alone or concurrently with intravenous metronidazole]) and their hospitalization status at the time of randomization (inpatient vs. outpatient).

The first stratification is based on SOC therapy as prescribed by the attending physician at the time of randomization and is comprised of the following categories: (1) oral vancomycin (which may be taken alone or concurrently with intravenous metronidazole, as described in Section 3.2.1.1.2) vs. oral metronidazole (alone, as described in Section 3.2.1.1.1) vs. oral fidaxomicin (which may be taken alone or concurrently with intravenous metronidazole, as described in Section 3.2.1.1.3). Patients receiving concurrent therapy of oral vancomycin and intravenous metronidazole should be entered into the vancomycin stratum. Patients receiving concurrent therapy of oral fidaxomicin and intravenous metronidazole should be entered into the fidaxomicin stratum. Although switches to SOC therapy following study enrollment are permitted as described in Section 3.2.1.1, patients will be randomized based on their SOC therapy at the time of randomization and will be subsequently analyzed using this stratification as described in the Statistical Analysis Plan (see Section 3.5.5.1).

In order to ensure diversification of SOC therapies as well as adequate study power, a minimum of 20% of the total patient population should be from the vancomycin stratum. The minimum proportion of patients entered into each stratum will be managed through a central randomization system. Enrollment into any stratum may be closed to manage these proportions.

Product: MK-3415A

14

Protocol/Amendment No.: 002-00

The second stratification is based on the current hospitalization status at the time of randomization. Patients will be stratified within each SOC therapy stratum based on inpatient or outpatient hospitalization status. Patients who are hospitalized or institutionalized (e.g., long-term care facility or rehabilitation center resident) should be entered into the inpatient stratum.

Patient stratification data will be selected by designated study personnel in the Interactive Voice Response System (IVRS).

3.2.3.5 Randomization/Allocation

Investigators are encouraged to enroll patients as soon as possible relative to the initiation of SOC therapy (including the same day as SOC therapy onset). Once a signed and dated consent form and the patient's medical history have been obtained, the inclusion and exclusion criteria have been met, and the biological samples have been collected, the patient will be assigned a randomization/allocation number via a centralized randomization system. Randomization will occur in a 1:1:1 ratio into 1 of the 3 treatment groups, as previously described.

The IVRS will automatically assign the patient a computer-generated randomization/allocation number provided to the IVRS vendor by the SPONSOR. Designated personnel will have access to the IVRS. The randomization/allocation number will never change and will be used to identify the patient for all procedures occurring after randomization.

A single patient cannot be assigned more than 1 allocation number.

3.2.3.6 Nonrandomized Patients

It is possible for a patient to provide written informed consent for study participation and be assigned a baseline/screening number, yet not be randomized to a study treatment group. In this event, the site staff must collect the following patient demographic and status information via eCRF:

- Visit date
- Demographics
- Adverse experiences (if the adverse experience caused the patient to be excluded from the study, or if the adverse experience occurred as a result of a protocol-specified intervention); and
- Disposition (primary reason for exclusion from the study)

3.2.3.7 Procedures Performed in Conjunction with Treatment Infusion (Day 1)

3.2.3.7.1 Vital Signs Pre-Infusion

As described in Section 3.2.3.3.3, each patient will have vital signs (body temperature [oral or oral equivalent], heart rate, respiratory rate, and blood pressure, height, and weight) measured pre-infusion on Day 1. Vital sign measurements are recommended to be performed just prior to the infusion. Vital sign measurements should be recorded on

Product: MK-3415A

15

Protocol/Amendment No.: 002-00

the appropriate eCRF. See Section 3.2.3.7.5 for vital sign measurements during and immediately following the completion of the infusion.

3.2.3.7.2 12-Lead Electrocardiogram Pre-Infusion

A 12-lead electrocardiogram (ECG) is required for all randomized patients. Baseline measurements should be taken just prior to infusion. A post-infusion ECG is also required to be conducted within 2 hours of the end of the infusion (see Section 3.2.3.7.8). It is recommended to leave all electrodes in place during the infusion as to reduce variability in the results of the post-infusion measurement. The results of the ECG should be recorded on the appropriate eCRF.

3.2.3.7.3 Dosage and Administration of Infusion

All monoclonal antibody preparations (i.e., MK-6072 or MK-3415A) and placebo will be administered as a single 250 mL intravenous infusion in 0.9% sodium chloride through a sterile 0.22 micron filter using a volumetric pump over approximately a 1-hour period on Day 1. The monoclonal antibody infusion should be prepared shortly before administration, whenever possible. Following dilution into the saline IV bag, both MK-3415 and MK-6072 are stable under ambient light conditions for 24 hours at room temperature prior to infusion (see the Investigator Brochure for information about infusion stability). The total infusion volume for all patients, regardless of dose administered or treatment arm (i.e., whether receiving placebo, one monoclonal antibody therapy [MK-6072] or both monoclonal antibodies [MK-3415A]) is to be 250mL. However, if the patient's underlying medical condition warrants caution in the administration of IV fluids (e.g., congestive heart failure [CHF]), the investigator may request the Unblinded Pharmacist to reduce the total infusion volume to 200 mL in an effort to decrease the risk of fluid overload. In this case, the dose of each monoclonal antibody would remain unchanged for patients receiving active treatment. The monoclonal antibodies and placebo are prepared as listed in Table 3-1.

Table 3-1

Clinical Supplies Dose and Volume

Product	Dosage	Volume [†]
MK-6072 (toxin B antibody)	10 mg MK-6072/kg of patient weight	Single infusion of 250 mL
MK-3415A (toxin A antibody and toxin B antibody)	10 mg MK-3415/kg of patient weight and 10 mg MK-6072/kg of patient weight	Single infusion of 250 mL
Placebo	0.9% sodium chloride	Single infusion of 250 mL
[†] The investigator may request the Unblinded Pharmacist to reduce the total infusion volume to 200 mL. The dose of each monoclonal antibody would remain unchanged.		

Product: MK-3415A

16

Protocol/Amendment No.: 002-00

It is important to record the details of the infusion, including start and stop times and date, on the appropriate eCRF. If a patient does not receive the entire infusion, it is still important to record the volume administered and reason the infusion was stopped. All patients must be on SOC therapy at the time of the infusion or SOC therapy should be scheduled to begin within a few hours following the infusion.

3.2.3.7.4 Unblinded Preparation of Infusion (Unblinded Pharmacist)

An Unblinded Pharmacist will be responsible to prepare and account for the monoclonal antibodies (MK-6072 or MK-3415A) and placebo following guidelines provided in the Pharmacy Binder. The Unblinded Pharmacist will know the treatment group assignments and calculate the amount of each monoclonal antibody (10 mg/kg per patient weight in kilograms) to add to a single bag of 0.9% sodium chloride to comprise a total infusion volume of 250 mL. Placebo will also be prepared by the Unblinded Pharmacist as a single 250 mL bag of 0.9% sodium chloride for administration. MK-3415A and MK-6072 should not be mixed or co-infused with other medications, as there are no data available on the compatibility of these monoclonal antibodies with other intravenous substances, additives, or medications. Additional details regarding clinical supplies storage, handling, and accountability can be found in Section 3.6 and the Pharmacy Binder provided by the SPONSOR.

The Unblinded Pharmacist will not be involved in any evaluations of the patient. All study personnel involved with the patient eligibility and evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must not have access to the treatment group assignment or the preparation of the infusion.

Due to slight differences in appearance between monoclonal antibody (MK-6072 or MK-3415A) and placebo, infusion bags will be covered in an opaque sleeve by the Unblinded Pharmacist to ensure that other study personnel and all patients remain blinded to clinical material assignment. The intravenous line (through which the infusion is administered) does not require opaque covering as the differences between the clinical materials are not visually distinguishable within the tubing.

3.2.3.7.5 Vital Signs During and Immediately Post-Infusion

Patients will be evaluated during the infusion for vital signs (body temperature [oral or oral equivalent], heart rate, respiratory rate, and blood pressure) at 30 minutes after the start of the infusion and at the end of the infusion. These results should be recorded on the appropriate eCRF.

For vital signs measured during the infusion, study personnel should indicate whether or not a change over time or an individual result is clinically significant and constitutes an adverse experience by reporting the event on the appropriate eCRF.

See Section 3.2.3.8.1.3 for additional vital signs measurements during the 12-Week study period.

Product: MK-3415A

17

Protocol/Amendment No.: 002-00**3.2.3.7.6 Infusion Reactions During and Post-Infusion**

Monoclonal antibodies have been known to cause infusion reactions. In some cases, these reactions are severe and rarely have fatal outcome. Severe reactions may be characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension or angioedema and may require immediate interruption of infusion. Hypersensitivity reactions (non-IgE mediated reactions) have also been observed upon treatment with monoclonal antibodies and may respond to adjustments in the infusion rate and medical management. Please refer to IB for a full assessment of the available clinical data for this compound.

Patients who experience infusion or hypersensitivity reactions in conjunction with the infusion of study drug should receive appropriate supportive care measures as deemed necessary by the treating physician, including but not limited to the items outlined in Table 3-2. Patients should be carefully observed until complete resolution of all signs and symptoms, if a reaction occurs. Report any adverse experiences according to the guidelines in Section 3.4.

Product: MK-3415A

18

Protocol/Amendment No.: 002-00

Table 3-2

Guidance on Infusion and Hypersensitivity Reactions

Symptoms During Infusion	Recommended Treatment
Grade 1 or Mild Symptoms: Mild reactions, such as: <ul style="list-style-type: none"> • Pruritus without rash • Transient bronchospasm (70-80% FEV1 of peak flow) • Nausea • Mild, persistent headache 	<ul style="list-style-type: none"> • Decrease rate of infusion until recovery from symptoms - infusion interruption not indicated • Consider antihistamine (i.e., 50 mg diphenhydramine PO) • Monitor patient until deemed medically stable in the opinion of the investigator • Complete infusion at initial planned rate
Grade 2 or Moderate Symptoms: Moderate reactions such as: <ul style="list-style-type: none"> • Localized urticaria • Rash • Flushing • Acute bronchospasm that requires treatment and normalizes to FEV1 50%-70% of peak flow • Hypotension with systolic BP ↓ by > 20 mmHg • Hypertension, recurrent, chronic ↑ >20 mmHg • Fever >38.5°C - ≤39.5°C 	<ul style="list-style-type: none"> • Interrupt infusion • Antihistamine recommended (i.e., 50 mg diphenhydramine IM or IV) • Monitor patient until resolution of symptoms • For bronchospasm, consider a beta-2-adrenergic agonist via inhaler or nebulizer. Consider giving corticosteroids • For hypotension, consider oral fluids • Treat hypertension • Treat other conditions as medically appropriate • Resume infusion after recovery of symptoms. Consider resuming at ½ initial infusion rate, then increase incrementally to the initial infusion rate • If symptoms develop after resumption, permanently discontinue infusion
Grade 3 or 4 or Severe Symptoms: Grade 3 is defined as: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4 is defined as: Life-threatening; pressor or ventilatory support indicated Severe reactions may include: <ul style="list-style-type: none"> • Acute bronchospasm that doesn't normalize with bronchodilator (FEV1 25%-50% of peak flow) • New onset dyspnea at rest • Generalized urticaria • Angioedema • Headache requiring narcotic treatment • Hypotension that requires new or change in IV fluid management • New onset fever >39.5°C 	<ul style="list-style-type: none"> • Permanently discontinue infusion • Consider bronchodilators and supplemental oxygen • Consider epinephrine up to 1 mg IV or SQ • Consider 50 mg diphenhydramine IV with solumedrol 125mg IV • Give anti-pyretic as needed • Monitor until comfortable that symptoms will not recur <p>Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine <p>Hospitalization may be indicated</p>
Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration Grading of reactions based on Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (November 2007, draft) [42]	

3.2.3.7.7 Blood Sample Post-Infusion

A blood sample for pharmacokinetic evaluation of MK-3415 and MK-6072 will be drawn within 2 hours after the infusion is completed or stopped (i.e., in the event the entire volume cannot be delivered). Serum will be separated in blood samples and then sent to the central laboratory for testing. Additional information will be provided by the

Product: MK-3415A

19

Protocol/Amendment No.: 002-00

SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

3.2.3.7.8 12-Lead Electrocardiogram Post-Infusion

The post-infusion ECG is required to be performed within 2 hours of the end of the infusion (See Section 3.2.3.7.2 for pre-infusion ECG details). The results of the ECG should be recorded on the appropriate eCRF.

3.2.3.8 Procedures Performed Post-Infusion (Day 1 through Week 12)

3.2.3.8.1 Clinical Follow-up

In all patients, study visits will occur in person on Day 1, Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days). At each visit, the stool count log should be reviewed by study personnel to monitor compliance and accuracy in completion. Additionally, the occurrence of all adverse experiences (serious and non-serious) and the use of all concomitant medications will be assessed during scheduled study visits through Week 4. Furthermore, the occurrence of serious adverse experiences and the use of all antibiotics, including those used to treat CDI, all anti-diarrheal medications and excluded medications/therapies will continue to be assessed during scheduled study visits from Week 4 through Week 12.

If there is a new episode of **diarrhea** during the 12-Week study period, please refer to Section 3.2.3.8.3 for procedures.

Full details regarding study procedures are included in the Study Flow Chart (Section 1.7).

