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001-00

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

Product: MK-3415A

Protocol/Amendment No.: 001-00

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TITLE:

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

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PRIMARY:

CLINICAL PHASE: III

US IND NUMBER: 12823

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

PROTOCOL

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

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 - Base Study for all Patients (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	22
2.1 Objectives and Hypotheses	22
2.1.1 Primary (Interim Analysis)	22
2.1.2 Primary (Final Analysis)	22
2.1.3 Secondary	23
2.1.4 Exploratory Objectives	25
2.2 Patient Inclusion Criteria	25
2.3 Patient Exclusion Criteria	26
2.4 Study Design and Duration	28

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
2.4.1 Summary of Study Design	28
2.4.2 Biomarker Assessments (Patients Enrolled After the Interim Analysis)	30
2.4.3 Treatment Plan	30
2.5 List of Efficacy/Pharmacokinetic/Immunogenicity Measurements	33
2.5.1 Efficacy	33
2.5.1.1 Primary Objective (CDI Recurrence)	34
2.5.1.2 Other Efficacy Measures (Secondary/ Exploratory Objectives)	34
2.5.2 Antibody Levels to Toxin A and Toxin B	34
2.5.3 Immunogenicity	35
2.6 List of Safety Measurements	35
2.7 Statistical Analysis Plan Summary	35
2.7.1 Efficacy Analyses	35
2.7.2 Safety Analyses	37
2.7.3 Power and Sample Size	37
2.7.4 Interim Analyses	39
3. PROTOCOL DETAILS	40
3.1 Rationale	40
3.1.1 Rationale for This Study	40
3.1.2 Rationale for Dose Regimen	42
3.1.3 Rationale for Patient Population and Primary Endpoint	42
3.1.4 Rationale for Adaptive Study Design	43
3.1.5 Rationale for Biomarker Evaluations in This Study	44
3.1.6 Rationale for Optional Specimen Collection for Genetic and Other Biomedical Research	44
3.2 Study Procedures	45
3.2.1 Concomitant Medication(s)/Treatment(s)	45

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.3.3.5 Blood and Urine Sample Collection	53
3.2.3.4 Stratification	53
3.2.3.5 Randomization/Allocation	54
3.2.3.6 Nonrandomized Patients	54
3.2.3.7 Procedures Performed in Conjunction With Treatment – Infusion (Day 1)	55
3.2.3.7.1 Vital Signs Pre-Infusion	55
3.2.3.7.2 12-Lead Electrocardiogram Pre-Infusion	55
3.2.3.7.3 Dosage and Administration of Infusion	55
3.2.3.7.4 Unblinded Preparation of Infusion (Unblinded Pharmacist)	56
3.2.3.7.5 Vital Signs During and Immediately Post-Infusion	57
3.2.3.7.6 Infusion Reactions During and Post-Infusion	57
3.2.3.7.7 Blood Sample Immediately Post-Infusion	58
3.2.3.7.8 12-Lead Electrocardiogram Immediately Post-Infusion	59
3.2.3.8 Procedures Performed Post-Infusion (Day 1 Through Week 12)	59
3.2.3.8.1 Clinical Follow-up	59
3.2.3.8.1.1 Loose Stool Counts and Body Temperature	59
3.2.3.8.1.2 Phone/Visit Contact to Assess and Record Loose Stool Counts and Body Temperature	60
3.2.3.8.1.3 Vital Signs	60
3.2.3.8.1.4 Physical Examination	60
3.2.3.8.2 Laboratory Follow-up	60
3.2.3.8.2.1 Stool Samples	60
3.2.3.8.2.2 Blood and Urine Samples	61
3.2.3.8.3 New Episode of Diarrhea	61
3.2.3.8.3.1 Unscheduled Visit	62

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.2.3.8.4 Procedures During the 9-Month Extended Follow-up (Through Month 12)	63
3.2.3.8.4.1 Randomization/ Allocation into 9-Month Extended Follow-up	63
3.2.3.8.4.2 Assessment of CDI recurrence in the 9-Month Extended Follow-up	63
3.2.3.8.4.3 Stool Sample Collection During the 9-Month Extended Follow-up	63
3.2.3.8.4.4 Blood Sample Collection During the 9-Month Extended Follow-up	64
3.2.3.9 Blinding/Unblinding	64
3.2.3.10 Discontinuation/Withdrawal from Study	65
3.3 Efficacy/Pharmacokinetic/Immunogenicity Measurements	66
3.3.1 Clinical Measurements for Efficacy (Assessment of Primary, Secondary, and Exploratory Efficacy Endpoints)	66
3.3.2 Immunologic and Bacteriologic Measurements	68
3.3.2.1 Toxigenic C. difficile Testing in Stool Specimens (Local Assays Specified in Appendix 6.1)	68
3.3.2.2 Anaerobic Stool Culture	68
3.3.2.2.1 Toxigenic Strain Typing	68
3.3.2.2.2 Antibacterial Susceptibility Testing	69
3.3.2.3 Detection of MK-3415 and MK-6072 in Stool Samples	69
3.3.2.4 Detection of MK-3415 and MK-6072 in Blood Samples	69
3.3.2.5 Detection of Antibodies to Toxin A and Toxin B in Blood Samples	69
3.3.2.6 Detection of Anti-Drug Antibody (ADA) to MK-3415 or MK-6072	70
3.3.2.7 Neutralizing Antibody in Samples Positive for ADA	70
3.3.3 External Data Monitoring Committee (eDMC)	70
3.3.3.1 eDMC Membership	70

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.3.3.2 Summary of eDMC Responsibilities	70
3.3.3.3 eDMC Meeting at the Interim Analysis	72
3.4 Safety Measurements	73
3.4.1 Clinical and Laboratory Measurements for Safety	73
3.4.1.1 Laboratory Safety Tests	73
3.4.2 Recording Adverse Experiences	74
3.4.3 Definition of an Overdose for This Protocol	74
3.4.3.1 Reporting of Overdose to SPONSOR	75
3.4.4 Reporting of Pregnancy to SPONSOR	75
3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR	75
3.4.5.1 Serious Adverse Experiences	75
3.4.6 Evaluating Adverse Experiences	75
3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences	78
3.5 Statistical Analysis Plan (SAP)	78
3.5.1 Responsibility for Analyses/ In-House Blinding	78
3.5.2 Hypotheses	79
3.5.3 Analysis Endpoints	79
3.5.3.1 Efficacy Endpoints	79
3.5.3.2 Safety Endpoints	82
3.5.4 Analysis Populations	83
3.5.4.1 Efficacy Analysis Populations	83
3.5.4.2 Safety Analysis Populations	83
3.5.5 Statistical Methods	83
3.5.5.1 Statistical Methods for Efficacy Analyses	84
3.5.5.2 Statistical Methods for Safety Analyses	86
3.5.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses	87

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
3.5.5.4 Other Analyses	88
3.5.5.4.1 Analysis of High Risk Demographic and Clinical Identifiers	88
3.5.5.4.2 Biomarker Substudy Analysis	88
3.5.5.4.3 Pharmacokinetic/ Population Pharmacokinetic Analysis	88
3.5.6 Multiplicity	88
3.5.7 Sample Size and Power Calculations	93
3.5.8 Combined Data (Subgroup Analyses and Effect of Baseline Factors)	97
3.5.9 Interim Analyses	97
3.5.9.1 Efficacy Interim Analyses	97
3.5.9.2 Safety Interim Analyses	98
3.5.10 Additional 9-Month Extended Follow-up	98
3.6 Labeling, Packaging, Storage, Dispensing, and Return of Clinical Supplies	99
3.6.1 Patient and Replacements Information	99
3.6.2 Product Descriptions	99
3.6.3 Primary Packaging and Labeling Information	100
3.6.4 Secondary Packaging and Labeling Information (kit)	100
3.6.5 Clinical Supplies Disclosure	100
3.6.6 Storage and Handling Requirements	100
3.6.7 Standard Policies / Return of Clinical Supplies	101
3.6.8 Distributing to Sites and Dispensing to Patients	102
3.7 Data Management	102
3.8 Biological Specimens	102
4. ADMINISTRATIVE AND REGULATORY DETAILS	103
4.1 Confidentiality	103
4.1.1 Confidentiality of Data	103

TABLE OF CONTENTS (CONT.)

Contents	Application Starting Page
4.1.2 Confidentiality of Subject/Patient Records	103
4.1.3 Confidentiality of Investigator Information	103
4.2 Compliance with Law, Audit, and Debarment	104
4.3 Compliance with Financial Disclosure Requirements	105
4.4 Quality Control and Quality Assurance	106
4.5 Compliance with Information Program on Clinical Trials for Serious or Life Threatening Conditions	106
4.6 Publications	106
5. LIST OF REFERENCES	108
6. APPENDICES	117
6.1 Acceptable C. Difficile Diagnostic Methods	117
6.2 Bristol Stool Chart	118
6.3 Modified Horn's Index	119
6.4 Charlson Index	120
6.5 Laboratory Safety Tests	122
6.6 Biomarker Evaluation in This Study	124
6.7 High Risk Demographic and Clinical Identifiers	131
7. ATTACHMENTS	132
8. SIGNATURES	146
8.1 SPONSOR'S REPRESENTATIVE	146
8.2 INVESTIGATOR	146

Product: MK-3415A

1

Protocol/Amendment No.: 001-00

1. SUMMARY

1.1 TITLE

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to *Clostridium difficile* toxin A), 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

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 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).

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 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

Product: MK-3415A

2

Protocol/Amendment No.: 001-00

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. Please refer to the CIB 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. Terms in bold are defined in Section 3.3.1.

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 A and/or toxin B. Patients with CDI who are receiving standard of care (SOC) therapy (metronidazole and/ or oral vancomycin, see Section 3.2.1.1) will be randomized in a 1:1:1:1 ratio into 1 of 4 treatment groups. On Day 1 (day of study therapy infusion), patients will receive MK-3415, MK-6072, MK-3415A, or placebo. Investigators are encouraged to enroll 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

Product: MK-3415A

3

Protocol/Amendment No.: 001-00

and laboratory adverse experiences in the 4 treatment groups through Week 4 (Day 29 ± 3 days), hereafter referred to as Week 4.

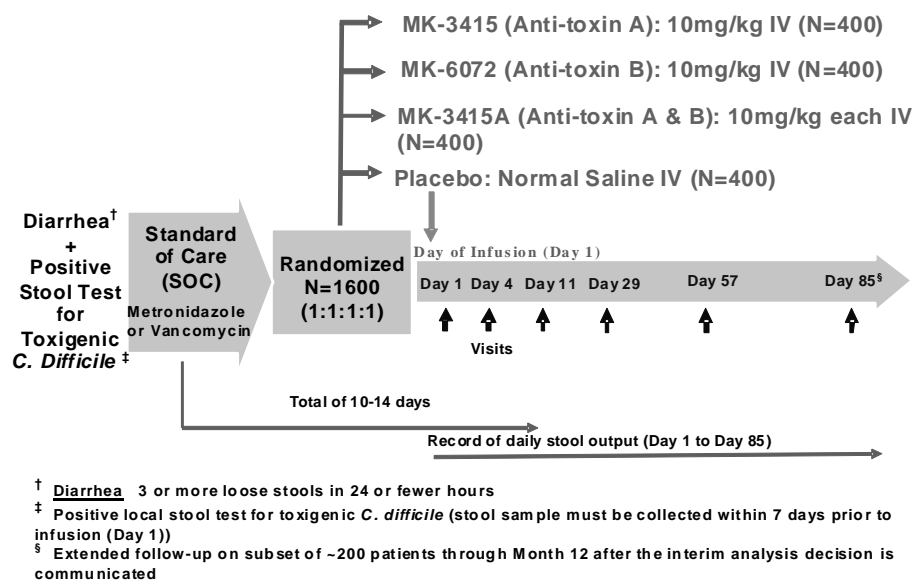
This study has an adaptive design whereby the *individual* monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped based on the results of a single interim analysis if there is a significant difference in the reduction of CDI recurrence when compared to MK-3415A (i.e., MK-3415A is significantly better than MK-3415 and/or MK-3415A is significantly better than MK-6072). The interim analysis will be conducted by a SPONSOR Unblinded Statistician and reviewed by an independent, external Data Monitoring Committee (eDMC).

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 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.: 001-00

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 up to 400 patients in each treatment group (to a maximum sample size of 1,600 patients). Actual enrollment will depend on the results of the interim analysis, as one or both of the individual monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped at the time of the interim analysis (Section 3.3.3 and 3.5.9). Thus, total enrollment will ultimately range from 1,120 patients (if only 2 groups are continued after the interim analysis) to 1,600 patients (if all 4 groups are continued after the interim analysis).

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Patients will be randomized at study onset in a 1:1:1:1 ratio into 1 of 4 treatment groups to receive one of the following:

- A single infusion of the MK-3415 (10 mg/kg of monoclonal antibody to *C. difficile* toxin A only), or
- 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 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 total infusion volume. 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. In this case, the dose of each monoclonal antibody would remain unchanged for patients receiving active treatment. The infusion is to be administered as soon as possible after preparation. Due to slight differences in appearance for MK-3415, MK-6072, and MK-3415A versus placebo (i.e. slight foaming may occur with MK-3415A), 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 2-hour period through a sterile 0.22 micron filter controlled by a volumetric pump.

Product: MK-3415A
Protocol/Amendment No.: 001-00

5

1.7 STUDY FLOW CHART - BASE STUDY FOR ALL PATIENTS (DAY 1 TO WEEK 12)

Activity	Time Point						
	#1	#2	#3	#4	#5	#6	Unscheduled
Study Visit							
Relative Day/Week of Study	Day 1	Week 1 (Day 4 ± 1 day)	Week 2 (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 (stool test for toxigenic <i>C. difficile</i>) [†]	X						X
Written Informed Consent	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 ~2-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
Adverse Experience Assessment [¶]	X						X
Collection of Prior/Concomitant Medication Use [#]	X (All medications [including SOC and other antibiotic therapies])				X (SOC and other antibiotic therapies 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	X	
PATIENT REPORTED OUTCOMES							
Daily Loose Stool Count (with stool count log) ^{¶¶}	X						
Daily Body Temperature (with stool count log) ^{##}	X (Days 1 to 14)						

3415A_001-00_ProtCore APPROVED — 20-Jul-2010
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3415A, Protocol 001-00 Issue Date: 20-Jul-2010

15

Product: MK-3415A
Protocol/Amendment No.: 001-00

6

Activity	Time Point						
Study Visit	#1	#2	#3	#4	#5	#6	Unscheduled
Relative Day/Week of Study	Day 1	Week 1 (Day 4 ± 1 day)	Week 2 (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 EFFICACY EVALUATIONS							
Stool Sample for anaerobic stool culture and other ancillary microbiological assessments (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 and 4	X Once weekly		
Record of Daily Loose Stool Counts on Electronic Case Report Form (eCRF) ^{§§§}	X						
Assessment of CDI Recurrence ^{†††}	X						
PHARMACOKINETICS (PK)							
Blood sample for anti-toxin A (MK-3415) & anti-toxin B (MK-6072) levels ^{†††}	X (pre- & post-infusion)	X	X	X	X	X	
CLINICAL SEROLOGY							
Blood sample for endogenous anti-toxin A & anti-toxin B antibodies ^{†††}	X			X		X	X
BIOMARKER SAMPLES (NOTE: BIOMARKER SUBSTUDY SAMPLES WILL BE COLLECTED ONLY IN A SUBSET OF PATIENTS ENROLLED FOLLOWING THE INTERIM ANALYSIS DECISION)							
Blood Sample for Dehydroepiandrosterone (DHEA) ^{††††}	X (All patients)						
Blood Sample for Cytomegalovirus (CMV) IgG ^{††††}	X (All patients)						
Blood Sample for Cytokine Profile ^{§§§§}	X (Only patients in Biomarker Substudy)						
Blood Sample for Immune Profile (Flow Cytometry) Sample ^{††††}	X (Only patients in Biomarker Substudy)						

3415A_001-00_ProtCore APPROVED — 20-Jul-2010
Worldwide

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3415A, Protocol 001-00 Issue Date: 20-Jul-2010

16

Product: MK-3415A
Protocol/Amendment No.: 001-00

7

Activity	Time Point						
	#1	#2	#3	#4	#5	#6	Unscheduled
Relative Day/Week of Study	Day 1	Week 1 (Day 4 ± 1 day)	Week 2 (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)
BIOMARKER SAMPLES (NOTE: BIOMARKER SUBSTUDY SAMPLES WILL BE COLLECTED ONLY IN A SUBSET OF PATIENTS ENROLLED FOLLOWING THE INTERIM ANALYSIS DECISION)							
Blood Sample for RNA Profiling Sample ^{***}	X (All patients)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)			
Stool Sample for 16s ribosomal RNA (rRNA) PCR deep sequencing of gut flora ^{****}	X (All patients)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)			
Sample for Genetic Evaluation of Single Nucleotide Polymorphism (SNP genotyping, optional) ^{*****}		X (Optional to all patients)					
MECHANISM OF ACTION: COLLECTED FROM SUBSET OF PATIENTS ENROLLED FOLLOWING THE INTERIM ANALYSIS DECISION							
Stool Sample for measurement of MK-3415 and MK-6072 ^{*****}	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)	X (Only patients in Biomarker Substudy)			X
<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 Hom'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> <p> 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.</p>							

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

Product: MK-3415A
Protocol/Amendment No.: 001-00

8

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

†	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 after Week 4 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, all SOC therapy and other antibiotic medications 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. 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 through Day 85 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) 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 and Week 4. Study personnel will then contact the patient once weekly from Week 5 to 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 Day 85 via the appropriate eCRF.
	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 study period, the investigator must send a stool sample for a test of toxigenic <i>C. difficile</i> (tested locally). Stool samples for toxigenic <i>C. difficile</i> testing for each new episode of diarrhea during the study period should use a diagnostic method 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 study period. In addition, the investigator must send another 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.
¶¶¶	Both pre-infusion (within 24 hours prior to infusion) and the immediate post-infusion sample (1 hour \pm 15 minutes after infusion) and other follow-up samples for pharmacokinetic assessments will be completed at scheduled study visits per the protocol (4-6 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 from <u>all patients</u> for endogenous baseline levels. Similar samples for antibody levels will be collected from <u>all patients</u> 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 for dehydroepiandrosterone (DHEA) levels from <u>all patients</u> .
††††	Blood sample (1.0 to 1.5 mL) will be collected within 24 hours prior to infusion for CMV IgG titers from <u>all patients</u> .

3415A_001-00_ProtCore APPROVED — 20-Jul-2010
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Product: MK-3415A
Protocol/Amendment No.: 001-00

9

####	Blood samples (0.25 mL) will be collected within 24 hours prior to infusion to measure a panel of serum cytokine levels from a <u>subset of patients enrolled in the Biomarker Substudy following the interim analysis decision</u>
	Blood sample (3 mL) will be collected within 24 hours prior to infusion for T-cell and B-cell subsets (measured via flow cytometry) from a <u>subset of patients enrolled in the Biomarker Substudy following the interim analysis decision</u>
****	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 enrolled in the Biomarker Substudy following the interim analysis decision</u> will be asked to provide samples at subsequent study visits (Visit 2 [Week 1, Day 4 ± 1 day], Visit 3 [Week 2, Day 11 ± 2 days], and Visit 4 [Week 4, Day 29 ± 3 days])
####	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 [Week 1, Day 4 ± 1 day], Visit 3 [Week 2, Day 11 ± 2 days], and Visit 4 [Week 4, Day 29 ± 3 days]) from a <u>subset of patients enrolled in the Biomarker Substudy following the interim analysis decision</u> . All samples will be sent to a central laboratory for 16S rRNA PCR deep sequencing of gut flora
++++	Blood samples (5 mL) will be collected at Visit 2 (Week 1, Day 4 ± 1 day) on an <u>optional</u> basis for single nucleotide polymorphism [SNP] genotyping
++++	Stool testing for the detection of antibodies of toxin A and toxin B (MK-3415 and MK-6072 antibodies) will be performed in the <u>subset of patients enrolled in the Biomarker Substudy following the interim analysis decision</u> at the specified visits and at unscheduled visits (at the time of new episodes of diarrhea) 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

Product: MK-3415A 10

Protocol/Amendment No.: 001-00

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

A 9-month extended follow-up period will be implemented to assess for CDI recurrence in a subset of patients (~200) who have completed the primary 12 Week study period. 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. Patients are eligible if they are enrolled in the study after the interim analysis decision is communicated. Certain investigator sites will participate in this extended follow-up period.

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

21

Product: MK-3415A

11

Protocol/Amendment No.: 001-00

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) 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 anti -toxin A (MK-3415) & anti-toxin B (MK-6072) levels [¶]			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 any 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). This sample may be collected via a rectal swab unless diarrhea is present at that visit. 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 antibody testing will also be drawn at an unscheduled visit at the time of a new episode of diarrhea .										

Product: MK-3415A

12

Protocol/Amendment No.: 001-00

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary (Interim Analysis)

Primary Objective #1: 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-3415 or MK-6072) 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 MK-3415 given with SOC therapy.

Primary Hypothesis #1b: 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 MK-6072 given with SOC therapy.

(NOTE: Primary Objective #1 will be tested at the interim analysis.)

2.1.2 Primary (Final Analysis)

Primary Objective #2: 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-3415 or MK-6072) with SOC therapy.

Primary Hypothesis #2a: 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 MK-3415 given with SOC therapy.

Primary Hypothesis #2b: 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 MK-6072 given with SOC therapy.

(NOTE: Primary Objective #2 will be tested at the final analysis. This objective will only evaluate MK-3415A relative to those individual monoclonal antibody treatment groups, if any, that remain following the interim analysis.)

Product: MK-3415A

13

Protocol/Amendment No.: 001-00

Primary Objective #3: To determine if treatment with a single infusion of monoclonal antibody therapy with SOC therapy (*combined* monoclonal antibody therapy [MK-3415A] and possibly the separate *individual* monoclonal antibody therapy [MK-3415 and/or 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 #3a: 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 #3b: Treatment with a single infusion of MK-3415 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 #3c: 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.

(NOTE: Primary Objective #3 will be formally tested at the final analysis. This analysis will be evaluated for the MK-3415A group and any individual monoclonal antibody treatment groups remaining following the interim analysis.)

Primary Objective #4: To evaluate the safety profile in patients receiving a single infusion of monoclonal antibody therapy (either as MK-3415, 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 #4: Administration of a single infusion of monoclonal antibody therapy (either as MK-3415, 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.

2.1.3 Secondary

NOTE: The various secondary efficacy objectives (Secondary Objectives #1 through #4 below) are focused on the comparison of MK-3415A versus placebo. However, these secondary efficacy objectives may also include the *individual* monoclonal antibody treatment groups (either MK-3415 or MK-6072) provided one (or both) of these regimens are not found to be different from MK-3415A for the *second* primary hypothesis **AND** demonstrate superiority versus placebo for the *third* primary hypothesis (as outlined above).

Product: MK-3415A

14

Protocol/Amendment No.: 001-00

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.