3.2.3.8.1.1 Loose Stool Counts and Body Temperature

All patients will receive a stool count log to record their daily loose stool output (Day 1 through Week 12 [Day 85 ± 5 days]) and daily body temperature (Day 1 through Day 14). The stool count log is recommended to be filled out nightly (at approximately the same time each day) based on the patient's recollection of their daily **loose stool** (Type 5 through Type 7 on the Bristol Stool Chart, as outlined in Appendix 6.2) activity for the past 24 hours. However, the Day 1 recording for **loose stool** should identify all **loose stools** from the time the infusion was initiated.

The stool count should be completed daily through Week 12 (Day 85 ± 5 days). In the event that a patient is unable to complete the stool count log for any reason, a designee (such as healthcare provider, caretaker, nurse, family member or friend) is permitted to aid the patient in filling out the log.

All patients will record their body temperature on Day 1 through Day 14. Oral thermometers will be provided by the SPONSOR. Otic temperatures are acceptable if measured by a medical professional in the setting of an inpatient (i.e. hospital, long-term care facility). Patients (or designee) should take their temperature at approximately the

Product: MK-3415A

20

Protocol/Amendment No.: 002-00

same time each evening. Temperatures should not be taken after the ingestion of hot food or liquids, after smoking, after exercise, or after a hot bath/shower.

If a patient has lost or misplaced his/her stool count log and/or thermometer, the patient should contact study personnel to obtain a replacement.

3.2.3.8.1.2 Phone/Visit Contact to Assess and Record Loose Stool Counts and Body Temperature

Study personnel will have contact by phone or in person with each patient daily to obtain the **loose stool** counts for the first 14 days of the study. Phone calls will be made 2 times per week to obtain **loose stool** counts during Week 3 through Week 12 to ensure completion of the stool count log and to determine if there is a new episode of **diarrhea**.

Patients should be instructed to contact study personnel immediately if they experience **any loose stools** after their initial **diarrhea** resolves (i.e., new **diarrhea**) or if they have any questions about the study or stool count log. Study staff should be the primary contact for the patient if there is a new episode of **diarrhea**. Please refer to Section 3.2.3.8.3 for procedures to be performed if there is a new episode of **diarrhea**.

3.2.3.8.1.3 Vital Signs

Vital signs (heart rate, blood pressure, respiratory rate, and body temperature) will also be assessed at scheduled visits during the clinical follow-up period: Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days).

Body temperature (oral or oral equivalent), heart rate, blood pressure, and respiratory rate will also be measured each time there is a new episode of **diarrhea** (during an unscheduled visit), as described in Section 3.2.3.8.3.

3.2.3.8.1.4 Physical Examination

A physical examination will be performed at the scheduled visits at Day 11 (± 2 days) and Week 12 (Day 85 ± 5 days). In addition, a physical examination should be performed each time there is an unscheduled visit for a new episode of **diarrhea**, as described in Section 3.2.3.8.3.

3.2.3.8.2 Laboratory Follow-up

Stool Samples

A subset of patients will provide stool samples for 16s rRNA PCR deep sequencing of gut flora at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days). These samples will be used for analysis, as described in Appendix 6.6.

A subset of patients will also provide stool samples for detection of MK-3415 and MK-6072 at Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), and at an unscheduled visit at the time of a new episode of **diarrhea** (see Section 3.2.3.8.3). These

Product: MK-3415A

21

Protocol/Amendment No.: 002-00

stool samples are intended to assess mechanism of action. Additional information can be found in Section 3.3 regarding the assay.

All samples will be sent to the designated central laboratory for testing. Study personnel are required to collect, store, and ship stool samples in accordance with the procedures provided by the SPONSOR in the Laboratory Manual.

3.2.3.8.2.1 Blood and Urine Samples

After Day 1, blood and urine samples will be collected for safety measurements, including a blood hematology panel, a blood chemistry panel, and urinalysis at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days) according to the Study Flow Chart (Section 1.7). The specific laboratory safety measurements are outlined in Appendix 6.5. In addition, at an unscheduled visit for a new episode of diarrhea, blood samples will be collected for a limited panel of safety measurements, as described in Appendix 6.5.

Blood samples will be collected for assessment of endogenous antibody levels to *C. difficile* toxin A and toxin B at Week 4 (Day 29 ± 3 days) and Week 12 (Day 85 ± 5 days), as described in the Study Flow Chart (Section 1.7).

Blood samples will be collected for assessment of pharmacokinetics of MK-3415 and MK-6072 at Day 4 (± 1 day), Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days), as described in the Study Flow Chart (Section 1.7).

Additionally, blood samples will be tested for ADA (including neutralizing antibody) at Day 11 (± 2 days), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 7 days), and Week 12 (Day 85 ± 5 days) as described in the Study Flow Chart (Section 1.7).

A subset of patients will provide additional blood samples at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days) for mRNA profiling. These samples will be used for analysis, as described in Appendix 6.6

Additionally, for patients consenting to samples for optional future biomedical research, there will be blood drawn at Day 4 (± 1 day) for SNP genotyping.

All samples will be sent to designated central laboratories for testing. Additional information can be found in Section 3.3 regarding specific assays. Study personnel are required to collect, store, and ship blood samples in accordance with the procedures provided by the SPONSOR in the Laboratory Manual.

3.2.3.8.3 New Episode of Diarrhea/ Unscheduled Visit

If **diarrhea** resolves (defined as ≤ 2 **loose stools** per day for at least 2 consecutive days) and subsequently begins again (3 or more **loose stools** in 24 or fewer hours) this will represent a new episode of **diarrhea**. If there is a new episode of **diarrhea** at any time during the 12-Week study period (or during the additional 9-Month extended follow-up

Product: MK-3415A

22

Protocol/Amendment No.: 002-00

period for those patients who participate in this extended follow-up period), an unscheduled visit should be conducted. It is important that a stool sample is provided for any new episode of **diarrhea** which occurs, so a stool test for toxigenic *C. difficile* can be performed for diagnosis of a possible CDI recurrence. At the time there is a new episode of **diarrhea**, a stool sample should first be tested locally by a method listed in Appendix 6.1. Preferably, the stool test for toxigenic *C. difficile* during the follow-up period will be the same method as used at study entry. It is critical to record the result of the local stool test for toxigenic *C. difficile* on the appropriate eCRF. **In addition, a stool sample must also be sent to the designated central laboratory for anaerobic culture and other ancillary microbiological assessments (microbial identification, toxigenic strain typing, and antibacterial susceptibility testing; see Sections 1.7 and 1.8).** Additionally, during the initial 12-Week study period, an optional stool sample will be collected and sent to the designated central laboratory for detection of MK-3415 and MK-6072 (see Section 1.7) for the Biomarker analysis.

Stool samples should not be collected by rectal swab throughout the 12-Week initial study period or during the additional 9-month extended follow-up period when there is a new episode of **diarrhea**. Rectal swab may be utilized for collection of stool samples only at the predefined study visits in the additional 9-month extended follow-up period (Months 6, 9, and 12) to assess for *C. difficile* carriage if **diarrhea** is not present. Appropriate infection control precautions and universal precautions should be observed for all specimen collection. Patients will receive stool collection, storage, and transport kits in the event a stool sample needs to be collected at home. Stool samples collected at home should be stored as directed using the materials provided until the sample can be returned to the study site. Importantly, directions will be provided by the SPONSOR on how to properly collect and transport the stool sample in order to minimize contamination and protect the heat-sensitive toxin.

At the Unscheduled visit, blood samples will be collected to test for endogenous anti-toxin A and anti-toxin B levels and a limited panel of safety laboratory tests will be performed. These limited safety tests are outlined in Appendix 6.5.

In addition, at each Unscheduled visit during the 12-Week study period, the patient's vital signs (body temperature, blood pressure, heart rate, and respiration rate) should be collected and a physical assessment should be performed. Adverse experiences will be recorded if the unscheduled visit occurs up to Week 4 of the study. See Section 3.4 for details on reporting adverse experiences. Results should be recorded on the appropriate eCRF.

3.2.3.8.4 Procedures During the Additional 9-Month Extended Follow-up (Through Month 12)

An extended follow-up period of 9 months will be conducted in a subset of ~300 patients at designated study sites who have completed the 12 -Week study period.

To participate in the extended follow-up, informed consent must be obtained from each potential patient prior to any study extended follow-up activities.

Product: MK-3415A

23

Protocol/Amendment No.: 002-00

3.2.3.8.4.1 Randomization/ Allocation into Additional 9-Month Extended Follow-up

Patients who continue in the additional 9-month extended follow-up period of this study will retain the randomization/allocation number that was assigned upon randomization into the main study. No new study identifiers will be assigned.

3.2.3.8.4.2 Assessment of CDI recurrence in the Additional 9-Month Extended Follow-up

If during the extended follow-up period (after Week 12 through Month 12), a patient experiences **diarrhea**, the same procedures should be followed for a new episode of **diarrhea** (see Section 3.2.3.8.3). The study staff should review with the patient the number of **loose stools** per day from the day there is a new episode of **diarrhea** each day until **diarrhea** resolves. The number of **loose stools** and date should be collected.

Patients will also be contacted monthly by phone by study personnel through Month 12 to assess for a new episode of **diarrhea**. Scheduled study visits will occur once every 3 months (i.e. Month 6, Month 9, Month 12 following the infusion [or 3, 6, and 9 months following the completion of the initial 12 -Week study period]). Scheduled visits for these particular months can take the place of the phone call.

3.2.3.8.4.3 Stool Sample Collection During the Additional 9-Month Extended Follow-up

Stool samples will be collected routinely at Month 6, Month 9, and Month 12 visits according to the Study Flow Chart (Section 1.8) to assess for carriage of *C. difficile*. These samples will be evaluated for anaerobic stool culture and other ancillary microbiological assessments [microbial identification, toxigenic strain typing, and antibacterial susceptibility testing of *C. difficile* isolates]. Rectal swab may be utilized for collection of these stool samples unless **diarrhea** is present on the day of the visit. These samples will be shipped to the designated central laboratory for the required testing.

Throughout the extended follow-up period, patients will be provided stool collection and transport kits to be used in the event there is a new episode of **diarrhea**. It is important that a stool sample is provided for any new episode of **diarrhea** for testing by the local laboratory (using one of the methods listed in Appendix 6.1) and for testing by the central laboratory. Please refer to Section 3.2.3.8.3 for further instructions regarding new episodes of **diarrhea**.

3.2.3.8.4.4 Blood Sample Collection During the Additional 9-Month Extended Follow-up

Blood samples will be collected routinely at the Month 6, Month 9, and Month 12 visits according to the Study Flow Chart (Section 1.8). A blood sample will also be collected if an unscheduled visit occurs due to a new episode of **diarrhea** (see Section 3.2.3.8.3).

Product: MK-3415A

24

Protocol/Amendment No.: 002-00

These samples will be tested for endogenous anti-toxin A and anti-toxin B levels (at all time points), pharmacokinetic assessment of MK-3415 and MK-6072 levels (at Month 6 and at the time of a new episode of **diarrhea** at an Unscheduled visit[s]), and ADA levels (including neutralizing antibody, at Month 6).

Serum will be separated from blood samples and sent to the central laboratory for testing. Study personnel are required to collect, store, and ship blood samples in accordance with the procedures provided by the SPONSOR in the Laboratory Manual.

3.2.3.9 Blinding/Unblinding

This is a double-blind study (operating under in-house blinding procedures) in which the patient enrolled, the study investigator, study center personnel, and the SPONSOR will be blinded to which clinical material is received until all patients have completed the study, the data have been screened for completeness and accuracy, and protocol violators have been identified. There will be an Unblinded Pharmacist at each study center who will prepare and account for the infusion bags of monoclonal antibodies (MK-6072 or MK-3415A) and placebo according to guidelines provided in the Pharmacy Binder. The Unblinded Pharmacist will not be involved in any evaluations for the patient. All study personnel involved with patient eligibility and the post-infusion evaluations of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must not have access to the treatment group assignment or the preparation of the infusion. Due to slight differences in appearance between monoclonal antibodies (MK-6072 or MK-3415A) and placebo, infusion bags will be covered in an opaque sleeve by the Unblinded Pharmacist to ensure that other study personnel and all patients remain blinded to clinical material assignment. The intravenous line (through which the infusion is administered) does not require opaque covering as the differences between the clinical materials are not visually distinguishable within the tubing.

Study blinding is employed to ensure the integrity of the data being collected. However, the safety of the patients participating in the study must not be compromised. In the case of a medical emergency, which necessitates the unblinding of a patient's treatment group, the investigator will be able to access the IVRS to determine the patient's treatment group assignment. The IVRS unmasking feature is intended to be used only in situations that require emergency unblinding of the patient (e.g., knowledge of the exact treatment group administered to the patient is necessary for treatment of a serious adverse experience). A specific SPONSOR representative will also have the ability to determine a patient's treatment group assignment in the event the investigator is unable to do so. If any patient is unblinded prior to the completion of the study (either accidental unblinding or emergency unblinding for a serious adverse experience), the investigator must promptly contact the appropriate SPONSOR representative to document the circumstances on the appropriate eCRF.

Importantly, every effort should be made to contact the appropriate designated SPONSOR personnel prior to performing an emergency unblinding of any patient. Please refer to Section 3.6.5 for more information.

Product: MK-3415A

25

Protocol/Amendment No.: 002-00**3.2.3.10 Discontinuation/Withdrawal from Study**

Patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 3.4 SAFETY MEASUREMENTS - DETAILS.

3.2.3.11 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox Redacted and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

Product: MK-3415A

26

Protocol/Amendment No.: 002-00

3.3 EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS

3.3.1 Clinical Measurements for Efficacy (Assessment of Primary, Secondary, and Exploratory Efficacy Endpoints)

NOTE: See Section 3.5.3 for definition of study endpoints.

Primary Efficacy Endpoint (CDI Recurrence)

The primary endpoint is the proportion of patients with CDI recurrence. The definition of CDI recurrence requires specific criteria be met from the measurement of 3 clinical variables. Those variables are: (1) **diarrhea**, (2) stool test for toxigenic *C. difficile*, and (3) the type and duration of SOC therapy. **Diarrhea** is defined as 3 or more **loose stools** in 24 or fewer hours [16]. **Loose stools** in this study are defined as Type 5, Type 6 and/or Type 7 as described by the Bristol Stool Chart (see Appendix 6.2). The daily count of **loose stools** will be recorded by the patient (or designee) in the stool count log following the infusion through Week 12 (Day 85 ± 5 days). Study personnel will review the **loose stool** counts with patients per the Study Flowchart in Section 1.7 in order to identify a new episode of **diarrhea**. Daily **loose stool** counts will be entered by study personnel in the appropriate eCRF. All new episodes of **diarrhea** will be tested for toxigenic *C. difficile* (see Section 3.2.3.8.3) to confirm *C. difficile* as the causative agent of the patients' **diarrhea**. Stool samples will be tested by local laboratories using an assay as listed in Appendix 6.1 and the results of the local stool test for toxigenic *C. difficile* will be recorded on the appropriate eCRF. The stool sample will also be tested by the central laboratory for anaerobic culture and other ancillary microbiological assessments (including microbial identification and toxigenic strain typing). The type and duration of all SOC therapy will be recorded in the appropriate eCRF as well as the reason for any change in SOC therapy.

Secondary Efficacy Endpoints

To assess the various secondary efficacy objectives, the same 3 clinical variables will be measured as planned for the primary efficacy endpoint: (1) **diarrhea** (via **loose stool** counts through Week 12 [Day 85 ± 5 days]), (2) stool test for toxigenic *C. difficile*, and (3) the type and duration of SOC therapy.

The evaluation of CDI recurrence in certain subgroups includes:

- Patients with or without a prior CDI history in the 6 months prior to enrollment will be assessed based on the information obtained in the eCRF.
- Patients with or without an epidemic *C. difficile* strain (e.g., BI/NAP1/027, 001, 078, and 106) will be assessed by stool evaluation at the central laboratory, including toxigenic strain typing. Toxigenic strain typing is a common method utilized for the identification of epidemic strains of *C. difficile*.

Product: MK-3415A

27

Protocol/Amendment No.: 002-00

- Patients with or without **clinically severe CDI at study entry**. **Clinically severe CDI** is defined as **diarrhea** and a score of ≥ 2 points based on the presence of 1 or more of the following:
 - >60 years old (1 point);
 - Body temperature $>38.3^{\circ}\text{C}$ ($>100.9^{\circ}\text{F}$) (1 point);
 - Albumin level <2.5 mg/dL (1 point);
 - Peripheral WBC count $>15,000$ cells/mm³ within 48 hours (1 point);
 - Endoscopic evidence of pseudomembranous colitis (2 points);
 - Treatment in ICU (2 points)

This severity grading is based on data from Zar, et. al. [11]. The information for this assessment will be obtained from what is recorded in the eCRF. Given an absence of validated scales, the Zar scale was selected based on its previous use in a clinical trial. Should an alternative scale (for defining **clinically severe CDI**) be validated and become a standard after the clinical trial has begun, it may be used in addition to or in lieu of the Zar scale. The use of an alternate scale would be determined *a priori* prior to any of the final analyses.

- Patient age (< 65 years of age or ≥ 65 years of age) will be assessed based on the information obtained in the eCRF.
- Patients with or without compromised immunity at study entry will be assessed based on information obtained in the eCRF. For this study, compromised immunity will be defined as the following: an active hematological malignancy (including leukemia, lymphoma, multiple myeloma), an active malignancy requiring recent cytotoxic chemotherapy, receipt of a prior hematopoietic stem cell transplant, receipt of a prior solid organ transplant, asplenia, or neutropenia/pancytopenia due to other conditions.

Exploratory Efficacy Endpoints

To assess the exploratory objective for the proportion of patients with clinical cure, 2 clinical variables will be measured: (1) **diarrhea** (via **loose stool** counts through Week 12 [Day 85 \pm 5 days]) and (2) the type and duration of SOC therapy. The remaining exploratory objectives will be measured by assessment of the number of **loose stools** per day that are recorded via stool log through Week 12 (Day 85 \pm 5 days) following the infusion.

Blood samples drawn on Days 1, 4, and 11 will undergo routine hematological assessment. The results of the WBC will be the basis for comparison of those with a WBC $> 10,000$ cells/mm³ at baseline and $\leq 10,000$ cells/mm³ by Day 4 (or Day 11).

Daily body temperature measurements will be recorded on the patient stool log from Day 1 to Day 14. The daily body temperature measurements will be the basis for comparison

Product: MK-3415A

28

Protocol/Amendment No.: 002-00

of those with an elevated temperature ($\geq 101.0^{\circ}\text{F}$ [38.4°C]) at baseline and resolution of this elevated temperature ($< 101.0^{\circ}\text{F}$ [38.4°C]) by Day 4 (or by Day 11).

3.3.2 Immunologic and Bacteriologic Measurements

3.3.2.1 Toxigenic *C. difficile* Testing in Stool Specimens (Local Assays Specified in Appendix 6.1)

The rapid immunoassays and diagnostic PCR assays included in Appendix 6.1 are commercially available. Assays likely to produce false positives and assays that detect the presence of toxin A only have been excluded. A positive result from one of these assays, from a sample collected within 7 days prior to infusion, is required for enrollment. If a patient experiences a new episode of **diarrhea**, the patient will be instructed to provide a stool sample to test for toxigenic *C. difficile* by one of the methods listed in Appendix 6.1. See Section 3.2.3.8.3 for additional details when a new episode of **diarrhea** occurs.

3.3.2.2 Anaerobic Stool Culture

Anaerobic stool culture will be performed at a designated central laboratory. Anaerobic stool culture will be used to isolate *C. difficile* from stool specimens collected at Visit 1 and at the time of a new episode of **diarrhea**.

The stools are thawed inside an anaerobic chamber. Approximately 0.25 mL of stool is mixed with ethanol. After about 10-20 minutes the sample is plated on CCFA-HT selective medium for *C. difficile* and incubated for 48 hours. If typical colonies are present, they are purified by plating on Brucella blood agar, Gram-stained, and identification is confirmed with a proline disk test. For stocking, cell paste is inoculated into vials containing 20% sterile skim milk and frozen at -70°C .

3.3.2.2.1 Toxigenic Strain Typing

Following anaerobic culture growth at the central laboratory, the *C. difficile* strain will be typed by both restriction endonuclease analysis (REA) and PCR ribotyping in order to determine the relationship, if any, between treatment outcome and strain type.

The HindIII REA typing system is a rapid, efficient, and highly sensitive typing method of DNA extraction which uses HindIII as the restriction enzyme. REA grouping will be able to determine the toxin classification of the isolates, including toxin variant types.

PCR Ribotyping is an easy, rapid, and reproducible method based on polymorphism in the 16S-23S intergenic spacer region of the RNA gene of *C. difficile*. PCR is used to amplify the gene sequence and the samples electrophoresed in agarose gel. Band separation patterns are used to identify serogroups and subgroups of *C. difficile* including toxin variant types. As an alternate genotypic method of typing *C. difficile*, the results of PCR ribotyping can be complementary to REA strain typing and assure the strain identity of the isolate.

Product: MK-3415A

29

Protocol/Amendment No.: 002-00

Following REA and/or PCR Ribotyping analysis, gene amplification for binary toxin may be performed for selective isolates.

3.3.2.2.2 Antibacterial Susceptibility Testing

Following anaerobic culture growth at the central laboratory, antibacterial susceptibility testing will be performed on all *C. difficile* isolates following CLSI standards using several antibiotics, including metronidazole, vancomycin, and fidaxomicin, as the test agents. Susceptibility testing against other antibiotics with known activity against *C. difficile* may also be performed.

Results of susceptibility testing will not be available to inform investigators regarding patient management/treatment decisions.

3.3.2.3 Detection of MK-3415 and MK-6072 in Stool Samples

As noted in the Study Flow Chart (Section 1.7), stool specimens will be collected in all subjects pre-dose on Day 1 and on an optional basis on Visits 2, 3, and 4 (Day 4 [\pm 1 day], Day 11 [\pm 2 days], and Week 4 [Day 29 \pm 3 days], respectively) and an unscheduled visit(s) for new episodes of **diarrhea**. For all subjects that consent to provide post-dose stool samples, their baseline and post baseline samples will be sent to a central laboratory for assessment of MK-3415 and MK-6072 levels. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

Following stool processing, MK-3415 and MK-6072 levels will be measured in the stool by immunoassay-based methods.

3.3.2.4 Detection of MK-3415 and MK-6072 in Blood Samples

As noted in the Study Flow Chart (Sections 1.7 and 1.8), blood samples will be collected to measure the concentrations of MK-3415 and MK-6072 for pharmacokinetics assessments. Serum will be separated from blood samples and sent to a central laboratory for testing. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

Serum MK-3415 and MK-6072 levels will be measured using immunoassay-based methods.

3.3.2.5 Detection of Endogenous Antibodies to Toxin A and Toxin B in Blood Samples

As noted in the Study Flow Chart (Sections 1.7 and 1.8), blood samples will be collected to assess endogenous anti-toxin A and anti-toxin B antibody levels during the study. Serum will be separated from blood samples and sent to a central laboratory for testing. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

Product: MK-3415A 30**Protocol/Amendment No.:** 002-00

Serum anti-toxin A antibody and anti-toxin B antibody levels will be measured using immunoassay-based methods.

3.3.2.6 Detection of Anti-Drug Antibody (ADA) to MK-3415 or MK-6072

As noted in the Study Flow Chart (Sections 1.7 and 1.8), the detection of ADA to MK-3415 and/or MK-6072 will also be performed on blood samples. Serum will be separated from blood samples and sent to a central laboratory for testing. Additional information will be provided by the SPONSOR for biological specimen processing, handling, and shipment in the Laboratory Manual.

Serum ADA levels will be measured by bridging immunoassay-based method. Testing will consist of a screening assay, a confirmatory assay (only on those samples that are reactive in the screening assay), and a titer assay (only on those samples shown to confirm positive).

3.3.2.7 Neutralizing Antibody in Samples Positive for ADA

If a sample at a given time point provides a confirmed positive ADA result(s), the sample will also be tested for neutralizing antibody using a cell-based Neutralizing Antibody Assay.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

One of the primary endpoints of this protocol is to evaluate safety of the various monoclonal antibody treatment groups (i.e., MK-6072 and MK-3415A) relative to placebo. The safety endpoints will include all adverse experiences, including clinical adverse experiences (plus infusion-related reactions) and laboratory adverse experiences. These adverse experiences will be identified based on careful assessment or measurement of patient symptoms, vital signs and/or physical examination findings, and other laboratory measures.

Serious clinical adverse experiences will be collected from the time of infusion until the Week 12 post-infusion visit. Other non-serious clinical adverse experiences will be collected from the time of infusion until Week 4 post-infusion. In particular, vital signs will be monitored just prior to the infusion, at 30-minute after the start of the infusion, at the end of the infusion, and at other scheduled and unscheduled visits per protocol. Body temperature will also be recorded by the patient on the stool log for Days 1 to 14. Body temperature assessments should be taken at the same time each day, preferably in the evening. Oral thermometers will be provided by the SPONSOR. Otic temperatures are acceptable if measured by a medical professional in the setting of an inpatient (i.e. hospital, long-term care facility).

In addition, the presence of infusion-specific reactions will also be evaluated for 24 hours following the start of infusion. These include any of the following: infusion-site adverse experiences, pyrexia, chills, rash, arthralgia, myalgia, joint swelling, obstructive airways disorder, bronchospasm, stridor, dysphonia, headache, fatigue, pruritus, urticaria,

Product: MK-3415A

31

Protocol/Amendment No.: 002-00

hypotension, hypertension, nasal congestion, nausea, vomiting, flushing, angiodema, dyspnea, and dizziness/lightheadedness.

Laboratory adverse experiences will be based on safety laboratory tests, including hematology, chemistry, and urinalysis (as outlined in Appendix 6.5). Please see Section 3.4.1.1 for more details on type of tests and timing of collection.

In addition, an ECG will also be conducted just prior to infusion and within 2 hours after the completion of the infusion.

3.4.1.1 Laboratory Safety Tests

Laboratory tests will involve collection of blood (for complete blood counts with white blood cell differential and platelets, liver function panel, serum electrolytes) and urine (for urinalysis with microscopic analysis). Blood and urine samples will be taken for initial testing within 24 hours of the infusion on Day 1. Visit 1 laboratory safety assessments are for baseline values only and results are not required for patient entry into the study. Thereafter, blood and urine will be collected at the scheduled post-infusion study visits at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days). Appendix 6.5 provides a complete list of laboratory safety tests at these defined visits.