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 *C. difficile* 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 assess infusion-specific reactions in the treatment group receiving a single infusion of monoclonal antibody therapy (either as MK-3415, 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

15

Protocol/Amendment No.: 001-00

2.1.4 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 groups (either MK-3415 or MK-6072) provided one (or both) of these regimens are not found to be different from MK-3415A for the second primary hypothesis AND demonstrate superiority versus placebo for the third primary hypothesis (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 $<101^{\circ}\text{F}$ [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: Toxigenic *C. difficile* positivity should be determined locally by a hospital/clinic/reference microbiology laboratory test using only those

Product: MK-3415A

16

Protocol/Amendment No.: 001-00

methodologies listed in Appendix 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 SOC therapy for CDI. SOC therapy is defined as the receipt of oral metronidazole, oral vancomycin, or intravenous metronidazole concurrent with oral vancomycin. 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).

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 infusion.

4. Patient is highly unlikely to become pregnant 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.
 - b. A 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.

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.
2. Patient with a planned surgery for CDI within 24 hours.

Product: MK-3415A

17

Protocol/Amendment No.: 001-00

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. Patient has received cholestyramine, rifaximin, nitazoxanide, or fidaxomicin 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.

NOTE: Patients receiving narcotic medications must be on stable doses.

10. Patient plans to take antiperistaltic agents, such as diphenoxyate hydrochloride/atropine sulfate (LOMOTIL™), at any time during the 14 days following infusion (Days 1 to 14).
11. 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.
12. 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.
13. Patient is not expected to survive for 72 hours.
14. 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.

Product: MK-3415A

18

Protocol/Amendment No.: 001-00

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 adaptive design study evaluating the efficacy, safety, and tolerability of monoclonal antibodies to *C. difficile* toxin A and/or toxin B as compared to placebo in adult patients (≥ 18 years of age) diagnosed with CDI. For study entry, patients must have **diarrhea** (passage of 3 or more **loose stools** in 24 or fewer hours [16]) and a positive stool test for toxigenic *C. difficile* as measured locally by one of the methods listed in Appendix 6.1. **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 4 treatment groups for the reduction of CDI recurrence:

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

Patients will be stratified based on 2 factors: (1) SOC therapy (vancomycin vs. metronidazole, 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 either the vancomycin or metronidazole stratum. Following stratification (see Section 2.4.3), patients will be randomized in a 1:1:1:1 ratio into 1 of 4 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). Investigators are encouraged to enroll patients and administer the 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 total 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

Product: MK-3415A

19

Protocol/Amendment No.: 001-00

>15,000 cells/mm³ (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 (adverse experiences and safety laboratory values), and through Week 12 for efficacy outcomes. The primary efficacy endpoint is the proportion of patients with CDI recurrence. Study visits will occur at Day 1, Week 1 (Day 4 ± 1 day), Week 2 (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 (using a stool count log) for 85 days following the infusion. Body temperature will be recorded daily by the patient (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 daily 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 85-day study period.

If there is a new episode of **diarrhea** (see Section 3.2.3.8.3), patients will be instructed to provide a stool sample 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). Stool culture and other ancillary microbiological assessments will be performed at a designated central laboratory. An unscheduled visit should be conducted with the patient, if the stool test for toxigenic *C. difficile* (performed locally) is positive (preferably within 72 hours of the positive local stool test for toxigenic *C. difficile*). Blood samples for endogenous anti-toxin A and anti-toxin B levels and limited safety laboratory tests (as outlined in Appendix 6.5) should be collected at this unscheduled visit.

This study has an adaptive design whereby treatment groups may be dropped based on the results of a single interim analysis. When the first 640 enrolled patients (40% of the targeted patient population) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12), an interim analysis will be conducted. This interim analysis will be conducted by a SPONSOR Unblinded Statistician and reviewed by an independent eDMC to evaluate the efficacy (and safety) of each individual monoclonal antibody treatment group (MK-3415 or MK-6072) relative to the combined monoclonal antibody therapy (MK-3415A) in the reduction of CDI recurrence. If there is a significant difference between treatment groups in the reduction of CDI recurrence (i.e., MK-3415A is significantly better than MK-3415 and/or MK-3415A is significantly better than MK-6072), then the less effective monoclonal antibody treatment groups (MK-3415

Product: MK-3415A

20

Protocol/Amendment No.: 001-00

and/or MK-6072) will be dropped from the study, and the other study groups will continue until the total patient population is enrolled (i.e., ~400 patients are fully enrolled in each remaining treatment group). Enrollment will continue in the 4 treatment groups until the results of the interim analysis are available. The patients enrolled during this time will not be included in the interim analysis and their data will have no bearing on the decisions made at the interim analysis.

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 ~200 patients who have completed the primary 12 Week study period. Patients are eligible if they were enrolled in the study after the interim analysis decision is communicated. The number of patients may increase if 3 or more treatment groups continue after the interim analysis such that ~300 patients will be enrolled if 3 treatment groups continue and ~400 patients will be enrolled if 4 treatment groups continue.

2.4.2 Biomarker Assessments (Patients Enrolled After the Interim Analysis)

Biomarker assessments will be conducted as part of this trial. Certain biomarkers will be collected in all patients. However, in a subset of patients, more intensive biomarker assessments will be performed at select sites (as part of a Biomarker Substudy, which will commence following the communication of the interim analysis decision). Assuming that 2 treatment groups remain after the interim analysis (i.e., the MK-3415A group and the placebo groups), the Biomarker Substudy group will consist of approximately 150 patients. The aims of this substudy are to explore associations among biologically-based baseline factors and CDI recurrence among placebo-treated patients and to help elucidate the mechanism of action (MOA) of MK-3415 and MK-6072. Please refer to Appendix 6.6 for additional information.

2.4.3 Treatment Plan

Overall, the study plans to enroll up to 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 treatment group. Overall enrollment will depend on the results of the interim analysis, as one or both of the individual monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped at the time of the interim analysis. Thus, total enrollment will ultimately range from 1,120 patients (if only 2 groups are continued after the interim analysis) to 1,600 patients (if all 4 groups are continued after the interim analysis).

Table 2-1 describes the treatment plan at study onset. If results at the interim analysis indicate that no treatment groups will be dropped, then the treatment plan will remain as in Table 2-1. Table 2-2 and Table 2-3 describe the potential treatment plans following the interim analysis where one or two treatment groups are respectively dropped.

Product: MK-3415A

21

Protocol/Amendment No.: 001-00

Table 2-1
Treatment Plan At Study Onset

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-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Metronidazole[†]	Inpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A

[†] A minimum of 20% of the total patient population should be from each SOC therapy 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

22

Protocol/Amendment No.: 001-00

Table 2-2

Treatment Plan Following Interim Analysis
(Assuming Continuation of 3 Treatment Groups)

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-3415 or MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415 or MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Metronidazole[†]	Inpatient	MAB	MK-3415 or MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415 or MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A

[†] A minimum of 20% of the total patient population should be from each SOC therapy 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

23

Protocol/Amendment No.: 001-00

Table 2-3

Treatment Plan Following Interim Analysis
(Assuming Continuation of 2 Treatment Groups)

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

[†] A minimum of 20% of the total patient population should be from each SOC therapy 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

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.

Product: MK-3415A

24

Protocol/Amendment No.: 001-00

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 Day 85 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 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 Day 85), (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 eCRF's (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 Day 85) and (2) the type and duration of SOC therapy. The remaining exploratory objectives will be measured by assessment of **loose stool** counts (through Day 85), 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 Antibody Levels to Toxin A and Toxin B

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 3.3.2.5), at the time of a new episode of **diarrhea** if associated with a positive stool test for toxigenic *C. difficile* (see Section 3.2.3.8.3), and during the 9-month extended follow-up period (Months 6, 9, and 12, see Section 3.2.3.8.4.4).

The blood sample collected within 24 hours prior to infusion and within 1 hour (\pm 15 minutes) after infusion on Day 1 will assess the pharmacokinetics of MK-3415 and MK-6072 (see Section 3.3.2.4). 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 Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 5 days). For patients in the 9-month extended follow-up period, a sample will also be collected at Month 6 to assess the pharmacokinetics of MK-3415 and MK-6072.

Product: MK-3415A

25

Protocol/Amendment No.: 001-00

2.5.3 Immunogenicity

A blood sample collected within 24 hours prior to infusion and at Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 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 3.3.2.6 for specific assay details.

2.6 LIST OF SAFETY MEASUREMENTS

Safety will be assessed through an evaluation of clinical and/or laboratory adverse experiences. Clinical and laboratory adverse experiences will be collected from the time the informed consent is signed through Week 4 post-infusion. 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, in 30-minute increments until the end of the infusion, at the end of the infusion, and at other scheduled visits per protocol. Laboratory tests, including hematology, chemistry, and urinalysis (as outlined in Appendix 6.5), will be performed pre-study, and at scheduled post-infusion study visits at Week 1 (Days 4 \pm 1 day), Week 2 (Days 11 \pm 2 days), and Week 4 (Day 29 \pm 3 days). 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.

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, interim analyses, and other statistical issues are provided in Section 3.5 of the protocol details.

2.7.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 2-4 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

Product: MK-3415A

26

Protocol/Amendment No.: 001-00

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.

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 (vancomycin vs. not vancomycin) and hospitalization status (in-patient vs. out-patient).

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.

Individual monoclonal antibody therapies (MK-3415 and MK-6072) will be compared separately to the combined monoclonal antibody therapy (MK-3415A), and the various active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared separately to placebo. Under the global null hypothesis that the four therapies (three 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.

Key Secondary Efficacy Analysis

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:

Product: MK-3415A

27

Protocol/Amendment No.: 001-00

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

Table 2-4

Summary of Analysis Strategy for Key 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			

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 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) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with Tier 1 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 1600 patients to be randomized in a 1:1:1:1 ratio to each of the four treatment groups (MK-3415A, MK-3415, MK-6072, and placebo). The following power calculations are based on a two group chi-square test for comparing independent proportions.

Product: MK-3415A

28

Protocol/Amendment No.: 001-00**Primary Endpoint - CDI Recurrence (Interim and Final Analyses)**

An interim analysis is planned when the first 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12). The purpose of this interim analysis is to evaluate if treatment with combined monoclonal antibody therapy (MK-3415A) is superior to treatment with either of the individual monoclonal antibody therapies (MK-3415 or MK-6072). If MK-3415A is found to be superior to MK-3415 or MK-6072, then further enrollment in one or both of these respective groups will be stopped. These two comparisons will be performed at a 1-sided alpha level of 0.050, as described in Section 3.5.6.

At the interim analysis, it is anticipated that 160 patients per group will be in the analysis population for the CDI recurrence endpoint. This will provide approximately 80% power to detect the following differences in the incidence of CDI recurrence between combined monoclonal antibody therapy (MK-3415A), π_1 , and the individual monoclonal antibody therapies (MK-3415 or MK-6072), π_2 :

π_1	π_2	Difference	Power
.08	.172	.092	80%
.09	.185	.095	80%
.10	.199	.099	80%

At the final analysis, 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 - (Final Analysis)

At the final analysis, 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

29

Protocol/Amendment No.: 001-00

Secondary Endpoint - CDI Recurrence in Subset of patients with Clinical Cure - (Final Analysis)

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%

2.7.4 Interim Analyses

One interim analysis will be performed in this study. Results will be reviewed by an eDMC. The endpoint, timing, and purpose of the interim analysis are summarized in Table 2-5 below. The decision rule and other statistical details are further described in Section 3.5.9.

Table 2-5

Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
CDI Recurrence	After the first 640 patients (40% of planned total number of randomized patients) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12).	Adapt study design by dropping individual monoclonal antibody groups (MK-3415 and/or MK-6072)

Product: MK-3415A

1

Protocol/Amendment No.: 001-00

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.: 001-00

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

Current therapeutic options for the treatment of *C. difficile* infection are limited to two antimicrobial agents, namely vancomycin and metronidazole. 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. While most cases of *C. difficile* infection resolve after withdrawal of the offending systemic antibiotic and treatment with either oral vancomycin or metronidazole, 15-30% of patients will experience recurrent disease. Recurrence rates appear to be similar after treatment with metronidazole or vancomycin. [10, 4, 11] 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 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

Product: MK-3415A

3

Protocol/Amendment No.: 001-00

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 CIB for a full assessment of the available preclinical and clinical data for this compound.