Blood will also be collected at unscheduled visits for a limited panel of safety laboratory tests in the event of an unscheduled visit for a new episode of **diarrhea** (see Section 3.2.3.8.3). Appendix 6.5 provides a list of the limited laboratory safety tests to be performed at these unscheduled visits.

Safety laboratory results will not be available to inform on patient management.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Product: MK-3415A 32**Protocol/Amendment No.:** 002-00

Adverse experiences may also occur in screened patients during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

For purposes of this trial, an overdose will be defined as receipt of the monoclonal antibody infusion above the predefined dose (i.e., >10 mg/kg of the monoclonal antibody against toxin B [MK-6072] or >10 mg/kg of either of the 2 monoclonal antibodies comprising MK-3415A [i.e. monoclonal antibody against toxin A {MK-3415} or monoclonal antibody against toxin B {MK-6072}]).

No specific information is available on the treatment/management of overdose of MK-6072 or MK-3415A. Infusion-related reactions and other hypersensitivity reactions should be treated supportively, if clinically indicated (see Section 3.2.3.7.6).

Any overdose of study drugs whether or not associated with an adverse experience must be reported within 24 hours to Merck & Co., Inc.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with (“results from”) the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology “accidental or intentional overdose without adverse effect.”

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a patient (spontaneously reported to them) which occurs during the 12-week (85 ± 5 days) follow-up period. All patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

Product: MK-3415A

33

Protocol/Amendment No.: 002-00

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any patient entered into this study or within 12-week (85 ± 5 days) follow-up period, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Selected Nonserious Adverse Experiences

These selected non-serious adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Experience Case Report Forms/Worksheets.

Events of clinical interest for this trial include:

- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***Note:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or Administrative Binder, or equivalent).

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-3 for instructions in evaluating adverse experiences.

Product: MK-3415A
Protocol/Amendment No.: 002-00

34

Table 3-3

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

Maximum Intensity	Mild	awareness of sign or symptom, but easily tolerated (for pediatric studies, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric studies, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric studies, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse experience is any adverse experience occurring at any dose that:	
	† Results in death; or	
	† Is life threatening; or places the patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death]; or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience); or	
	† Is a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is an overdose (Whether accidental or intentional) Any overdose whether or not associated with an adverse experience must be reported within 24 hours	
Relationship to test drug	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †)	
	Duration Record the start and stop dates of the adverse experience If less than 1 day, indicate the appropriate length of time and units	
	Action taken Did the adverse experience cause the test drug to be discontinued?	
	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience will be provided by an investigator who is a qualified physician The investigator's signed/dated initials on the source document or worksheet, that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done This initialed document must be retained for the required regulatory time frame The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse experience based upon the available information	
	The following components are to be used to assess the relationship between the test drug and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	
	Exposure	Is there evidence that the patient was actually exposed to the test drug such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors


3415A, Protocol 002-00 Issue Date: 09-Aug-2011

Product: MK-3415A
Protocol/Amendment No.: 002-00

35

Relationship to test drug (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was the dose of test drug discontinued or reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge If no, this is a negative dechallenge (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the test drug; or (3) the study is a single-dose drug study)
	Rechallenge	Was the patient reexposed to the test drug in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge If no, this is a negative rechallenge (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U S CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements		
Record one of the following:		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug The temporal sequence of the AE onset relative to the administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause Depending on data collection method employed, drug relationship may be further graded as follows:
	Definitely related	There is evidence of exposure to the test drug The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause Dechallenge is positive Rechallenge (if feasible) is positive The AE shows a pattern consistent with previous knowledge of the test drug or test drug class
	Probably related	There is evidence of exposure to the test drug The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE is more likely explained by the test drug than by another cause Dechallenge (if performed) is positive
	Possibly related	There is evidence of exposure to the test drug The temporal sequence of the AE onset relative to administration of the test drug is reasonable The AE could have been due to another equally likely cause Dechallenge (if performed) is positive
No, there is not a reasonable possibility of drug relationship		Patient did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE (Also entered for a patient with overdose without an associated AE) Depending on data collection method employed, drug relationship may be further graded as follows:
	Probably not related	There is evidence of exposure to the test drug There is another more likely cause of the AE Dechallenge (if performed) is negative or ambiguous Rechallenge (if performed) is negative or ambiguous
	Definitely not related	The patient did not receive the test drug OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR There is another obvious cause of the AE

3415A_002-00_ProtDet APPROVED — 09-Aug-2011
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3415A, Protocol 002-00 Issue Date: 09-Aug-2011

70

Product: MK-3415A

36

Protocol/Amendment No.: 002-00

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to other secondary, exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/ In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. The analyses and summaries described in Sections 3.5.5.4.1 and 3.5.5.4.2 are the responsibility of the Epidemiology and Experimental Medicine departments of the SPONSOR. The analyses and summaries described in Section 3.5.5.4.3 are the responsibility of the Clinical PK/PD department of the SPONSOR.

The 12-Week base period of this study will be conducted as a double-blind study under in-house blinding procedures. The official, final database for the base period will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete. The CSR will be finalized after results from the base study are complete.

The additional 9-month extended follow-up period of this study will include approximately 300 patients (100 per treatment group). Depending on the speed with which the extension-participating patients are enrolled, it is possible that patients will still be continuing in the extended follow-up period when the 12-Week primary study period (i.e., base study) is completed and data have been unblinded to treatment for analysis of the primary endpoint (unblinded to internal Merck personnel). In this case, the CSR will be amended to include these results following the completion of the additional 9-month extended follow-up period.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in IVRS.

3.5.2 Hypotheses

Objectives and hypotheses of the study are stated in Section 2.1.

Product: MK-3415A

37

Protocol/Amendment No.: 002-00

3.5.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below.

3.5.3.1 Efficacy Endpoints

CDI Recurrence: Defined as the development of a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode.

The primary efficacy endpoint will be the proportion of patients with CDI recurrence assessed through the Week 12 (Day 85 \pm 5 days) primary study period using the FAS population (see Section 3.5.4.1). A sensitivity analysis will be conducted to ascertain the potential effects of switching SOC therapy on the treatment effect. Any discrepancies between this sensitivity analysis and the primary analysis will be investigated and explained.

CDI recurrence will be assessed as a secondary efficacy endpoint in subgroups of the FAS population. These assessments will use the same definition for CDI recurrence as defined for the primary endpoint, but will be limited to the following subsets of patients: 1) subset of patients with clinical cure of the initial CDI episode and 2) other subgroups as defined in Sections 3.3.1 and 3.5.8.

Time to CDI recurrence will be assessed as an exploratory efficacy endpoint. The start date of CDI recurrence will be the first date of the new episode of **diarrhea**. For patients who are lost to follow up prior to a CDI recurrence, time to event will be considered right censored at the date of the last stool record. Patients who complete the 12-Week study period without documented CDI recurrence will be censored at the date of the last completed stool record. For patients who fail to achieve a clinical cure, time to event will be considered right censored at the date of infusion of study medication (Day 1).

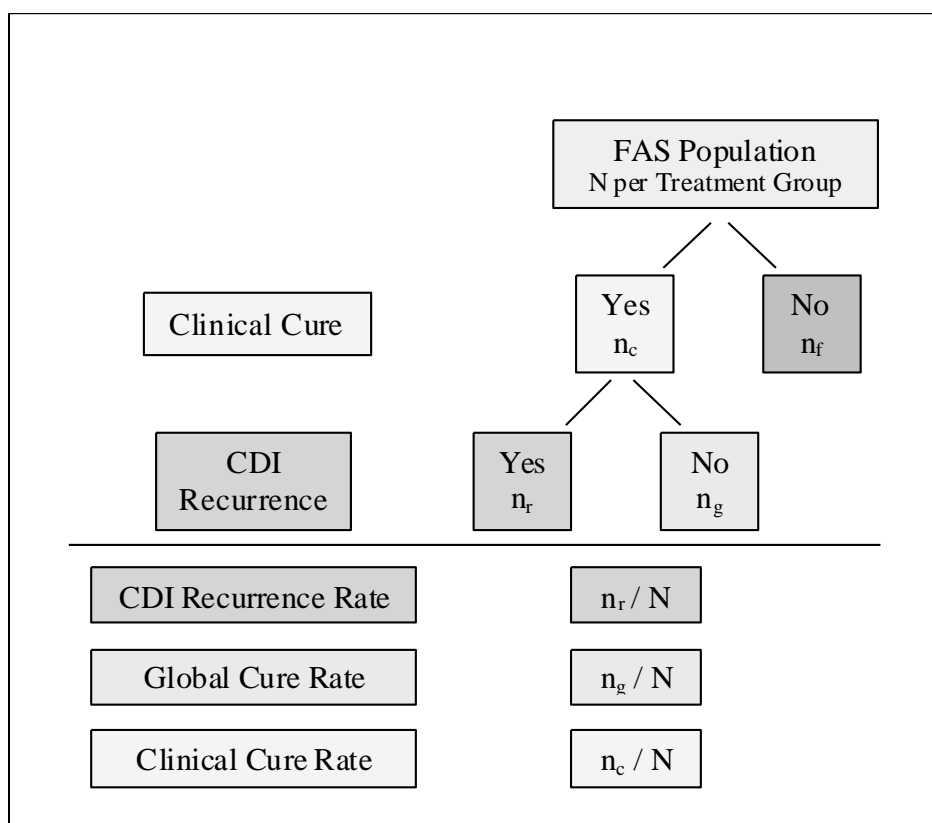
Global Cure: Defined as clinical cure of the initial CDI episode AND no CDI recurrence through Week 12. The proportion of patients with global cure will be assessed as a secondary efficacy endpoint.

Clinical Cure: Defined as patient received ≤ 14 days of SOC therapy AND the patient has no **diarrhea** (≤ 2 **loose stools** per 24 hours) for two consecutive days following completion of SOC therapy for the initial CDI episode. Patients requiring > 14 days of SOC therapy for the initial CDI episode will be considered a failure for the clinical cure endpoint. The proportion of patients with clinical cure will be assessed as an exploratory efficacy endpoint.

Please see Figure 3-1 for a diagram of the above efficacy endpoints.

Figure 3-1

Populations for Efficacy Endpoints



Resolution of Initial CDI Episode: Defined as the time from randomization to the end of **diarrhea** during the initial CDI episode (i.e., time to first of two consecutive days with ≤ 2 **loose stools**). Patients will be censored at end of SOC window (≤ 14 days) for this endpoint. Resolution of Initial CDI episode will be assessed as an exploratory efficacy endpoint.

Stool Counts during Initial CDI Episode: Defined as the daily number of **loose stools** reported on the patient stool log. Summary statistics including the median will be provided by study day starting from the day after infusion (Day 2) through Study Day 14. Stool Counts during Initial CDI Episode will be assessed as an exploratory efficacy endpoint.

Product: MK-3415A

39

Protocol/Amendment No.: 002-00

WBC on Days 4 and 11: Defined as the proportion of patients whose elevated baseline WBC ($>10,000$ cells/mm³) decreases to $\leq 10,000$ cells/mm³ by Day 4 or Day 11. WBC on Days 4 and 11 will be assessed as an exploratory efficacy endpoint.

Body Temperature on Days 4 and 11: Defined as the proportion of patients whose elevated baseline body temperature ($\geq 101.0^{\circ}\text{F}$ [38.4°C]) decreases to $<101.0^{\circ}\text{F}$ [38.4°C] by Day 4 or Day 11. Body Temperature on Days 4 and 11 will be assessed as an exploratory efficacy endpoint.

Diarrhea Recurrence: Defined as the development of a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) whether or not a positive stool test for toxigenic *C. difficile* is available following clinical cure of the initial CDI episode. The proportion of patients with **diarrhea** recurrence will be assessed as an exploratory efficacy endpoint.

3.5.3.2 Safety Endpoints

A description of safety measures is contained in Section 3.4.1. The analysis of safety results will follow a tiered approach (see Section 3.5.5.2 for further detail).

The broad clinical and laboratory adverse experience categories consisting of the percentage of patients with any adverse experience, a drug-related adverse experience, a serious adverse experience, an adverse experience which is both drug-related and serious, and who discontinued due to an adverse experience will be considered Tier 1 endpoints. Infusion-specific reactions, as previously defined in Section 2.6, will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [17], an unconditional, asymptotic method.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as endpoints of special interest will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

Changes from baseline in laboratory values, vital signs, and ECG parameters that are not pre-specified endpoints of special interest will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change-from-baseline values will be provided.

Product: MK-3415A

40

Protocol/Amendment No.: 002-00

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as basis for the efficacy analyses unless otherwise indicated in Section 3.5.3.1. The FAS population is a subset of all randomized patients with patients excluded for the following reasons:

- Failure to receive infusion of study medication
- Lack of a positive local stool test for toxigenic *C. difficile* (as per Appendix 6.1)

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary efficacy endpoint. The Per-Protocol population excludes patients due to important deviations from the protocol that may affect the results of the primary efficacy endpoint(s). The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to the final unblinding of the database and will be documented in a separate memo.