3.1.2 Rationale for Dose Regimen

As noted in Section 3.1.1, data from both the primary and relapse disease hamster models supports administration of MK-3415/MK-6072/MK-3415A. Given the protection provided for *C. difficile* infection in hamsters administered MK-3415/MK-6072/MK-3415A, the serum concentrations of the monoclonal antibodies in the surviving hamsters were measured as a correlate for a dose that might be protective in humans. Peak median (range) serum anti-toxin A and anti-toxin B at 48 hours after challenge in the survivors were 359 $\mu\text{g/mL}$ (209-1010) and 261 $\mu\text{g/mL}$ (128-805), respectively. These concentrations are comparable to the serum concentrations of healthy human subjects who received 10 mg/kg of each monoclonal antibody in Phase I (MK-3415/MK-6072/MK-3415A). When 10 mg/kg of each monoclonal antibody was 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.

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

Product: MK-3415A

4

Protocol/Amendment No.: 001-00

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 group. 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 Adaptive Study Design

Results from the Phase II study of MK-3415A support its efficacy as a combination of monoclonal antibodies for toxin A and toxin B. However, the clinical efficacy data for each individual component of MK-3415A (i.e., MK-3415 and MK-6072) is limited. The current study will be performed using an adaptive design. This approach represents an efficient method to evaluate the contribution of individual monoclonal antibody components (MK-3415 [10 mg/kg of monoclonal antibody to *C. difficile* toxin A] and MK-6072 [10 mg/kg of monoclonal antibody to *C. difficile* toxin B] relative to the combined product, MK-3415A (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]) by using the results of an interim analysis (conducted when 40% of the targeted patient population have been enrolled and have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12). This approach allows for 1 or both of the individual monoclonal antibody treatment groups (MK-3415 and/or MK-6072) to be dropped at the interim analysis if the results are not comparable to those seen in the combination monoclonal antibody group (MK-3415A), thereby allowing for effective use of resources for the portion of the study conducted following the interim analysis. In recognition of the unmet medical need for new therapies to address the growing *C. difficile* epidemic, the adaptive design should provide the most efficient way to determine

Product: MK-3415A

5

Protocol/Amendment No.: 001-00

the optimal therapeutic approach. Importantly, an independent external Data Monitoring Committee (eDMC) will review the results of the interim analysis. The eDMC will use the guidelines proposed in Table 3-5 (Statistical Evaluation Plan and Multiplicity Strategy) and in Section 3.5.9 to make recommendations about modifications to the study design.

The interim analysis uses a one-sided p-value of 0.05 to provide evidence that the individual monoclonal antibody therapy groups (MK-3415 and/or MK-6072) could be dropped relative to the combination group (MK-3415A). With this approach, the potential of dropping individual monoclonal antibody treatment groups inappropriately in the face of no true differences relative to combination monoclonal antibody (MK-3415A) treatment group remains relatively low. This p-value choice is appropriate since available preclinical data from multiple sources have demonstrated that a combination monoclonal antibody product (MK-3415A) was associated with better responses in CDI as compared to the individual monoclonal antibody treatment groups (MK-3415 or MK-6072). Additionally, as previously summarized in Section 3.1.1, available clinical data from the prior Phase II study have demonstrated that a combination monoclonal antibody product (MK-3415A) was associated with a statistically significant difference relative to placebo in the prevention of CDI recurrence [15]. Finally, available clinical data from an earlier Phase II study have demonstrated no numerical difference between individual monoclonal antibody therapy (MK-3415) as compared to placebo [37].

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 with assays performed on samples collected at study entry in all patients. In addition, after the interim analysis decision is communicated, more intensive analyses will be collected in a subset of ~150 patients who participate in the Biomarker Substudy. Participants in the Biomarker Substudy will have assays performed on samples collected at study entry and several post-infusion visits. Please refer to Appendix 6.6 for additional information.

3.1.6 Rationale for Optional Specimen Collection for Genetic and Other Biomedical Research

As part of this study, Merck Research Laboratories would like to conduct genetic and other biomedical research on specimens routinely and specifically collected during this clinical study. Genetic and other biomedical research on such fluids and specimens may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Conduct of genetic and other biomedical research that is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) may only be

Product: MK-3415A

6

Protocol/Amendment No.: 001-00

obtained from appropriately consented patients as an optional procedure (refer to “Consent and Collection of Specimens for Genetic and Other Biomedical Research” section). The objective of collecting specimens for future 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 patients receive the correct dose of the correct drug at the correct time.

3.2 STUDY PROCEDURES

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

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, or intravenous metronidazole concurrently with oral vancomycin) 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 the infusion.

NOTE: SOC medications will NOT be provided by the SPONSOR.

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 (i.e., 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 total 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.

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.

Product: MK-3415A

7

Protocol/Amendment No.: 001-00**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].

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].

Vancomycin 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, nitazoxanide, or fidaxomicin 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. Patients receiving narcotic medications must be on stable doses.
- Receipt of antiperistaltics, such as diphenoxylate hydrochloride/atropine sulfate (LOMOTIL™), through Day 14 of the follow-up period after infusion.
- 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 SOC therapy (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.

Product: MK-3415A

8

Protocol/Amendment No.: 001-00

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, 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.

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

Product: MK-3415A

9

Protocol/Amendment No.: 001-00

pharmacokinetic measurements), anti-drug antibody (ADA), neutralizing antibody (if positive ADA is detected), and blood chemistry and hematology (as part of safety monitoring). 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). In addition, blood will also be collected prior to infusion for certain biomarkers in all patients enrolled in the study. These will include serum dehydroepiandrosterone [DHEA] level, cytomegalovirus [CMV] IgG titer, and mRNA profiling. In addition, stool will also be collected for 16s rRNA PCR deep sequencing of gut flora in all patients per protocol. Providing consent allows these samples to be obtained from all patients.

3.2.3.1.2 Consent and Collection of Specimens for Genetic and Other Biomedical Research

During this study, a separate signed informed consent will be administered to cover the conduct of genetic and other biomedical research, including 1) optional blood specimen(s) and 2) specimens remaining after the main study is completed (e.g., blood, body fluids and/or tissue).

Review committees (IRBs/ERCs) and/or individual sites may choose not to participate, and in some cases local regulations may prevent conduct of genetic and other biomedical research on collected specimens. Under such circumstances, this information should be communicated to Merck Research Laboratories by the local study representative of the associated agencies and/or IRBs/ERCs, when initial submission takes place. Such declaration will not lead to protocol amendment. However, a Protocol Clarification Letter could be issued by the MRL clinical team.

Only those patients who have consented to allow the genetic and other biomedical research may have additional, optional blood specimen(s) drawn. The investigator or designate is responsible for explaining the optional nature of the conduct of genetic and other biomedical research and that participation in the associated clinical study is not dependent upon giving consent or additional samples for such research. The investigator or designate is also responsible for verifying the patient's written consent before obtaining any additional blood specimens for such research. Collection of the additional specimens may occur at any visit after the corresponding consent has been signed.

In some cases, the approval of this consent form and the associated protocol procedures (e.g., collection of blood specimens) may proceed independently from the associated main clinical study through review (by Agencies, IRBs/ERCs, Independent Ethical Committees, Privacy Committees, etc.). In such cases, the Clinical Study approval should not be delayed by the consent approval process for the optional specimen collection for genetic and other biomedical research. If the latter consent is denied, additional blood specimens for genetic and other biomedical research will not be collected and main study specimens will not be used for that purpose. If the consent for optional specimen collection for genetic and other biomedical research is delayed, the

Product: MK-3415A

10

Protocol/Amendment No.: 001-00

additional blood specimens must not be collected and main study specimens will not be used for genetic and other biomedical research until approval is granted. In either event, specimen testing defined as part of the main study would not be affected by the consent process for genetic and other biomedical research.

For additional background information, see Attachments "Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research Collected from Clinical Trials Sponsored by Merck & Co., Inc.: A Guideline for Clinicians and Privacy Board Members," and "Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff."

3.2.3.1.3 Informed Consent for Biomarker Substudy (Patients Enrolled at Select Sites Following the Interim Analysis Decision)

Sites will need to be pre-approved by their IRB or ERC in order to enroll patients into this substudy. A patient who has consented to participate in the Biomarker Substudy may continue in the main study if they decide to no longer continue in the Biomarker Substudy. Discontinued patients will be replaced in the Biomarker Substudy to achieve 150 patients (or more) who complete the Biomarker Substudy.

The Biomarker Substudy will include the collection of additional blood and stool samples. Additional blood samples include a serum cytokine panel, flow cytometry (T-cell/B-cell subsets), and mRNA profiling at predefined protocol time points. Additionally, as part of the Biomarker Substudy, stool samples will be collected for 16s rRNA PCR deep sequencing of gut flora and for detection of MK-3415 and MK-6072 at predefined protocol time points. These additional samples will be collected at the same time as the samples for the main study and therefore will not require extra study visits. Additional details pertaining to this subset of patients included in the Biomarker Substudy are found in Sections 3.2.3.8.2.1 and 3.2.3.8.2.2, as well as Appendix 6.6.

3.2.3.1.4 Informed Consent for 9-Month Extended Follow-up (Patients Enrolled Following the Interim Analysis Decision)

An extended follow-up period of 9 months will be conducted in a subset of ~200 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 B antibodies, pharmacokinetic assessment of MK-3415 and MK-6072, and presence of anti-drug antibodies (ADA).

Patients are eligible if they were enrolled in the study after the interim analysis decision is communicated. Therefore, the extended follow-up will only be in patients from those treatment groups that continue following the interim analysis decision, although patient treatment groups will remain blinded. The number of patients may increase if 3 or more treatment groups continue after the interim analysis decision such that ~300 patients will be enrolled if 3 treatment groups continue and ~400 patients will be enrolled if 4 treatment groups continue. 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.

Product: MK-3415A

11

Protocol/Amendment No.: 001-00

Certain investigator sites will participate in this extended follow-up period. Sites will need to be pre-approved by their IRB or ERC in order to enroll patients into this extension. Patients who participate in the Biomarker Substudy can also consent to participate in this 9-month extended follow-up period.

3.2.3.1.5 Informed Consent for Future Use of Biological Samples

Samples are being collected during the course of this study to assess the safety, tolerability, and efficacy of MK-3415, MK-6072, and MK-3415A. Every effort has been made to keep the volume of samples collected for the study procedures to a minimum. However, in the event that any samples are left over after completion of all study-related procedures, these samples could be a valuable resource for future research. For stool samples, this may include testing for other bacteria (organism types and counts) as well as toxigenic *C. difficile* testing. For blood samples, this may include testing for anti-toxin antibody levels.

By signing the main consent form, patients are only giving their permission to use these samples for the study-related procedures. Before any leftover samples can be used for any research other than that specified in the protocol, patients must sign an additional consent form for future use of biological samples. This additional consent should make it clear that:

- No additional samples will be collected beyond what is needed for the main study (i.e., the consent for future use only applies to leftover samples after completion of all study-related procedures).
- No genetic testing (other than that specified in this protocol) will be performed using the leftover samples.
- Consent for future use of leftover samples is optional. If the patient does not wish that leftover samples be used for research not specified in the study procedures, their participation in the main study or their medical care will not be affected in any way.
- Consent for future use of leftover samples can be withdrawn at any time, even if the patient does not withdraw consent for the main study.
- Although the use of these samples may lead to scientific advances that may help others, it is very unlikely that the patient will receive any direct benefit by allowing their leftover samples to be used.

The same measures to maintain confidentiality and privacy will be applied to leftover samples as those applied when these samples are used in the main study. The duration of retention of samples following overall completion of the study will be no more than 10 years.