A sensitivity analysis will be conducted on the subset of the FAS population with a positive stool culture for toxigenic *C. difficile* at the central laboratory. Due to the impact of collection, storage and transport conditions on *C. difficile* recovery, it is anticipated that about 70-75% of patients will have *C. difficile* isolated at the central laboratory at baseline. Any discrepancies between this sensitivity analysis and the primary analysis will be investigated and explained.

Details on the approach to handling missing data are provided in Section 3.5.5.

3.5.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized patients who receive infusion of study medication. Patients will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most patients, this will be the treatment group to which they are randomized.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

3.5.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 3.5.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 3.5.6. Nominal p-values will be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

Product: MK-3415A 41**Protocol/Amendment No.:** 002-00

Unless otherwise stated, all statistical tests will be conducted at the $\alpha=0.025$ (1-sided) level.

3.5.5.1 Statistical Methods for Efficacy Analyses

Primary Efficacy Analyses

CDI Recurrence: Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with CDI recurrence between the treatment groups. The strata will be the same as those used for the randomization: SOC antibiotic therapy at the time of randomization (metronidazole vs. vancomycin vs. fidaxomicin) and hospitalization status (in-patient vs. out-patient). See Section 3.2.3.4 for more details regarding stratification. Stratification levels may be combined for analysis if very low numbers of patients are observed in any given level. Decisions regarding collapsing of categories will be made prior to unblinding the data. This approach will apply to all other methods with stratification described below.

The proportion of patients with CDI recurrence will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who develop a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) associated with a positive local or central lab stool test for toxigenic *C. difficile* following clinical cure of the initial CDI episode. The denominator will be the number of patients in the FAS population. Every effort will be made to obtain CDI recurrence information for each randomized patient. In the case of lost follow up, the last available stool records will be used to assess for CDI recurrence. Patients lacking any post-randomization endpoint data subsequent to infusion of study medication will contribute only to the denominator of this proportion.

A declaration of superiority to placebo for the MK-3415A treatment group will be considered a successful outcome for the trial.

A sensitivity analysis will be conducted for proportion of patients with CDI recurrence using Miettinen and Nurminen's method [17] without adjusting for SOC antibiotic therapy and hospitalization status.

Secondary Efficacy Analyses

CDI Recurrence in Certain Predefined Subgroups (as outlined in the Secondary Objectives): These analyses will employ the same analytical approach as the primary efficacy analysis. If the percentage of patients failing to achieve clinical cure of the initial CDI episode exceeds 10%, an additional sensitivity analysis will be conducted to compare recurrence rates between treatment groups among clinical cure patients stratified by the propensity of achieving clinical cure using Miettinen and Nurminen's method [17] for stratified data. The propensity of clinical cure will be calculated from a logistic regression model predicting clinical cure from important baseline factors among all patients included in the FAS population.

Product: MK-3415A

42

Protocol/Amendment No.: 002-00

Global Cure: Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with global cure between the treatment groups. The proportion of patients with global cure will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who achieve clinical cure of the initial CDI episode AND have no CDI recurrence through Week 12. The denominator will be the number of patients in the FAS population.

Exploratory Efficacy Analyses

Clinical Cure: Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with clinical cure between the treatment groups. The proportion of patients with clinical cure will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who have received ≤ 14 days of SOC therapy AND have no **diarrhea** (≤ 2 loose stools per 24 hours) for two consecutive days following completion of SOC therapy for the initial CDI episode. The denominator will be the number of patients in the FAS population. Patients lacking any post-randomization endpoint data subsequent to infusion of study medication will be considered failures with respect to clinical cure of their initial episode and thus will contribute only to the denominator of this proportion.

Time to CDI Recurrence: The nonparametric Kaplan-Meier method will be used to estimate the time to CDI recurrence distribution for each treatment group. Treatment differences in time to CDI recurrence will be assessed using the stratified log-rank test. The start date of CDI recurrence will be the first date of the new episode of **diarrhea**. For patients who are lost to follow up prior to a CDI recurrence, time to event will be considered right censored at the date of the last stool record. Patients who complete the 12-Week study period without documented CDI recurrence will be censored at the date of the last completed stool record. For patients who fail to achieve a clinical cure for the initial CDI episode, time to event will be considered right censored at the date of infusion of study medication (Day 1).

Time to Resolution of Initial CDI Episode: The nonparametric Kaplan-Meier method will be used to estimate the time to resolution of initial CDI episode distribution for each treatment group. Treatment differences in time to resolution of initial CDI episode will be assessed using the stratified log-rank test. The start date of resolution of initial CDI episode will be the first of two consecutive days with ≤ 2 loose stools. Patients who reach the end of the SOC window (≤ 14 days) without documented resolution of initial CDI episode will be censored at the last date of SOC therapy within the window. For patients who are lost to follow up prior to resolution of initial CDI episode, time to event will be considered right censored at the date of the last stool record within the SOC window.

Stool Counts during Initial CDI Episode: No formal comparisons are planned for this endpoint. Summary statistics including the median will be provided by study day starting from the day after infusion (Study Day 2) through Study Day 14. Stool counts associated with new episodes of **diarrhea** will be excluded from this summary.

Product: MK-3415A

43

Protocol/Amendment No.: 002-00

WBC and Body Temperature on Days 4 and 11: No formal comparisons are planned for these endpoints. Summary statistics including the proportion of patients with decreases for each of these measurements (as defined in Section 3.5.3.1), the difference in proportions between treatment groups, and 95% confidence intervals for the difference (Miettinen and Nurminen's method [17]) will be provided.

Diarrhea Recurrence: Miettinen and Nurminen's method [17] for stratified data will be used to compare the proportion of patients with **diarrhea** recurrence between the treatment groups. The proportion of patients with **diarrhea** recurrence will be calculated as follows for each treatment group. The numerator will be the number of patients within the FAS population who develop a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) whether or not a positive stool test for toxigenic *C. difficile* is available following clinical cure of the initial CDI episode. The denominator will be the number of patients in the FAS population. In the case of lost follow up, the last available stool records will be used to assess for **diarrhea** recurrence. Patients lacking any post-randomization endpoint data subsequent to infusion of study medication will contribute only to the denominator of this proportion.

3.5.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences, laboratory tests, vital signs, physical examination, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 3-4). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p values and 95% confidence intervals provided for (separate) comparison between active monoclonal antibody therapy (MK-6072 and MK-3415A) to placebo. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons (each of the active monoclonal antibody therapies vs. placebo); only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as endpoints of special interest will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals

Product: MK-3415A

44

Protocol/Amendment No.: 002-00

should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Changes from baseline in laboratory and vital signs that are not pre-specified as endpoints of special interest will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided in table format.

The broad clinical and laboratory adverse experiences categories consisting of the percentage of patients with any adverse experience(s), a drug-related adverse experience(s), a serious adverse experience(s), an adverse experience which is both drug-related and serious, and who discontinued due to an adverse experience will be considered Tier 1 endpoints. Infusion-specific reactions, as previously defined in Section 2.6, will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [17], an unconditional, asymptotic method.

Missing values will be handled using the Data-As-Observed (DAO) approach.

Table 3-4

Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint [†]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Any adverse experience	X	X	X
	Any Drug-Related adverse experience	X	X	X
	Any Serious adverse experience	X	X	X
	Any Serious and Drug-Related adverse experience	X	X	X
	Discontinuation due to adverse experience	X	X	X
Tier 2	Infusion-specific Reactions		X	X
	Specific adverse experiences or SOCs [‡] (incidence ≥ 4 of patients in one of the treatment groups)		X	X
Tier 3	Specific adverse experiences or SOCs [‡] (incidence < 4 of patients in all of the treatment groups)			X
	Change from Baseline Results (laboratory)			X
95% confidence intervals will be based on the method of Miettinen and Nurminen [17]				
[†] Adverse Experience references refer to both Clinical and Laboratory adverse experiences				
[‡] Includes only those endpoints not pre-specified as Tier 1 endpoints				
Note: SOC=System Organ Class; X = results will be provided				

Product: MK-3415A

45

Protocol/Amendment No.: 002-00

3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

This section describes the patient demographic and baseline characteristics that will be assessed. The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, race, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

A summary of the number of patients randomized by site will be provided by treatment group.

3.5.5.4 Other Analyses

The analyses and summaries described in Sections 3.5.5.4.1 and 3.5.5.4.2 will be conducted by the Epidemiology and Experimental Medicine departments of the SPONSOR. The analyses and summaries described in Section 3.5.5.4.3 will be conducted by the Clinical PK/PD department of the SPONSOR.

3.5.5.4.1 Analysis of High Risk Demographic and Clinical Identifiers

An analysis to identify patients at high risk for CDI recurrence will be performed using the data from the placebo group from this clinical trial. Data from this particular study for the analysis to identify patients at high risk for CDI recurrence may be pooled with data collected from other similar studies to allow for a more robust assessment. Details of this analysis are included in Appendix 6.7.

3.5.5.4.2 Biomarker Analysis

Exploratory analyses will be performed in an effort to develop a classification model to identify patients at high risk for CDI recurrence. Only patients in the placebo group of this trial will be used for the analyses to develop a classification model. A classification tool with demographic and clinical predictors will be combined with biomarkers to create one single prediction model. Additionally, gene expression and changes in gut flora will be evaluated to determine the mechanism of action of monoclonal antibody therapy. Data from this particular study for the biomarker analysis may be pooled with similar data collected from other similar studies to allow for a more robust assessment. Details of biomarker analyses are included in Appendix 6.6.

3.5.5.4.3 Pharmacokinetic/ Population Pharmacokinetic Analysis

Serum pharmacokinetic samples for this study (antibodies to toxin A [MK-3415] and toxin B [MK-6072]) will be analyzed using a population pharmacokinetic analysis approach. This analysis will be used to estimate serum pharmacokinetic parameters (e.g., C_{1hr}) of antibodies to both toxin A and toxin B as well as the serum concentration versus

Product: MK-3415A

46

Protocol/Amendment No.: 002-00

time profile for each patient with valid pharmacokinetic measurements. Variability in pharmacokinetics will also be estimated, including an assessment of sources of variability which may include demographic factors, disease state, and co-administered medications. A separate data analysis plan will be written prior to pharmacokinetic analysis of the data for this study.

3.5.6 Multiplicity

This protocol has a single primary endpoint, CDI recurrence, which will be used for two (MK-3415A compared to placebo, MK-6072 compared to placebo) treatment comparisons. The comparisons will take place sequentially. First, the combined monoclonal antibody therapy (MK-3415A) will be compared to placebo. If this comparison demonstrates superiority of MK-3415A over placebo, the individual monoclonal antibody therapy (MK-6072) will be compared to placebo. Under the global null hypothesis that the three therapies (two active treatments and placebo) are equal, the overall probability of making a false claim of superiority for any of the experimental treatment groups is controlled at level 0.025, one-sided. The multiplicity adjustments are described below and the entire evaluation plan and multiplicity strategy is presented in Table 3-5.

Sequential testing approach will be employed to control the overall probability of making a false claim of superiority for either of the experimental treatment groups at 0.025. The first test in the sequence will be the evaluation of MK-3415A versus placebo with a p-value cut-off of 0.025 (1-sided). If this is significant, then the MK-6072 monoclonal antibody therapy group will be compared to placebo. The p-value cut-off will be 0.025 (1-sided). A p-value that is >0.025 for the MK-3415A versus placebo comparison will not be considered statistically significant and will halt further testing in the sequence.

Table 3-5

Statistical Evaluation Plan and Multiplicity Strategy for the Primary Hypotheses

Stage	Comparison(s)	Multiplicity Strategy	p-value cut-off for individual comparisons	Purpose
1	MK-3415A vs. PBO	Fixed Sequence [†]	0.025	Evaluate effectiveness of MK-3415A group
2	MK-6072 vs. PBO	Fixed Sequence [†]	0.025	Evaluate effectiveness of MK-6072 group
MK-3415A is the combined administration of monoclonal antibodies (MAbs) to Toxin A and B MK-6072 is MAb to Toxin B only; PBO = placebo [†] The first test in the sequence will be the evaluation of MK-3415A vs. placebo with a p-value cut-off of 0.025 (1-sided). If significant, then MK-6072 will be compared to placebo. The p-value cut-off will be 0.025 (1-sided).				

Product: MK-3415A

47

Protocol/Amendment No.: 002-00

3.5.7 Sample Size and Power Calculations

This study has a planned sample size of 1200 patients to be randomized in a 1:1:1 ratio to each of the three treatment groups (MK-6072, MK-3415A and placebo). The following power calculations are based on a two group chi-square test for comparing independent proportions. Assumptions about the incidence of CDI recurrence among patients on MK-3415A are based on recent results from the Phase II clinical study of a single infusion of this investigational product [15]. In that study, CDI recurrence was observed in 7% (7/101) of MK-3415A patients. The incidence of CDI recurrence among patients on SOC therapy is assumed to be between 20 and 25%. These estimates are based on: (1) the Phase II clinical study of a single infusion of MK-3415A [15] where 25% (25/99) of patients taking SOC therapy had CDI recurrence, (2) recently reported pooled results from the vancomycin and fidaxomicin arms of two Phase III fidaxomicin trials (26% and 14.3%, respectively, based on 4 weeks of follow-up) [43, 44], and (3) assumptions/limitations regarding the prevalence of fidaxomicin use in the trial (where 0% fidaxomicin use corresponds to an assumed 25% recurrence rate in the placebo/SOC therapy group while a 20% recurrence rate is expected in this group if fidaxomicin use is as prevalent as 15% in the trial).