Product: MK-3415A

12

Protocol/Amendment No.: 001-00

3.2.3.2 Assignment of Baseline 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 number 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 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 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 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.

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

Product: MK-3415A

13

Protocol/Amendment No.: 001-00

having **diarrhea** for a diagnosis of CDI. This number of **loose stools** should be from the day on which the patient has **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.

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. Collection of vital signs at other times during the study are 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.

Product: MK-3415A

14

Protocol/Amendment No.: 001-00

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. This sample will also be tested for detection of MK-3415 /MK-6072 levels in the subset of patients entered into the Biomarker Substudy (following the interim analysis decision). 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. In the subset of patients who participate in the Biomarker Substudy (enrolled following the interim analysis decision), blood samples will also be collected within 24 hours prior to infusion for a cytokine panel and flow cytometry (T-cell and B-cell subsets). All blood samples will be tested by designated central laboratories.

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 (vancomycin vs. metronidazole [as prescribed by the attending physician]) and their hospitalization status (inpatient or outpatient).

Product: MK-3415A

15

Protocol/Amendment No.: 001-00

A minimum of one fifth (20%) of the total patient population should be enrolled into each SOC therapy stratum (i.e., at least 20% in the vancomycin stratum and at least 20% in the metronidazole stratum). Patients receiving concurrent therapy of oral vancomycin and intravenous metronidazole should be entered into the vancomycin stratum. The minimum proportion of patients entered into each stratum will be managed through a central randomization system. Enrollment into either stratum may be closed to manage these proportions.

The second stratification is based on the current hospitalization status. 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). Stratification by these factors at study entry will continue following the interim analysis.

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 an allocation number via a centralized randomization system. Randomization will occur in a 1:1:1:1 ratio into 1 of the 4 treatment groups as previously described.

Following the interim analysis (See Sections 3.3.3 and 3.5.9), randomization into the study may adjust to a 1:1:1 ratio into 1 of 3 treatment groups or a 1:1 ratio into 1 of 2 treatment groups if the results of the interim analysis conclude that 1 or 2 of the individual monoclonal antibody treatment groups (MK-3415 or MK-6072) can be dropped. However, if the results at the interim analysis indicate that no treatments groups are dropped, then a 1:1:1:1 randomization ratio will be maintained to the completion of the study. Enrollment will continue in the 4 treatment groups until the results of the interim analysis are available (See Section 2.4.1).

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

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 number, yet not be randomized to a study treatment group. In this

Product: MK-3415A

16

Protocol/Amendment No.: 001-00

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 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-3415, MK-6072, MK-3415A) and placebo will be administered as a single 250 mL intravenous infusion through a sterile 0.22 micron filter using a volumetric pump over approximately a 2-hour period on Day 1. The monoclonal antibody infusion should be administered as soon after preparation as possible. 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.

Product: MK-3415A

17

Protocol/Amendment No.: 001-00

Table 3-1

Clinical Supplies Dose and Volume

Product	Dosage	Volume [†]
MK-3415 (toxin A antibody)	10 mg MK-3415/kg of patient weight	Single infusion of 250 mL
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.		

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.

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-3415, 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. 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-3415, 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

Product: MK-3415A

18

Protocol/Amendment No.: 001-00

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) every 30 minutes during 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.

3.2.3.7.6 Infusion Reactions During and Post-Infusion

Monoclonal antibodies may 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.

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

19

Protocol/Amendment No.: 001-00

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 at the bedside 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 Immediately Post-Infusion

A blood sample for pharmacokinetic evaluation of MK-3415 and MK-6072 will be drawn 1 hour ± 15 minutes 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 20

Protocol/Amendment No.: 001-00

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

3.2.3.7.8 12-Lead Electrocardiogram Immediately 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, Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 5 days). At each visit, the stool count log should be reviewed by study personnel to monitor compliance and accuracy in completion. The occurrence of adverse experiences and the use of concomitant medications will be assessed during scheduled study visits through Week 4.

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

3.2.3.8.1.1 Loose Stool Counts and Body Temperature

All patients will receive a stool count log to record their daily stool output (Day 1 through Day 85) 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.

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 should take their temperature at approximately the 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.

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

Product: MK-3415A

21

Protocol/Amendment No.: 001-00

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 and Week 4. Weekly phone calls will be made through the remainder of the 12 Week study period 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: Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 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 Week 2 (Day 11 \pm 2 days) and Week 12 (Day 85 \pm 5 days). In addition, a physical examination should be performed each time there is an unscheduled visit, as described in Section 3.2.3.8.3.

3.2.3.8.2 Laboratory Follow-up

3.2.3.8.2.1 Stool Samples

The subset of patients participating in the Biomarker Substudy, which begins enrolling after the interim analysis decision is communicated, will provide stool samples for 16s rRNA PCR deep sequencing of gut flora at Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), and Week 4 (Day 29 \pm 3 days). These samples will be used for the Biomarker Substudy analysis, as described in Appendix 6.6.

The patients participating in the Biomarker Substudy will also provide stool samples for detection of MK-3415 and MK-6072 at Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), and at an unscheduled visit at the time of a new episode of **diarrhea** (see Section 3.2.3.8.3). These stool samples are intended to assess mechanism of action. Additional information can be found in Section 3.3 regarding the assay.

Product: MK-3415A

22

Protocol/Amendment No.: 001-00

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.

3.2.3.8.2.2 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 Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), and Week 4 (Day 29 \pm 3 days) according to the Study Flow Chart (Section 1.7). The specific laboratory safety measurements are outlined in Appendix 6.5. In addition, in the event there is a new episode of **diarrhea** and an unscheduled visit occurs, 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 \pm 3 days) and Week 12 (Day 85 \pm 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 Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 5 days), as described in the Study Flow Chart (Section 1.7).

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

Patients participating in the Biomarker Substudy will provide additional blood samples at Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), and Week 4 (Day 29 \pm 3 days) for mRNA profiling. These samples will be used for the Biomarker Substudy analysis, as described in Appendix 6.6

Additionally, for patients consenting to samples for optional genetic testing, there will be blood drawn at Week 1 (Day 4 \pm 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

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 9-Month extended follow-up period for those patients who participate in this extended follow-up period), the patient should collect a stool sample and store it frozen until it can be provided to study personnel and

Product: MK-3415A

23

Protocol/Amendment No.: 001-00

those study personnel should be contacted immediately to report the new episode of diarrhea. Patients will receive stool collection and transport kits. Importantly, directions will be provided by the SPONSOR in the Laboratory Manual on how to properly collect and transport the stool sample in order to minimize contamination and protect the heat-sensitive toxin.

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, a stool sample will be sent to the designated central laboratory for detection of MK-3415 and MK-6072 (see Section 1.7) for the subset of patients entered in the Biomarker Substudy (enrolled after the interim analysis decision has been communicated).

Stool samples should not be collected by rectal swab throughout the 12-Week initial study period or during the 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 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.

3.2.3.8.3.1 Unscheduled Visit

If the local stool test for toxigenic *C. difficile* is positive, an unscheduled visit should be scheduled and conducted with the patient (preferably within 72 hours of the positive local stool test for toxigenic *C. difficile*). At the unscheduled visit, blood samples will be collected to test for endogenous anti-toxin A and anti-toxin B levels. In addition, at this unscheduled visit, a limited panel of safety laboratory tests will be collected. 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

Product: MK-3415A

24

Protocol/Amendment No.: 001-00

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

An extended follow-up period of 9 months will be conducted in a subset of ~200 patients who have completed the 12 Week study period. Patients are eligible if they were enrolled in the study after the interim analysis is completed and the decision is communicated. Therefore, the extended follow-up will only be in patients from treatment groups that continue following the interim analysis decision, although patient treatment group will be unknown to maintain the study blinding. The number of patients may increase if 3 or more treatment groups continue after the interim analysis decision is communicated such that ~300 patients will be enrolled if 3 treatment groups continue and ~400 patients will be enrolled in 4 treatment groups continue.

Certain investigator sites will participate in this extended follow-up 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.

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

Patients who continue in the 9-month extended follow-up period of this study will retain the 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 9-Month Extended Follow-up

If during the extended follow-up period (after Week 12 through Month 12), a patient experiences **diarrhea**, study personnel should be contacted immediately, a stool sample should be collected and stored frozen until it can be provided to study personnel, and an unscheduled visit planned if the local stool test for toxigenic *C. difficile* is positive (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 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.

Product: MK-3415A

25

Protocol/Amendment No.: 001-00

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. A stool sample collected upon the return of **diarrhea** should be stored frozen by the patient until it can be provided to site personnel. 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 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). 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 ADA (including neutralizing antibody, at Month 6).

Serum will be separated from blood samples and sent to the central laboratory for testing. All of these samples will be shipped to a central laboratory. 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 (and its designee) 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-3415, 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-3415, 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.

Product: MK-3415A

26

Protocol/Amendment No.: 001-00

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.

Additional information regarding maintenance of blinding for the interim analysis is found in Sections 3.3.3. and 3.5.9.

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.

Patients who optionally donate blood, body fluids and/or tissue for genetic and other biomedical research analyses may request that their specimen(s) be removed from storage and destroyed in accordance with the terms outlined in the associated consent form. Patients should be informed that withdrawal from the main study does not cause the withdrawal and destruction of the optional specimens for genetic and other biomedical research. Requests for withdrawal and destruction of the optional specimens for genetic and other biomedical research should be made in writing to the investigator. In turn, the investigator must promptly inform MRL so that appropriate follow-up can be initiated. The investigator will be informed when the associated specimens are destroyed and should notify the patient that specimen destruction is complete.

Product: MK-3415A

27

Protocol/Amendment No.: 001-00

A patient participating in the Biomarker Substudy may discontinue from those procedures and still continue in the main study. In this case, the patient would be replaced in the Biomarker Substudy. Please consult the eCRF Entry Guidelines for instructions regarding the completion of the appropriate eCRFs.

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 in the stool count log following the infusion through Day 85. 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 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 Day 85), (2) stool test for toxigenic *C. difficile*, and (3) the type and duration of SOC therapy.

The evaluation of CDI recurrence in certain key 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.

Product: MK-3415A

28

Protocol/Amendment No.: 001-00

- 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*.
- 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 Day 85) 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 for 85 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).

Product: MK-3415A

29

Protocol/Amendment No.: 001-00

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 of those with an elevated temperature ($\geq 101^{\circ}\text{F}$ [38.4°C]) at baseline and resolution of this elevated temperature ($< 101^{\circ}\text{F}$ [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 in the US and in other countries. 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 central laboratory. Anaerobic stool culture will be used to isolate *C. difficile* from stool specimens in patients.

The stools are thawed inside an anaerobic chamber. Approximately 0.25 mL of stools are 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 ribosomal 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

30

Protocol/Amendment No.: 001-00

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 and vancomycin, 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 for assessment of MK-3415 and MK-6072 levels in approximately 150 patients (i.e., the subset participating in the Biomarker Substudy). Stool 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 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.

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

Product: MK-3415A

31

Protocol/Amendment No.: 001-00**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.

3.3.3 External Data Monitoring Committee (eDMC)

An independent, unblinded eDMC will be appointed and responsible for the review of the interim efficacy data for this study. The eDMC will also review the accumulated safety data from the study, in conjunction with the scheduled interim efficacy review. The responsibilities of the eDMC are described in the subsections that follow. Refer to Sections 3.5.1 and 3.5.9 for further details pertaining to the interim analysis.

The roles and responsibilities of the eDMC and logistical details will be summarized in an eDMC Charter.

3.3.3.1 eDMC Membership

The eDMC will be comprised of 3-7 independent (i.e., non-SPONSOR) experts in operational, medical, and biostatistical aspects of clinical trials, specifically including senior national (and possibly international) healthcare leaders, clinicians, and/or statisticians. One member of the eDMC will serve as Chairperson. No member of the eDMC may participate as a primary investigator, a member of the Scientific Advisory Committee (SAC), or be involved in any other way with the conduct of the study. Only the SPONSOR Unblinded Statistician, SPONSOR Unblinded Statistical Programmer, and the eDMC will be aware of the treatment-level results of the interim analysis. The Unblinded Statistician and Unblinded Statistical Programmer must adhere to the same confidentiality requirements as the eDMC members.

3.3.3.2 Summary of eDMC Responsibilities**Efficacy Data Review**

A primary responsibility of the eDMC is to evaluate the efficacy data from this study *at the interim review only*. The purpose of the interim analysis is to evaluate whether the

Product: MK-3415A

32

Protocol/Amendment No.: 001-00

individual monoclonal antibody groups (MK-3415 and MK-6072) meet success criteria related to Primary Objective #1 of the study (relative to the combined monoclonal antibodies, MK-3415A). The interim analysis is planned to be performed when the first 640 enrolled patients (40% of the targeted patient population) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12). The accumulated data will be summarized and analyzed according to the analysis plan for Primary Objective #1 of the study, as described in Section 3.5.9. A SPONSOR Unblinded Statistician and SPONSOR Unblinded Statistical Programmer will be responsible for preparing the unblinded interim summary of efficacy data for this study. The Unblinded Statistician will present a report of the treatment-level unblinded results to the eDMC.

Enrollment will continue into the 4 treatment groups until the interim analysis decision is communicated. Following the eDMC review of the data and recommendation, enrollment may continue in 4 treatment groups or be adjusted to randomize patients equally into 2 or 3 treatment groups. The eDMC may reserve the authority to request summaries of any other efficacy data that the committee determines to be of interest. The need for additional reports at the interim analysis will be assessed by the eDMC.

The eDMC will formally meet once to review the data as prepared by the SPONSOR Unblinded Statistician. Following their meeting, the eDMC Chairperson will be responsible for reporting post-meeting decisions and/or recommendations (e.g., discontinuation of specific treatment group(s)) to a steering committee comprised of Merck Senior Management members (Merck Senior Management Committee, or MSMC). The MSMC may discontinue the study in the event of efficacy concerns reported by the eDMC. The treatment-level results will not be provided to the MSMC unless there is concern that the study should be stopped.

Safety Data Review

Another primary responsibility of the eDMC is to evaluate the safety data from this study at the interim analysis (coinciding with the efficacy interim analysis). Specifically, at the time of the interim analysis, the SPONSOR Unblinded Statistician will provide the eDMC with the following:

- **Serious Adverse Experiences:** A listing of serious adverse experiences that have occurred during the study, including allocation number, adverse experience term, and date (relative to infusion) will be provided. These will also be grouped based on treatment group, and categorized by whether they were drug-related or led to death or study discontinuation.
- **Most Common Adverse Experiences:** Counts of the most common (≥ 4 of patients in any treatment group) adverse experiences will be provided by treatment group, sorted by adverse experience term. These will also be grouped based on drug relationship and seriousness.

Product: MK-3415A

33

Protocol/Amendment No.: 001-00

- **Infusion-specific Reactions:** Counts of all infusion-specific reactions, as defined in Section 2.6, will also be provided. All infusion-specific reactions will be presented by treatment group, sorted by term. These will also be grouped based on drug relationship and seriousness.

The eDMC may reserve the authority to request summaries of any other safety data that the committee determines to be of interest. The need for additional reports at the interim analysis will be assessed by the eDMC. In the event that at the interim review a significant safety signal is identified in a treatment group, the eDMC may recommend that the treatment group be discontinued.

3.3.3.3 eDMC Meeting at the Interim Analysis

Prior to the interim review, the eDMC will be oriented to the protocol and the details of data collection and analysis in order to plan for this interim review. This introduction to the study will be an open session involving blinded members of the SPONSOR protocol team.

A formal face-to-face or teleconference meeting of the eDMC will be scheduled for the predefined interim analysis. This meeting will incorporate a closed session for eDMC members and the SPONSOR Unblinded Statistician to strictly maintain the blinding of data. The eDMC and the SPONSOR Unblinded Statistician will keep all interim study results (both efficacy and safety) strictly confidential.

All eDMC members should be present for the interim review. The Unblinded Statistician will provide the report of efficacy and safety results at the interim and the eDMC will make a recommendation to the MSMC. This may include a recommendation to discontinue an individual monoclonal antibody treatment group (MK-3415 and/or MK-6072) in relation to Primary Objective #1 (per Section 3.5.9). Additionally, if a significant safety signal is observed in a treatment group, the eDMC may recommend discontinuation of the treatment group.

After the interim analysis meeting, it is the role of the eDMC to notify the MSMC in writing regarding its recommendations. The actual results for the various treatment groups will not be provided to the MSMC, the investigator, study site staff, or blinded SPONSOR personnel. In the event that the eDMC recommends that further enrollment in one or both of the individual monoclonal antibody therapy groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the group(s) to be stopped. It will be the responsibility of the MSMC to implement the recommendations of the eDMC and to ensure the investigators and the respective Institutional Review Boards (IRBs)/Independent Ethical Committees (IECs) are properly notified. The MSMC will inform the protocol team of modifications to the protocol. The investigator, study site staff, and blinded SPONSOR personnel will remain strictly blinded to specific patient treatment group assignments until the study has ended.

Product: MK-3415A

34

Protocol/Amendment No.: 001-00

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-3415, 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.

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, in 30-minute increments until the end 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, 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. Thereafter, blood and urine will be collected at the scheduled post-infusion study visits at Week 1 (Day 4 \pm 1 day), Week 2 (Day 11 \pm 2 days), and Week 4 (Day 29 \pm 3 days). Appendix 6.5 provides a complete list of laboratory safety tests at these defined visits.

Blood will be also 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

Product: MK-3415A 35

Protocol/Amendment No.: 001-00

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.

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 monoclonal antibody against toxin A [MK-3415] and/or >10 mg/kg of monoclonal antibody against toxin B [MK-6072]).

No specific information is available on the treatment/management of overdose of MK-3415, 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.

Product: MK-3415A

36

Protocol/Amendment No.: 001-00

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 study or within 14 days of completing the study. 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.

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 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, 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.

3.4.6 Evaluating Adverse Experiences

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

Product: MK-3415A
Protocol/Amendment No.: 001-00

37

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	
Duration	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 †)	
	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?	
Relationship to test drug	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 001-00 Issue Date: 20-Jul-2010

Product: MK-3415A
Protocol/Amendment No.: 001-00

38

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_001-00_ProtDet APPROVED — 20-Jul-2010
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Product: MK-3415A

39

Protocol/Amendment No.: 001-00

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 key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to 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 9-month extended follow-up period of this study will include approximately 200 patients who are enrolled following communication of the interim analysis decision. Patients who are enrolling in this study prior to communication of the interim analysis decision will not be eligible to participate in the 9-month extended follow-up period. 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 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.

Planned interim analyses are described in Section 3.5.9. Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be

Product: MK-3415A

40

Protocol/Amendment No.: 001-00

maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Patient-level unblinding will be restricted to the SPONSOR Unblinded Statistician and the SPONSOR Unblinded Programmer who will be preparing the interim analysis and who will have no other responsibilities associated with the study. Treatment-level results of the interim analysis will be provided by the SPONSOR Unblinded Statistician to the eDMC.

The eDMC will serve as the primary reviewer of the results of the interim analysis and will make recommendations for modification to an executive committee (MSMC) of the SPONSOR. The treatment-level results will not be provided to the MSMC unless there is concern that the study should be stopped. In the event that the eDMC recommends that further enrollment in one or both of the individual monoclonal antibody therapies treatment groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the treatment groups(s) to be stopped. No additional information (e.g., summary statistics or p-values) will be shared with the SPONSOR. Additional logistical details will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 3.5.9.

Prior to final study unblinding, the SPONSOR Unblinded Statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses.

3.5.2 Hypotheses

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

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 certain key 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

Product: MK-3415A

41

Protocol/Amendment No.: 001-00

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.

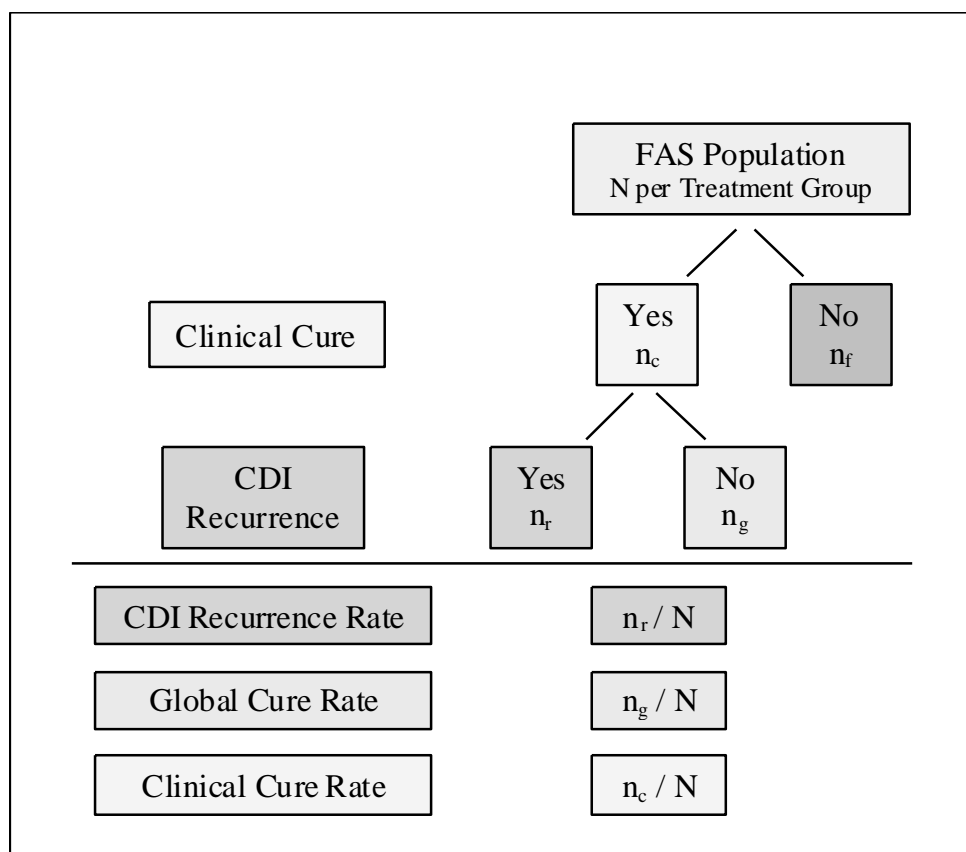
Product: MK-3415A

42

Protocol/Amendment No.: 001-00

Figure 3-1

Populations for Key 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.

Product: MK-3415A

43

Protocol/Amendment No.: 001-00

Stool Counts during Initial CDI Episode will be assessed as an exploratory efficacy endpoint.

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 associated with a positive stool test for toxigenic *C. difficile* 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) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with Tier 1 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

44

Protocol/Amendment No.: 001-00

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)
- Lack of any post-randomization endpoint data subsequent to infusion of study medication

A supportive analysis using the Per-Protocol (PP) population will be performed for the primary and key secondary efficacy endpoints. The Per-Protocol population excludes patients due to important deviations from the protocol that may substantially 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 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

Product: MK-3415A

45

Protocol/Amendment No.: 001-00

between the endpoint and the treatment effect rather than formal tests of hypotheses. 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 (vancomycin vs. not vancomycin) and hospitalization status (in-patient vs. out-patient). 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.

A declaration of superiority to placebo for the MK-3415A treatment group will be considered a successful outcome for the trial. Details regarding the decision to stop enrollment in MK-3415 and/or MK-6072 treatment groups at the interim analysis, and the multiplicity adjustments that will be applied to control the overall rate of declaring any of the active treatment groups superior to placebo under the null hypothesis at 2.5%, are provided in Section 3.5.6.