Primary Endpoint - CDI Recurrence

It is anticipated that 400 patients per group will be in the analysis population for the CDI recurrence endpoint. Comparisons between monoclonal antibody therapy groups and placebo will be performed at a 1-sided alpha level of 0.025. This will provide approximately 95% power to detect the following differences in the incidence of CDI recurrence between monoclonal antibody therapy, π_1 , and placebo, π_2 :

π_1	π_2	Difference	Power
.08	.163	.083	95%
.09	.176	.086	95%
.10	.189	.089	95%

Secondary Endpoint - Global Cure

It is anticipated that 400 patients per group will be in the analysis population for the global cure endpoint. Comparisons between monoclonal antibody therapy groups and placebo will be performed at a 1-sided alpha level of 0.025. This will provide approximately 90% power to detect a 10 percentage point difference in the proportion of patients achieving global cure (80% for monoclonal antibody therapy versus 70% for placebo).

Product: MK-3415A

48

Protocol/Amendment No.: 002-00

Secondary Endpoint - CDI Recurrence in Subset of Patients with Clinical Cure

It is anticipated that 85 to 90% of all randomized patients, regardless of treatment group, will achieve a clinical cure for the initial CDI episode (see definition in Section 3.5.3.1). The following power calculations are based on an anticipated 350 patients per treatment group in the subset of all randomized patients who achieve a clinical cure. Comparisons between monoclonal antibody therapy groups and placebo will be performed at a 1-sided alpha level of 0.025. This will provide approximately 95% power to detect the following differences in the incidence of CDI recurrence between monoclonal antibody therapy, π_1 , and placebo, π_2 :

π_1	π_2	Difference	Power
.08	.172	.092	95%
.09	.185	.095	95%
.10	.197	.097	95%

3.5.8 Combined Data (Subgroup Analyses and Effect of Baseline Factors)

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary and secondary endpoints (CDI recurrence and Global Cure) will be estimated within each category of the following classification variables if there are at least 25 patients in each subgroup in each treatment group:

- Hospitalization Status (pre-stratification variable)
- SOC therapy (pre-stratification variable)
- *C. difficile* strain (BI/NAP1/027 versus non-BI/NAP1/027 strain) at study entry
- Any epidemic *C. difficile* strain (BI/NAP1/027, 001, 078, and 106 strains versus non-BI/NAP1/027, non-001, non-078, and non-106 strains) at study entry
- Prior history of CDI (presence versus absence of prior CDI episode within the 6 months prior to enrollment)
- Age at Study Entry (<65 years versus ≥ 65 years)
- **CDI Severity at Study Entry** (clinically severe versus not clinically severe at study entry)
- Region (U.S. versus ex-U.S.)
- Patients with compromised immunity at study entry (presence of compromised immunity versus absence of compromised immunity)

The criteria for the various subgroups are defined in Section 3.3.1. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. The SPONSOR may also pool the data from this

Product: MK-3415A

49

Protocol/Amendment No.: 002-00

study with data from other Phase III studies to obtain more precise estimates of the treatment effect in these subgroups.

3.5.9 Interim Analyses

No interim analyses are planned for this study. However, this trial (with three treatment groups) is part of a Phase 3 development program that also includes an adaptive Phase 3 trial (Protocol 001 [MODIFY I]) employing a factorial design with four treatment groups: MK-3415A, MK-3415, MK-6072, and placebo. Both of these trials will be enrolling patients simultaneously. Protocol 001 (MODIFY I) contains an interim analysis designed to evaluate the individual monoclonal antibody therapies (MK-3415 or MK-6072) relative to the combined monoclonal antibody therapy (MK-3415A). If there is sufficient evidence of superiority for MK-3415A over either MK-3415 or MK-6072, then further enrollment in one or both of these study treatment groups for Protocol 001 (MODIFY I) will be stopped. Should this interim analysis result in a decision to stop further enrollment in the MK-6072 treatment group for Protocol 001 (MODIFY I), then further enrollment in the MK-6072 treatment group for this trial (Protocol 002 [MODIFY II]) will also be stopped. Based on the FDA draft guidance for industry (DGFI) entitled “Adaptive Design Clinical Trials for Drugs and Biologics” (Section IV, Part E - Study Design Changes That Are Not Considered Adaptive Design), this modification to Protocol 002 (MODIFY II) is considered to be a reactive revision based on information from a source external to the study. Per the DGFI, this revision does not fall into the category of adaptive design and should not introduce a bias into the study.

3.5.10 Additional 9-Month Extended Follow-up

The additional 9-month extended follow-up period of this study will include approximately 300 patients (100 per treatment group). Depending on the speed with which the extension-participating patients are enrolled, it is possible that patients will still be continuing in the extension when the 12-Week (Day 85 \pm 5 days) primary follow-up period (i.e., base study) is completed and data have been unblinded to treatment for analysis of the primary endpoint (unblinded to internal Merck personnel). In this case, CSR will be amended to include these results following the completion of the additional 9-month extended follow-up period.

No formal statistical analyses are planned for the additional 9-month extended follow-up data. Summary statistics of demographic, efficacy, and safety data will be provided.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Patient and Replacements Information

Clinical supplies will be packaged to support enrollment of approximately 1200 patients.

Clinical supplies will be packaged as open-label supplies according to a component schedule generated by the SPONSOR. Clinical supplies will be assembled in a double-blind fashion by an Unblinded Pharmacist or designee, according to the IVRS allocation.

Product: MK-3415A 50**Protocol/Amendment No.:** 002-00**3.6.2 Product Descriptions**

Investigational clinical materials will be provided by the SPONSOR as summarized in Table 3-6.

Table 3-6

Product Descriptions

Product Name & Potency	Dosage Form	Comments
MK-3415 toxin A antibody (25 mg/mL)	Sterile solution for IV infusion	MK-3415 combined with MK-6072 is MK-3415A
MK-6072 toxin B antibody (25 mg/mL)	Sterile solution for IV infusion	MK-6072 combined with MK-3415 is MK-3415A

The investigator or the site will supply 0.9% sodium chloride to be used as placebo and to prepare MK-6072 and MK-3415A infusions. The pharmacist or designee will record the lot number and expiration date.

Other clinical supplies (oral metronidazole; intravenous metronidazole, oral vancomycin, or oral fidaxomicin) will be prescribed/administered by the attending physician.

3.6.3 Primary Packaging and Labeling Information

Supplies will be packaged in **glass vials** as described in Table 3-7 below.

Table 3-7

Packaging of Clinical Supplies

Product Name & Potency	Fill Count	Dosing Instructions
MK-3415 toxin A antibody (25 mg/mL)	40 mL	Administer per protocol.
MK-6072 toxin B antibody (25 mg/mL)	40 mL	Administer per protocol.

Container label text may include the following:

<ul style="list-style-type: none"> • Packaging Lot Trace ID # • Component ID # • Space for Allocation # • Fill Count & Dosage Form • Product name & potency • Re-evaluation date 	<ul style="list-style-type: none"> • Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable) • Translation Key (If applicable)
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Product: MK-3415A

51

Protocol/Amendment No.: 002-00

3.6.4 Secondary Packaging and Labeling Information (kit)

There will be no secondary packaging.

3.6.5 Clinical Supplies Disclosure

The IVRS should be used in order to unblind patients and to unmask drug identity. The SPONSOR will not provide disclosure envelopes with the clinical supplies. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Prior to unblinding, the investigator will attempt to contact the clinical monitor. Any unblinding that occurs at the site must be documented.

3.6.6 Storage and Handling Requirements

MK-3415 and MK-6072 should be kept in a secured location at a **controlled temperature of 2-8°C** and **protected from light**.

All clinical drug supplies will be shipped to the sites as a refrigerated product to be stored at 2°C to 8°C (35.6°F to 46.4°F). Upon receipt at the investigational site, the drug supplies should be removed from the outer secondary shipping box and placed immediately into the refrigerator. The temperature monitoring device must be deactivated upon receipt of the shipment. Directions for inactivation are specified in the *Instructions to Site*, which are enclosed with each shipment. The temperature monitoring device will indicate whether the shipment has remained within the specified temperatures. Return the temperature monitoring device according to instructions accompanying the shipment. **Notify the SPONSOR immediately if the temperature monitoring device is in alarm. Store and hold product until instructed otherwise.**

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained. Supplies should be stored in the original nested box with the lid closed to minimize exposure to light. **If the refrigerator in which the study drug is stored deviates from the 2°C to 8°C (35.6°F to 46.4°F) range, study drug dispensing should be suspended and the SPONSOR should be contacted immediately. The drug supplies must NOT be frozen.**

It is strongly recommended that a non-frost free laboratory grade refrigerator is used to store the study drug. This type of refrigerator is less likely to have wide temperature fluctuations, so it will be more likely to stay within the 2°C to 8°C (35.6°F to 46.4°F) temperature range. A daily refrigerator temperature log must be maintained at the site. The refrigerator must be equipped with an appropriately calibrated min/max thermometer and/or circular chart temperature recorder. The temperature log will be reviewed by the SPONSOR throughout the study. An appropriate back up system (i.e. alarm, generator) and study site personnel telephone numbers should be in place in the event of a refrigerator failure.

Product: MK-3415A

52

Protocol/Amendment No.: 002-00

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol. Documentation of temperature monitoring should be maintained.

3.6.7 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated individuals (i.e., Unblinded Pharmacist[s]) have access. Clinical supplies are to be administered only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount administered to the subjects/patients, and the amount remaining at the conclusion of the study. The Clinical Research Associate (CRA) should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all unused clinical supplies must be returned as indicated in the Sponsor Contact Information. Partial or empty vials should be properly discarded as biohazardous waste. United States sites should follow instructions for the Clinical Supplies Return Form (V464) and contact your SPONSOR representative for review of shipment and form before shipping. Sites outside of the United States should check with their local country SPONSOR personnel for appropriate documentation that needs to be completed for vial accountability.

3.6.8 Distributing to Sites and Dispensing to Patients

The appropriate study personnel will have access to an Interactive Voice Response System (IVRS) to allocate patients, to assign drug to patients and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

Product: MK-3415A

1

Protocol/Amendment No.: 002-00

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

Product: MK-3415A

2

Protocol/Amendment No.: 002-00

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the SPONSOR, and subsidiaries, affiliates and agents of the SPONSOR, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies

In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects/patients, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the SPONSOR.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any

Product: MK-3415A

3

Protocol/Amendment No.: 002-00

other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the SPONSOR as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the SPONSOR prematurely terminates a particular trial site, the SPONSOR will promptly notify that site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck & Co., Inc. in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Product: MK-3415A

4

Protocol/Amendment No.: 002-00

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, <http://clinicaltrials.gov/>. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The SPONSOR will work with the authors to submit a manuscript describing study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), whichever is later. These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

Product: MK-3415A

5

Protocol/Amendment No.: 002-00

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3. Significant contributions to study execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend the integrity of the data, method(s) of data analysis, and the scientific content of the manuscript.

The SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

Product: MK-3415A

1

Protocol/Amendment No.: 002-00

5. LIST OF REFERENCES

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Product: MK-3415A

2

Protocol/Amendment No.: 002-00

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Product: MK-3415A

3

Protocol/Amendment No.: 002-00

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Product: MK-3415A

4

Protocol/Amendment No.: 002-00

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Product: MK-3415A

5

Protocol/Amendment No.: 002-00

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Product: MK-3415A

6

Protocol/Amendment No.: 002-00

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Product: MK-3415A

7

Protocol/Amendment No.: 002-00

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8

Protocol/Amendment No.: 002-00

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Product: MK-3415A

9

Protocol/Amendment No.: 002-00

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Product: MK-3415A

10

Protocol/Amendment No.: 002-00

6. APPENDICES

6.1 ACCEPTABLE *C. DIFFICILE* DIAGNOSTIC METHODS

- 1.) Cell Culture Cytotoxin Assays, OR
- 2.) Stool Culture with Toxigenic Strain Typing, OR
- 3.) Stool Culture with Toxin Detection from *C. difficile* isolates, OR
- 4.) One of the following commercially available assays:

Manufacturer	Assay Name	Assay Type	Specificity (%) [†]
Becton Dickinson	BD GeneOhm	PCR	95.5
Biomérieux	VIDAS <i>C. difficile</i> Toxins A and B	ELFA	99.8
Cepheid	GeneExpert	PCR	94
Medical Chemical Corp.	GastroTect	EIA	97
Meridian	Premier	EIA	97.3
	Illumigene	PCR	95.3
	Immunocard Toxins A and B	EIA	98.4
Oxoid/Remel	Xpect <i>C. difficile</i> Toxin A/B	EIA	96.2
	ProSpecT A and B	EIA	96.2
ProdeSS	ProGastro CD	PCR	94.7
TechLab (assays may also be distributed by Inverness Medical)	Tox A/B QuikChek	EIA	99.7
	<i>C. diff</i> QuikChek Complete	EIA	99.4
	<i>C. difficile</i> Tox A/B II [‡]	EIA	100
[†] Specificity data as reported in the manufacturer's product insert. [‡] <i>C. difficile</i> Tox A/B II assay can be run with or without the TechLab Fecal-Quik Prep assay. PCR=polymerase chain reaction, ELFA=enzyme-linked fluorescent assay, EIA=enzyme immunoassay.			








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11

Protocol/Amendment No.: 002-00

6.2 BRISTOL STOOL CHART

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid

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12

Protocol/Amendment No.: 002-00

6.3 MODIFIED HORN'S INDEX

Modified Horn's Index^{1,2}

Horn's Index Score		Description of Severity
Level 1	Low	A single mild illness
Level 2	Moderate	More severe disease but uncomplicated recovery
Level 3	Major	Major complications or multiple conditions requiring treatment
Level 4	Extreme	Catastrophic illness likely leading to death

¹ Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infect Control Hosp Epidemiol.* 2002;23: 653-9

² McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile* associated diarrhea in a cohort of hospitalized patients. *J Infect Dis* 1990;162:678-684.

Product: MK-3415A

13

Protocol/Amendment No.: 002-00

6.4 CHARLSON INDEX

Answer the following questions based on review of the patient's medical history in the patient chart.

Indicate YES or NO for Questions 1-13.

1. AIDS? ☐ Yes ☐ No
2. Cerebrovascular disease? ☐ Yes ☐ No
3. Chronic pulmonary disease? ☐ Yes ☐ No
4. Congestive heart failure? ☐ Yes ☐ No
5. Connective tissue disease? ☐ Yes ☐ No
6. Dementia? ☐ Yes ☐ No
7. Hemiplegia? ☐ Yes ☐ No
8. Leukemia? ☐ Yes ☐ No
9. Malignant lymphoma? ☐ Yes ☐ No
10. Peripheral vascular disease? ☐ Yes ☐ No
11. Ulcer disease? ☐ Yes ☐ No
12. Myocardial infarction? ☐ Yes ☐ No
13. Any tumor? ☐ Yes ☐ No

For Question 14, if the patient has diabetes mellitus indicate if it exists with or without end organ damage.

14. Diabetes mellitus? ☐ None
☐ Without end organ damage
☐ With end organ damage

For Questions 15 and 16, indicate the severity of the disease.

15. Liver disease? ☐ None
☐ Mild
☐ Moderate
☐ Severe

Liver disease severity level examples:

- Severe: patients with cirrhosis, portal hypertension and a history of variceal bleeding.
- Moderate: cirrhosis with portal hypertension, but without bleeding.
- Mild: cirrhosis without portal hypertension or chronic hepatitis.

Product: MK-3415A 14

Protocol/Amendment No.: 002-00

16. Renal disease?
- ☐ None
 - ☐ Mild
 - ☐ Moderate
 - ☐ Severe

Renal disease severity level examples:

- Severe: patients on dialysis, those who had a transplant, and those with uremia.
- Moderate: patients with serum creatinine of >3 mg%.
- Mild: patients with serum creatinine of 2-3 mg%.

For Question 17, if the patient has a malignant solid tumor, indicate if it is metastatic or non-metastatic.

17. Malignant solid tumor?
- ☐ None
 - ☐ Non-metastatic
 - ☐ Metastatic

Product: MK-3415A

15

Protocol/Amendment No.: 002-00

6.5 LABORATORY SAFETY TESTS

Those in bold will be included in the limited safety panel at the time a new episode of diarrhea occurs.

The test in bold italics will only be performed on Day 1.

Blood chemistry tests

serum alanine aminotransferase test

serum albumin test

serum aspartate aminotransferase test

serum chloride test

serum creatinine test

serum glucose test

serum potassium test

serum sodium test

serum alkaline phosphatase test

serum bicarbonate test

serum blood urea nitrogen test

serum calcium test

total serum bilirubin test

total serum protein test

creatinine clearance (calculated)

plasma lactate

Hematology laboratory tests

absolute blood neutrophil count

absolute blood basophilic leukocyte count

absolute blood eosinophilic leukocyte count

absolute blood lymphocyte count

absolute blood monocyte count

blood hemoglobin test

blood platelet count

red blood cell count

white blood cell count

whole blood hematocrit

Urinalysis tests

total urine ketones test

urine appearance test

urine bacteria screen

urine blood test

urine color test

urine creatinine test

urine glucose test

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16

Protocol/Amendment No.: 002-00

urine leukocyte esterase test
urine pH measurement
urine protein test
urine red blood cell count
urine specific gravity measurement
urine white blood cell count
urine microscopic analysis: casts and crystals (only performed for abnormal/positive
dipstick results)

Microscopic evaluation done on urine if a positive dipstick parameter or if abnormalities occur

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17

Protocol/Amendment No.: 002-00

6.6 BIOMARKER EVALUATION IN THIS STUDY

Rationale for Biomarker Evaluations in this Study

A question of interest in the treatment of CDI is how best to identify patients at high risk for CDI recurrence. Although it is possible that risk assessment based on standard demographic and clinical factors (age, co-morbidities, inpatient status) may be sufficient to assess the patient's risk for CDI recurrence, the addition of biomarkers to a demographic/clinical prediction algorithm or as stand-alone classifiers may be of added value. Biomarkers will be collected as part of this trial. *The major aim of biomarker collections in this study is to determine the value of biomarkers of recurrence risk, either when added to a demographic/clinical prediction algorithm, or as stand-alone classifiers.*

Additionally, further elucidation of the mechanism of action (MOA) of monoclonal antibodies (i.e., MK-6072 and MK-3415A) is of interest. Two possible methods for assessing MOA include assessing diversity changes in gut flora (from stool) after MK-6072 or MK-3415A administration, and changes in gene expression in blood over time. *Therefore, the second aim for biomarker collections in this study is to determine whether gene expression or changes in gut flora can elucidate the MOA of MK-6072 or MK-3415A.*

Prior studies have yielded conflicting results regarding demographically- and clinically-based predictors of recurrence. In a set of small studies with a narrow patient population, Hu et al. developed two classification rules. The first predictor was based on age >65 years, severe/fulminant illness, and additional antibiotic use after CDI therapy. This predictor yielded an area under the receiver-operator characteristic curve (AUROC) of 0.80 (95% CI 0.67 – 0.92) in the validation cohort [32]. The second classifier added Day 12 IgG anti-toxin A endogenous antibody to the clinical factors; this second rule yielded an AUROC of 0.62 in the validation cohort. Overall, the patients included in this study represented a very ill, inpatient population. Notably, 30% of subjects in the 63-subject derivation cohort died during the course of the study and could not be assessed for recurrence. In the remaining 70% of subjects, 50% experienced CDI recurrence, a higher rate as compared to other literature. In the validation cohort of this study (n = 89 patients), 45% were immunosuppressed and 30% were in the ICU. An additional 20% died or were lost to follow-up. Also, for the clinical prediction rule in the derivation cohort (n=44 patients) in this study, the authors reported a sensitivity of 0.77 and a specificity of 0.77 which yielded a positive likelihood ratio ($LR_p = \text{sensitivity}/(1 - \text{specificity})$) of 3.35. The 90% CI for LR_p was (1.73, 6.67). Similarly, for the clinical prediction rule in the validation cohort (n=64 patients), the authors reported a sensitivity of 0.54 and a specificity of 0.76 which yielded a LR_p of 2.25. The 90% CI for LR_p was (1.27, 4.14). For the combined prediction rule, there were only 16 patients in the derivation cohort and 26 in the validation cohort that had antibody data. Thus, the confidence intervals are large and difficult to interpret.

Product: MK-3415A

18

Protocol/Amendment No.: 002-00

In a separate study of hospitalized subjects, Garey, et al. examined the relationship between an IL-8 polymorphism and CDI recurrence [45]. The recurrence rate was 24%, and the association with the IL-8 polymorphism was significant.

Age is considered to be a significant risk factor for CDI recurrence [36, 46, 47]. Aging is also associated with immunosenescence [48, 49, 50, 51, 52, 53, 54, 55], suggesting that one of the possible explanations for the association between age and risk of CDI recurrence may be immunosenescence.

Based on these data, several assays will be employed to examine predictors of CDI recurrence in this study. The following assays, which will be evaluated at baseline (within 24 hours prior to infusion on Day 1) in this study, may help to identify a novel laboratory biomarker classifier to predict patients at risk of CDI recurrence:

Blood that is collected at baseline (within 24 hours prior to infusion on Day 1) in all patients:

- Cytomegalovirus (CMV) IgG titer
- Serum dehydroepiandrosterone (DHEA)
- Gene (messenger RNA [mRNA]) expression
- Baseline endogenous anti-toxin A and anti-toxin B antibodies (described in Section 3.3.2.4)

Blood that is collected at baseline (within 24 hours prior to infusion on Day 1) in ~ 170 patients in each treatment group.

- Cytokine panel
- Absolute B lymphocyte count (via flow cytometry)
- CD4:CD8 ratio (via flow cytometry)
- CD8⁺/CD28⁻ and CD8⁺/CD57⁺ cell subsets (via flow cytometry)
- Unswitched and switched memory B-cell subsets (via flow cytometry)

Blood that is collected at Day 4 visit

- Single Nucleotide Polymorphism (SNP) Genotyping

Stool that is collected at baseline (prior to infusion on Day 1) in all patients

- Gut flora diversity (using 16s ribosomal RNA [rRNA] PCR deep sequencing or possibly other techniques) [Should an alternative method for determining gut flora diversity be validated and/or become a standard after the clinical trial has begun, it may be used in addition to or in lieu of 16s rRNA deep sequencing].

Blood samples to assess gene (mRNA) expression will also be collected at predefined post-infusion visits *in a subset of approximately 300 patients*. In addition, in this same set of approximately 300 patients, additional stool samples will be collected at predefined post-infusion visits to further assess the gut flora diversity to assess changes after study

Product: MK-3415A

19

Protocol/Amendment No.: 002-00

drug administration. These additional assays will seek to determine a mechanism of action (MOA) of recovery from CDI with use of monoclonal antibodies.

Immune Risk Panel

Flow Cytometry

Blood samples will be collected within 24 hours prior to infusion on Day 1 for flow cytometry assessment in ~170 subjects from each treatment arm. Specific panels of cell types will be assessed as follows:

CD4/CD8 ratio: This biomarker was first studied in relation to immune function in the context of HIV progression [56]. It was demonstrated that those with a ratio <1 (adult reference range, 0.8 – 4.0) were more likely to progress to AIDS than those with higher ratios. It has also been demonstrated that in adults >65 years of age, a lower ratio is predictive of greater mortality risk [57, 58, 55]. Thus, CD4:CD8 ratio may be a more specific predictor of poor immune function than age alone.

CD8⁺/CD28⁻ and CD8⁺/CD57⁺ cell subsets: As with CD4:CD8 ratio, certain T-cell subsets have been linked to immunosenescence [59, 60, 61, 62] and are associated with persistent and chronic inflammation [63, 64]. Specifically, the CD8⁺/CD28⁻ T-cell population is associated with both ageing and with mortality in the elderly [65]. CD8 and CD57 expression are generally mutually exclusive, so that a high percentage CD8⁺/CD57⁺ T-cell subsets would indicate impaired CD8⁺ T-cell function [66]. It has been suggested that alterations in T-cell subset proportions may result from chronic antigen stimulation such as with long-term CMV infection [67], so both CMV-specific and T-cell subset biomarkers will be tested for determination of which is more sensitive and specific.

Unswitched and switched memory B-cell subsets and absolute B-lymphocyte count: Much of the response to *C. difficile* infection stems from antibody against *C. difficile* toxins, rendering B-cell subsets appropriate targets for biomarker discovery. Lower plasma B cell counts and fewer IgA-producing cells have been observed in the mucosa of *C. difficile* infection patients with recurrence [68], and lower proportions of switched memory B cells are associated with poor vaccine response and greater risk of autoimmune disease [69].

Cytokine Profiles

Serum samples will be collected within 24 hours prior to infusion on Day 1 for measurement of inflammatory cytokines in ~170 subjects from each treatment arm. Several reports have documented changes in average levels of certain cytokines (e.g., CXCL10, TNFaRII, IL6, ICAM-1, and others) associated with aging [70, 71, 72], or age-related mortality [58]. Thus, a panel of serum cytokines will be screened for inclusion in a model for prediction of risk of CDI recurrence. The assay to be used is the RulesBasedMedicine™ Human Inflammation MAP™ Cytokine Panel.

Product: MK-3415A

20

Protocol/Amendment No.: 002-00

Cytomegalovirus (CMV) IgG Levels

Serum samples will be collected within 24 hours prior to infusion on Day 1 for assessment of CMV IgG titers in all patients. A series of reports in non-overlapping groups of elderly patients suggest that serum IgG reactivity against CMV correlates with poor *ex vivo* immune responses as well as with mortality [73, 74, 75] and premature aging [76]. CMV seropositivity is specifically associated with CD8+/CD28- cytotoxic T-cell percentage and inversely with CD4/CD8 ratio [55], and alternations in other CD8+ T-cell subsets [67]. Titers will be assessed by ELISA assay and will be tested for co-linearity with other immune risk markers and for their association with CDI recurrence.

Dehydroepiandrosterone (DHEA)

Levels of dehydroepiandrosterone (DHEA) are known to decline with age [92, 93], and the correlation of endocrinesenescence with immunosenescence has been recently described in a number of inflammatory conditions [94, 95, 96, 97]. It has been considered as an adjuvant to enhance vaccine responsiveness in aging adults with limited success [98, 99, 100]. Its role as a potential biomarker of risk of CDI recurrence will be assessed via a serum sample drawn on Day 1 prior to infusion in all patients.

mRNA profiling

Gene expression profiling has successfully discriminated between patients with different acute infections [77], those with acute versus chronic hepatitis B infection [78], patients with chronic fatigue syndrome [79], and those with sepsis versus systemic inflammatory response syndrome [80]. A gene expression signature has been successfully implemented in clinical practice to classify patients most at risk for acute cellular rejection of cardiac allograft tissue, minimizing the need for biopsy of the endomyocardium [81]. These applications of gene expression profiling suggest that a baseline profile may provide additional information in classifying patients at risk for CDI recurrence. Furthermore, rapid changes in RNA expression from immune response genes might elucidate the mechanism of action (MOA) of the monoclonal antibodies (i.e., MK-3415, MK-6072, and MK-3415A).

Peripheral blood will be collected for RNA profiling on Day 1 (prior to infusion) in all patients. In addition, peripheral blood will be collected for RNA profiling collected in the subset of patients. Peripheral blood will be collected at Day 4, Day 11, and Week 4 for RNA profiling. Affymetrix arrays with probes to all known expressed RNAs will be used to examine associations between baseline RNA signatures and risk of CDI recurrence. Follow-up time points will be analyzed to determine which genes change the most during treatment and determine which if any genes change differentially between monoclonal antibody treated patients and placebo patients. Differentially expressed genes will be analyzed to determine which pathways are differentially affected by monoclonal antibody treatment in order to provide a greater mechanistic understanding of the monoclonal antibody treatment.

Product: MK-3415A

21

Protocol/Amendment No.: 002-00

Single Nucleotide Polymorphism (SNP) Genotyping

A blood sample will be collected from a subset of patients at the Day 4 visit in order to perform retrospective SNP genotyping to examine associations between particular genotypes and outcome. The focus will be on the analysis of the following:

- Known IL-8 polymorphisms as IL-8 is known to be involved in leukocyte trafficking to the gut and colonic inflammation [82, 83, 84, 85, 86, 87, 88, 89, 90]; a common polymorphism may be associated with risk of CDI recurrence [45]
- eSNPs identified from co-variation of DNA and expression profiling in other blood data sets that may be associated with immunosenescence and CDI recurrence risk
- Gene networks associated with the P2X7 gene due its known role in the host response to *C. difficile* infection [91]

Dehydroepiandrosterone (DHEA)

Levels of dehydroepiandrosterone (DHEA) are known to decline with age [92, 93], and the correlation of endocrinesenescence with immunosenescence has been recently described in a number of inflammatory conditions [94, 95, 96, 97]. It has been considered as an adjuvant to enhance vaccine responsiveness in aging adults with limited success [98, 99, 100]. Its role as a potential biomarker of risk of CDI recurrence will be assessed via a serum sample drawn on Day 1 prior to infusion in all patients.

PCR Deep Sequencing of Gut Flora (Stool Specimens)

It is hypothesized that the speed of recovery of global bowel complexity or specific bowel commensal enterocytes is associated with likelihood of recurrent *C. difficile* infection (i.e., the more rapid the recovery, the less risk of recurrence). As a result, stool samples will be collected for 16s rRNA PCR deep sequencing of gut flora at baseline (Day 1) from all patients. In addition, stool samples will be collected for rRNA gut flora PCR deep sequencing in the subset of patients at Day 4 (± 1 day), Day 11 (± 2 days), and Week 4 (Day 29 ± 3 days). Baseline diversity, at time of administration of SOC antibiotics, may serve as a pre-monoclonal antibody biomarker of risk of recurrence. The ensuing time points may elucidate the speed of gut flora recovery and its association with recurrence. A diversity index for each patient will be calculated based on the distribution of species found by sequencing and then either (1) the rate of diversity increase in monoclonal antibody treated samples will be compared to control, or (2) the average diversity will be compared between treated and control at two time points post-therapy.

Analyses Performed for Biomarker

Only subjects in the placebo group of the sub-study will be used in the analysis. *A priori*, it is difficult to predict what statistical model is best suited to this type of data. Three approaches to developing classification models will be considered, including logistic regression models (LRM), classification and regression trees (CART), and discriminant

Product: MK-3415A

22

Protocol/Amendment No.: 002-00

analysis. Only data from the placebo group will be used to develop a classifier of CDI recurrence.

Univariate logistic regression analyses (with recurrent CDI (yes/no) as the outcome variable) will be conducted for all of the baseline biomarkers of interest, and all variables that are significant at $\alpha=0.1$ will be included in a multivariable logistic regression model. Further model refinement may be conducted.

Classification and Regression Tree (CART) methodology will also be used to develop a classifier of recurrent CDI. Random forests may be used to determine which variables are important for prediction of recurrent CDI. These variables will then be used in the CART analysis. A random forest is a collection of many decision trees where each tree is constructed based on a different bootstrap sample of the data. Each tree predicts the class for the points that are not in that particular bootstrap sample. Random forest outputs the class that is the mode of the class's output by individual trees. At each node, rather than choosing the best split among all predictor variables, a random sample of the predictor variables is used.

Additionally, discriminant analysis may be used to develop a classifier of recurrent CDI. Discriminant analysis develops a classification criterion using a measure of generalized squared distance. Each observation is then classified into a group from which it has the smallest generalized squared distance.

Starting with the FAS population, an analysis to identify patients at high risk for CDI recurrence will be performed using the placebo group of the clinical trial data from this study. Baseline demographic, clinical, and biological patient characteristics which are thought to be associated with recurrence of CDI will be assessed. Variables of interest include those that are based on the published literature, as well as those suggested by expert *C. difficile* consultants. Baseline variables, including but not limited to the following, will be evaluated as potential predictors of recurrent CDI: age, sex, race, ethnicity, WBC count, albumin, temperature, severe/fulminant underlying disease (Horn's index), co-morbid conditions (Charlson co-morbidity index), initial therapy for CDI (vancomycin/metronidazole/fidaxomicin), continuation of offending antibiotic after CDI diagnosis, use of additional antibiotics, use of antacid/anti-ulcer agents, history of CDI, number of prior episodes of CDI, ICU admission, and antibodies to toxins A and B. In addition, all of the biomarkers mentioned above will be included in this evaluation.

Each of the potential predictor variables will be evaluated to determine availability and completeness of reporting in the clinical trial data. Descriptive statistics will be used to summarize characteristics of the study population. Continuous variables will be described using means, standard deviations, and ranges. Discrete variables will be described using counts and percentages.

Accuracy of the classifiers obtained from the above methods will be compared by the area under the ROC curve. An area of 1 represents a perfect test, an area of 0.5 represents a failed test, and an area of 0.7 represents a fair test.

Product: MK-3415A

23

Protocol/Amendment No.: 002-00

Sensitivity, specificity, positive likelihood ratio ($LRp = \text{sensitivity} / (1 - \text{specificity})$), positive and negative predictive values of the classifiers obtained from the above methods will be evaluated and compared. 90% confidence intervals (CIs) will be computed for sensitivity, specificity and LRp.

While there are 3 different methods that may be considered for building the classification model, no multiplicity adjustment will be made since the objective is simply to build a classification model that has the pre-specified properties. Once this model is defined, it will have to be validated in an independent sample.

It should be further noted that the underlying diseases and concomitant medications may confound some of the biomarker measurements. It is unknown what proportion of study subjects this will comprise; therefore, we plan to conduct a subpopulation analysis for these subjects.

Sample Size and Power for Biomarkers

The recurrence rate of CDI expected in the placebo group is 20%. A sample size of 170 in the placebo group with a CDI recurrence rate of 20%, a true sensitivity of 0.8, true LRp of 4, yields ~84% power for the lower bound of the 90% CI for LRp to be >2 and lower bound of 90% CI for sensitivity to be >0.6. If the true LRp = 3, there is ~74% power for the lower bound of the 90% CI for LRp to be >2 and lower bound of 90% CI for sensitivity to be >0.6. A lower bound of 2 for the LRp is higher than that from previous classifiers, and would thus represent an improvement on what is currently known.

Product: MK-3415A

24

Protocol/Amendment No.: 002-00

6.7 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

6.7.1 Scope of Future Biomedical Research

The DNA specimens collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA specimens will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

6.7.2 Definitions

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.³
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.⁴
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.²
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

6.7.3 Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-study.

b. Informed Consent

³ National Cancer Institute: <http://www.cancer.gov/dictionary/?searchTxt=biomarker>

⁴ International Conference on Harmonization: Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; <http://www.ich.org/LOB/media/MEDIA3383.pdf>.

Product: MK-3415A

25

Protocol/Amendment No.: 002-00

Informed consent for specimens (i.e., DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Subjects are not required to participate in the Future Biomedical Research sub-study in order to participate in the main trial.

Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-study's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other study purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

Product: MK-3415A

26

Protocol/Amendment No.: 002-00

6.7.4 Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject's clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the study to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority.

Product: MK-3415A

27

Protocol/Amendment No.: 002-00

6.7.5 Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6.7.6 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact MERCK using the designated mailbox Redacted and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MERCK to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the patient of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the patient's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

6.7.7 Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Product: MK-3415A

28

Protocol/Amendment No.: 002-00

Specimens from the site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

6.7.8 Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for **future biomedical** research purposes only as specified in this sub-study will not be used for any other purpose.

6.7.9 Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation, and absence of good clinical practices standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all sites who participated in the Merck clinical trial, and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., Disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

Product: MK-3415A

29

Protocol/Amendment No.: 002-00

6.7.10 Gender, Ethnicity, and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for **future biomedical research**. When studies with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

6.7.11 Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc) to be reassociated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

6.7.12 Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in **future biomedical research**.

6.7.13 Questions

Any questions related to the future biomedical research should be e-mailed directly to
Redacted

3415A, Protocol 002-00 Issue Date: 09-Aug-2011

122

Product: MK-3415A 30

Protocol/Amendment No.: 002-00

7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff

Merck*
Code of Conduct for Clinical Trials

I. Introduction**A. Purpose**

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of patient safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (e.g., Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues**A. Study Conduct****1. Study Design**

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design (i.e., patient population, duration, statistical power) must be adequate to address the specific purpose of the study. Research subjects must meet protocol entry criteria to be enrolled in the study.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to study initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Study sites are monitored to assess compliance with the study protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the study, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the study results and conclusions. Merck funding of a study will be acknowledged in publications.

III. Patient Protection**A. IRB/ERC review**

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect patient safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the patient informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that patient welfare is of primary importance. Potential patients will be informed of the risks and benefits of, as well as alternatives to, study participation. At a minimum, study designs will take into account the local standard of care. Patients are never denied access to appropriate medical care based on participation in a Merck clinical study.

All participation in Merck clinical trials is voluntary. Patients are enrolled only after providing informed consent for participation. Patients may withdraw from a Merck study at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding patient confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations**A. Payments to Investigators**

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll patients in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for patient referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible patients.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the study. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the study protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc.

Pharmacogenomics Informational Brochure



for IRBs/IECs & Investigational Site Staff

I N D U S T R Y
I-PW/G
PHARMACOGENOMICS WORKING GROUP

This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

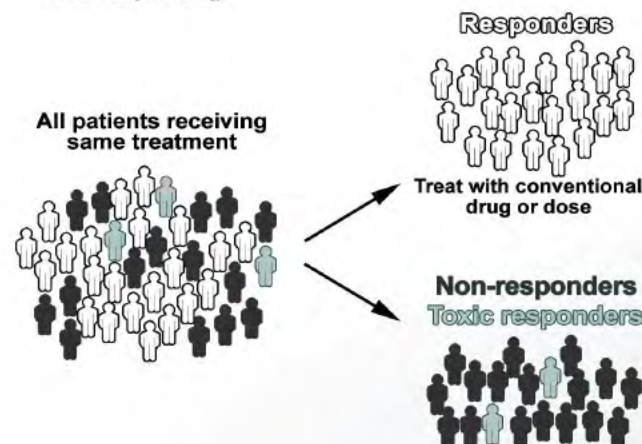
Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA¹, and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the

purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

- i) tests **required** for prescribing
- ii) tests **recommended** when prescribing
- iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies². These elements build upon existing basic elements of informed consent for clinical research on human subjects³.

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the

conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006⁴.

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15¹. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)¹. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request)	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data

usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form².

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)^{5, 6} serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: <http://www.i-pwg.org>

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA),

EMA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued^{1, 3, 7-18}, and are available through: <http://www.i-pwg.org>. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions¹⁹.

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: <http://www.i-pwg.org>.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: <http://www.i-pwg.org>.

Glossary

Identified Data and Samples Identified data and samples are labeled with personal **identifiers** such as name or **identification** numbers (e.g., social security or national insurance number). The use of **identified** data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples Coded data and samples are labeled with at least **one specific** code, and **do not carry any personal identifiers**.

Single-Coded Data and Samples: are usually labeled with a single **specific** code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-Identified) Data and Samples: are initially labeled with a single **specific** code and do not carry any personal **identifiers**. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional **confidentiality** and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples Anonymized data and samples are initially single or double coded but the link between the subjects' **identifiers** and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject **re-identification**.

Anonymous Data and Samples Anonymous data and samples are never labeled with personal **identifiers** when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

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<http://www.i-pwg.org>

Product: MK-3415A

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Protocol/Amendment No.: 002-00

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAMESIGNATUREDATE

8.2 INVESTIGATOR

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAMESIGNATUREDATE