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 Key Subgroups: These analyses will employ the same analytical approach as the primary efficacy analysis.

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.

Product: MK-3415A

46

Protocol/Amendment No.: 001-00

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.

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.

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

Product: MK-3415A

47

Protocol/Amendment No.: 001-00

the FAS population who develop a new episode of **diarrhea** (3 or more **loose stools** in 24 or fewer hours) whether or not associated with a positive 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. In the case of lost follow up, the last available stool records will be used to assess for **diarrhea** recurrence.

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 between-group comparisons. 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; 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 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

Product: MK-3415A

48

Protocol/Amendment No.: 001-00

considered Tier 1 endpoints. Infusion-specific reactions, as previously defined in Section 2.6, will be considered Tier 2 endpoints. P-values (Tier 1) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of patients with Tier 1 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				

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.

Product: MK-3415A

49

Protocol/Amendment No.: 001-00

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 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 Substudy Analysis

Exploratory analyses will be performed in an effort to develop a classification model based on pre-treatment biomarkers 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. Additionally, gene expression and changes in gut flora will be evaluated to determine the mechanism of action of monoclonal antibody. 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_{max}) of antibodies to both toxin A and toxin B as well as the serum concentration versus 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, that will be used for multiple treatment comparisons at two analysis times (one interim analysis and a final analysis). Individual monoclonal antibody therapies (MK-3415 and MK-6072) will be compared separately to the combined monoclonal antibody therapy (MK-3415A), and the various active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared separately to placebo. Under the global null hypothesis that the four therapies (three active treatments and placebo) are equal, the overall probability of

Product: MK-3415A

50

Protocol/Amendment No.: 001-00

making a false claim of superiority for any of the experimental treatment groups is controlled at level 0.025, one-sided.

Under the global null hypothesis that the three active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) are equal and are all superior to placebo, the multiplicity strategy will not attempt to control the overall probability of making a false claim of superiority for the combined monoclonal antibody therapy (MK-3415A) over either of the individual monoclonal antibody therapies (MK-3415 and/or MK-6072) at a specific level. Instead, each of these comparisons will be made at the nominal level of 0.050, one sided. Simulation results presented in Section 3.5.7 provide information regarding the overall probability of making a Type I error for this global null hypothesis.

The SPONSOR believes that a p-value cut-off of 0.050 (one-sided) for each comparison is appropriate to provide evidence that the individual monoclonal antibody groups (MK-3415 and/or MK-6072) are less effective than the combined monoclonal antibody therapy (MK-3415A) and that further evaluation of one or both of these study treatment groups can be stopped. This belief is supported by the simulation results which indicate that the likelihood of incorrectly dropping one or both individual monoclonal antibody groups at the interim is less than 9% and the likelihood of incorrectly dropping one or both individual monoclonal antibody groups at either the interim or the final analysis is less than 15%. The rationale for this decision is further discussed in Section 3.1.4.

The multiplicity adjustments are described below and the entire evaluation plan and multiplicity strategy is presented in Table 3-5 and Figure 3-2.

Combined Monoclonal Antibody Therapy (MK-3415A) vs. Individual Monoclonal Antibody Therapies (MK-3415 or MK-6072)

These two treatment group comparisons (MK-3415A vs. MK-3415; MK-3415A vs. MK-6072) will be performed at the interim analysis and, conditionally, at the final analysis. Each of these comparisons will be made using a p-value cut-off of 0.050 (1-sided). A significant finding for either of these two comparisons at either analysis time will result in that treatment group (MK-3415 and/or MK-6072) being dropped from further evaluation. Further enrollment in one or both of these groups will be stopped if a significant finding for either of these two comparisons occurs at the interim analysis.

Prior to performing these comparisons at the interim analysis, a comparison of MK-3415A vs. placebo will be conducted employing a p-value cut-off of 0.050 (1-sided). This is essentially an evaluation of the sensitivity of the study. If the combined monoclonal antibody therapy group (MK-3415A) is not differentiating from placebo, it is extremely unlikely that the various active monoclonal groups will differentiate from each other. The MK-3415A vs. placebo comparison is a gate that must be passed in order to conduct the remainder of the interim analysis. If not fulfilled, there will be no further treatment group comparisons (MK-3415A vs. MK-3415; MK-3415A vs. MK-6072) at the interim analysis. No study conclusions will be based on this comparison.

Active Monoclonal Antibody Therapy (MK-3415, MK-6072, MK-3415A) vs. Placebo

At the final analysis, all remaining monoclonal antibody therapy groups (i.e., those that have not been dropped from further evaluation based on the criteria described above) will

Product: MK-3415A

51

Protocol/Amendment No.: 001-00

be compared to placebo. The combination of a sequential testing approach and Dunnett's methodology will be employed to control the overall probability of making a false claim of superiority for any 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 remaining monoclonal antibody therapy groups (MK-3415 and/or MK-6072) will be compared to placebo simultaneously. The p-value cut-off will be 0.025 (1-sided) if only one group remains and 0.01355 (1-sided) if two groups remain. Based on Dunnett's method, a p-value cutoff of 0.01355 for these comparisons will control the overall probability of a Type I error at level 0.025. 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.

Multiplicity for Key Secondary Efficacy Endpoint - Global Cure

Treatment group comparisons for the key secondary endpoint of global cure will only be evaluated if the primary endpoint (CDI recurrence) is significant for a particular treatment comparison.

Product: MK-3415A
Protocol/Amendment No.: 001-00

52

Table 3-5

Statistical Evaluation Plan and Multiplicity Strategy

Analysis	Stage	Comparison(s)	Multiplicity Strategy	p-value cut-off [§] for individual comparisons	Purpose
Interim [†]	1	MK-3415A vs PBO	None	0.050	Study validity check required to perform Stage 2. No conclusions made
Interim [†]	2	MK-3415A vs MK-6072 MK-3415A vs MK-3415	None	0.050	Decision to stop enrollment in MK-3415 and/or MK-6072 groups
Final	3	MK-3415A vs MK-6072 MK-3415A vs MK-3415	None	0.050	Decision to stop further testing of MK-3415 and/or MK-6072 groups
Final	4	MK-3415A vs PBO MK-6072 vs PBO MK-3415 vs PBO	Fixed Sequence & Dunnett's [‡]	0.025 0.025 or 0.01355	Evaluate effectiveness of remaining MAb groups

PBO = placebo
MAB = monoclonal antibody
[†] Interim analysis is planned when the first 640 patients (40% of planned patient enrollment) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12).
[‡] 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-3415 and/or MK-6072 will be compared to placebo simultaneously. The p-value cut-off will be 0.025 (1-sided) if only one treatment group remains and 0.01355 (1-sided) if two treatment groups remain (Dunnett's method to control overall probability of a Type I error at level 0.025).
[§] All p-value cut-offs are 1-sided.
^{||} If remaining after testing in Stage 2 and Stage 3.

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

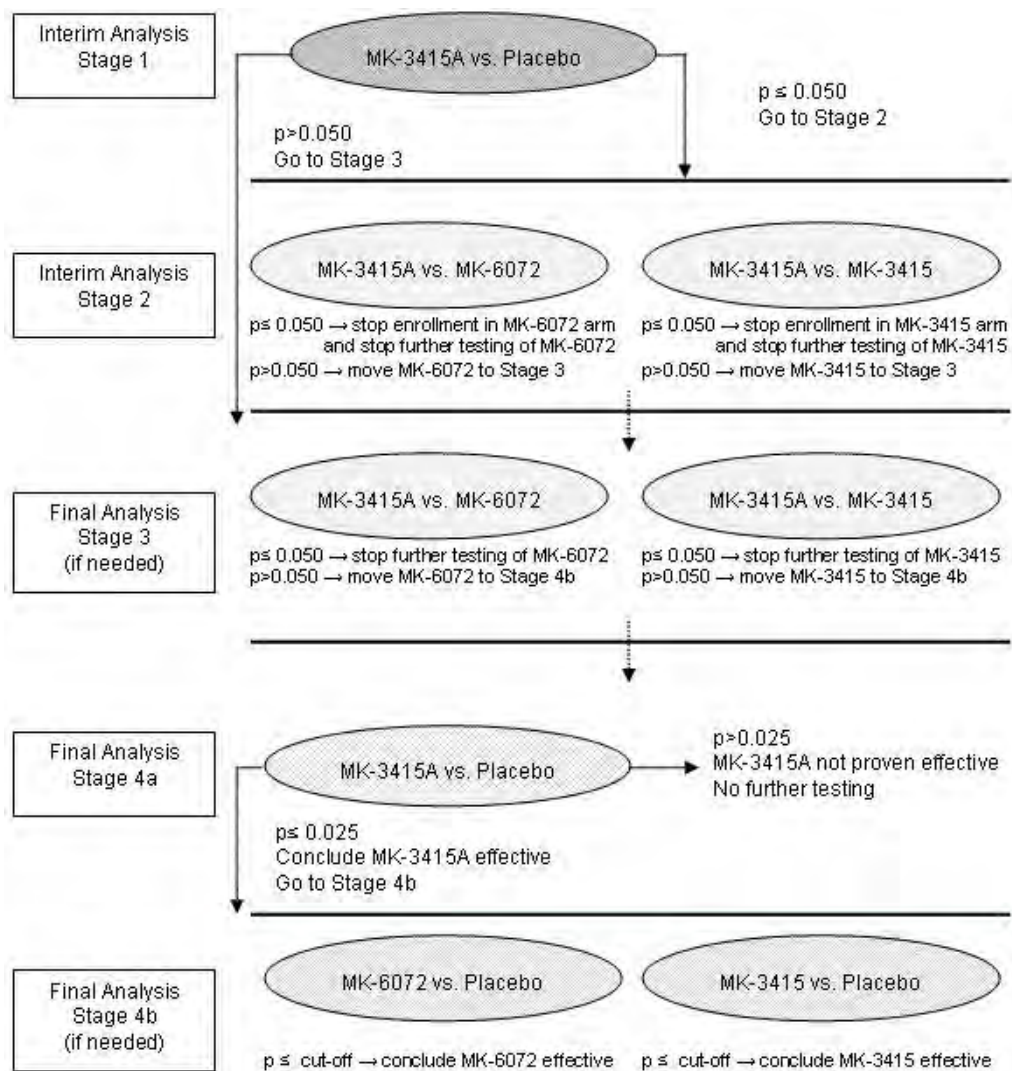
Product: MK-3415A

53

Protocol/Amendment No.: 001-00

Figure 3-2

Statistical Evaluation Plan and Multiplicity Strategy
Primary Endpoint - CDI Recurrence



Notes:

- 1) All p-values cut-offs are 1-sided.
- 2) p-value cut-off at Stage 4b is 0.025 if only 1 group remains (MK-6072 or MK-3415) and 0.01355 if 2 groups remain (MK-6072 and MK-3415).

Product: MK-3415A

54

Protocol/Amendment No.: 001-00**3.5.7 Sample Size and Power Calculations**

This study has a planned sample size of 1600 patients to be randomized in a 1:1:1:1 ratio to each of the four treatment groups (MK-3415A, MK-3415, MK-6072, 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 are based on recent results from the Phase II clinical study of a single infusion of MK-3415A [15]. In that study, CDI recurrence was observed in 7% (7/101) of MK-3415A patients and in 25% (25/99) of placebo patients. These placebo results are supported by recently reported results from the SOC therapy control arms of two Phase III fidaxomicin trials (24% and 25%) [43, 44].

Primary Endpoint - CDI Recurrence (Interim and Final Analyses)

An interim analysis is planned when the first 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12). The purpose of this interim analysis is to evaluate if treatment with combined monoclonal antibody therapy (MK-3415A) is superior to treatment with either of the individual monoclonal antibody therapies (MK-3415 or MK-6072). If MK-3415A is found to be superior to MK-3415 or MK-6072, then further enrollment in one or both of these respective groups will be stopped. These two comparisons will be performed at a 1-sided alpha level of 0.050, as described in Section 3.5.6.

At the interim analysis, it is anticipated that 160 per group will be in the analysis population for the CDI recurrence endpoint. This will provide approximately 80% power to detect the following differences in the incidence of CDI recurrence between combined monoclonal antibody therapy (MK-3415A), π_1 , and the individual monoclonal antibody therapies (MK-3415 or MK-6072), π_2 :

π_1	π_2	Difference	Power
.08	.172	.092	80%
.09	.185	.095	80%
.10	.199	.099	80%

At the final analysis, 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 :

Product: MK-3415A

55

Protocol/Amendment No.: 001-00

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

Secondary Endpoint - Global Cure - (Final Analysis)

At the final analysis 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).

Secondary Endpoint - CDI Recurrence in Subset of Patients with Clinical Cure - (Final Analysis)

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%

Simulation Results - CDI Recurrence - Interim and Final Analyses

Table 3-6 provides the results of a simulation study examining the operating characteristics of the tests for CDI recurrence within the design. A 50,000 replication simulation was performed to estimate Type 1 error under the two null hypotheses and to estimate power for eight different alternative hypotheses.

For the primary endpoint of CDI recurrence, individual monoclonal antibody therapies (MK-3415 and MK-6072) will be separately compared to combined monoclonal antibody therapy (MK-3415A) **and** active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared to placebo. Under the global null hypothesis (Null #1) that the four therapies (three active and placebo) are equal, a multiplicity strategy is designed to control at 2.5% the probability of falsely concluding that one or more of the

Product: MK-3415A

56

Protocol/Amendment No.: 001-00

active monoclonal antibody therapies is effective. Under this null hypothesis, the decision to drop one or both of the individual monoclonal antibody therapies from further investigation is not a Type I error.

Under the global null hypothesis (Null #2) that the three active monoclonal antibody therapies are equal and are all superior to placebo, the multiplicity strategy will not attempt to control the overall probability of making a false claim of superiority for the combined monoclonal antibody therapy over either of the individual monoclonal antibody therapies at a specific level. Instead, each of these comparisons will be made at the nominal level of 0.050, one sided. The rationale for this decision is included in Section 3.1.4. Under this null hypothesis, the conclusion that one or more of the active monoclonal antibody therapies is effective is not a Type I error.

The simulation results show that the Type 1 error for the first null hypotheses (Null #1) is controlled at 2.4% and Type 1 error for the second null hypotheses (Null #2) is controlled at 14.1%. The simulation also indicates that the design provides sufficient power to select an effective treatment regimen. Under these conditions, the overall probability of demonstrating effectiveness with at least one active treatment group exceeds 99%. The probability of dropping an individual monoclonal antibody group (MK-3415 or MK-6072) ranges from about 54% when the difference is 6 percentage points versus the combined monoclonal antibody (MK-3415A) to about 93% when the difference is 13 percentage points versus the combined monoclonal antibody (MK-3415A).

Product: MK-3415A
Protocol/Amendment No.: 001-00

57

Table 3-6

Simulation Study (50,000 Replications) of Operating Characteristics for CDI Recurrence Endpoint

	CDI Recurrence Rates				Superiority to PBO for at least one MAb	Drop MK- 3415 at interim	Drop MK- 6072 at interim	Drop both MK-3415 & MK-6072 at interim	Drop either MK-3415 or MK-6072 at either analysis
	Placebo	MK-3415	MK-6072	MK-3415A					
Null 1	21%	21%	21%	21%	2.36% [†]	1.2%	1.2%	<1%	9.7%
Null 2	21%	8%	8%	8%	>99%	5.1%	5.2%	1.5%	14.1% [†]
Alternative 1	21%	18%	8%	8%	>99%	84.7%	5.2%	5.2%	>99%
Alternative 2	21%	18%	14%	8%	>99%	84.7%	53.6%	50.7%	>99%
Alternative 3	21%	18%	18%	8%	>99%	84.7%	84.5%	76.6%	>99%
Alternative 4	21%	14%	14%	8%	>99%	53.7%	53.6%	37.5%	96.4%
Alternative 5	21%	21%	8%	8%	>99%	93.4%	5.2%	5.2%	>99%
Alternative 6	21%	21%	14%	8%	>99%	93.4%	53.6%	53.1%	>99%
Alternative 7	21%	21%	18%	8%	>99%	93.4%	84.5%	82.8%	>99%
Alternative 8	21%	21%	21%	8%	>99%	93.4%	93.4%	90.9%	>99%
[†] Type 1 error estimated (<0.025) using simulation with 50,000 replicates.									

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

Product: MK-3415A

58

Protocol/Amendment No.: 001-00

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 key secondary endpoints 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-027/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 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

The eDMC will carefully monitor the formal safety and efficacy interim results of this trial. A description of the structure, function, and guidelines for decision-making by the eDMC will also be outlined in the eDMC charter.

3.5.9.1 Efficacy Interim Analyses

There is one planned interim efficacy analysis that will be performed during the course of the blinded portion of this study. The purpose of the interim analysis is 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 will be stopped.

Product: MK-3415A

59

Protocol/Amendment No.: 001-00

The interim analysis will be conducted by a SPONSOR Unblinded Statistician (in conjunction with a SPONSOR Unblinded Programmer). These individuals will have no other responsibilities with respect to this study. The SPONSOR Unblinded Statistician will review the results from this interim analysis with the independent eDMC. The eDMC will use the guidelines proposed in Table 3-5 (Statistical Evaluation Plan and Multiplicity Strategy) to make recommendations about modifications to the study design.

In the event that the eDMC recommends that further enrollment in one or both of the individual monoclonal antibody therapy groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the group(s) to be stopped. No additional information (e.g., treatment group summary statistics or p-values) will be shared with the SPONSOR.

The interim efficacy analysis is planned when the first 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12). The patient population for this interim analysis will be those patients who have concluded follow-up (i.e., completed the 12 Week study period or discontinued prior to Week 12) at the time of the interim analysis database lock. Study enrollment will be ongoing at the time of this interim analysis. It is recognized that additional patients will have been randomized and will be ongoing in the study at the time of database lock for the interim analysis. These patients will not be included in the formal interim analysis (i.e., p-value calculations) and their data will have no bearing on the decision criteria for the interim analysis. However, the eDMC will be provided with listings of important demographic, efficacy, and safety data for these ongoing patients. Data collected from these patients will also be included in a summary listing in the final CSR, but a separate analysis combining these patients together with the patients included in the interim analysis is not planned.

3.5.9.2 Safety Interim Analyses

The eDMC will review safety data of the ongoing study at close, regular intervals as specified in the eDMC charter. Safety data will be summarized by blinded treatment groups and will be provided by the SPONSOR Unblinded Statistician during the blinded portion of the trial. At the formal interim analysis, an interim report of the safety data and any specific safety analyses previously requested by the eDMC up to that point will be provided.

3.5.10 Additional 9-Month Extended Follow-up

The 9-month extended follow-up period of this study will include approximately 200 patients who are enrolled following communication of the interim analysis decision. Patients who are enrolling in this study prior to communication of the interim analysis decision will not be eligible to participate in the 9-month extended follow-up period. 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

Product: MK-3415A 60**Protocol/Amendment No.:** 001-00

personnel). In this case, CSR will be amended to include these results following the completion of the 9-month extended follow-up period.

No formal statistical analyses are planned for the 9-month extended follow-up data. Summary statistics of key 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 1600 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.

3.6.2 Product Descriptions

Investigational clinical materials will be provided by the SPONSOR as summarized in Table 3-7.

Table 3-7

Product Descriptions

Product Name & Potency	Dosage Form	Comments
MK-3415 toxin A antibody (25 mg/mL)	Injectable Solution - Vial	MK-3415 combined with MK-6072 is MK-3415A
MK-6072 toxin B antibody (25 mg/mL)	Injectable Solution - Vial	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-3415, MK-6072, and MK-3415A. The pharmacist or designee will record the lot number and expiration date.

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

Product: MK-3415A 61

Protocol/Amendment No.: 001-00

3.6.3 Primary Packaging and Labeling Information

Supplies will be packaged in **glass vials** as described in Table 3-8 below.

Table 3-8

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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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

Product: MK-3415A

62

Protocol/Amendment No.: 001-00

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.

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.

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 dispensed only in accordance with the protocol. The Unblinded Pharmacist at the investigator site is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

Product: MK-3415A 63

Protocol/Amendment No.: 001-00

U.S. sites should follow instructions for the Clinical Supplies Return Form (R464) and contact your SPONSOR representative for review of shipment and form before shipping.

Sites outside of the United States should check with local country Merck personnel for appropriate documentation that needs to be completed for drug 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.: 001-00

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.: 001-00

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.: 001-00

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.: 001-00

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.: 001-00

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.

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1

Protocol/Amendment No.: 001-00

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Protocol/Amendment No.: 001-00

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Product: MK-3415A

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Product: MK-3415A

5

Protocol/Amendment No.: 001-00

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Product: MK-3415A

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Protocol/Amendment No.: 001-00

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7

Protocol/Amendment No.: 001-00

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8

Protocol/Amendment No.: 001-00

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Product: MK-3415A

9

Protocol/Amendment No.: 001-00

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Product: MK-3415A

10

Protocol/Amendment No.: 001-00

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 Toxins A and B	ELFA	99.8
Cepheid	GeneExpert	PCR	94
Medical Chemical Corp.	GastroTect	EIA	97
Meridian	Premier	EIA	97.3
	Immunocard Toxins A and B	Lateral Flow Immunoassay	98.4
Oxoid/Remel	Xpect C difficile Toxin A/B	EIA	96.2
	Prospect A and B	EIA	96.2
Prodecs	ProGastro CD	PCR	94.7
TechLab (assays may also be distributed by Inverness Medical)	Tox A/B QuikChek	EIA	99.7
	C. diff Quik Chek Complete	Lateral Flow Immunoassay	99.4
	C. difficile Tox A/B II [‡]	EIA	100
[†] Specificity data as reported in the manufacturer's product insert.			
[‡] C. difficile Tox A/B II assay can be run with or without the TechLab Fecal-Quik Prep assay.			








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11

Protocol/Amendment No.: 001-00

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.: 001-00

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.: 001-00

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 1-11.

- | | |
|----------------------------------|--|
| 1. AIDS? | <input type="radio"/> Yes <input type="radio"/> No |
| 2. Cerebrovascular disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 3. Chronic pulmonary disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 4. Congestive heart failure? | <input type="radio"/> Yes <input type="radio"/> No |
| 5. Connective tissue disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 6. Dementia? | <input type="radio"/> Yes <input type="radio"/> No |
| 7. Hemiplegia? | <input type="radio"/> Yes <input type="radio"/> No |
| 8. Leukemia? | <input type="radio"/> Yes <input type="radio"/> No |
| 9. Malignant lymphoma? | <input type="radio"/> Yes <input type="radio"/> No |
| 10. Peripheral vascular disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 11. Ulcer disease? | <input type="radio"/> Yes <input type="radio"/> No |

For Question 12, if the patient has diabetes mellitus indicate if it exists with or without end organ damage.

- | | |
|------------------------|--|
| 12. Diabetes mellitus? | <input type="radio"/> None |
| | <input type="radio"/> Without end organ damage |
| | <input type="radio"/> With end organ damage |

For Questions 13 and 14, indicate the severity of the disease.

- | | |
|--------------------|--------------------------------|
| 13. Liver disease? | <input type="radio"/> None |
| | <input type="radio"/> Mild |
| | <input type="radio"/> Moderate |
| | <input type="radio"/> 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.: 001-00

14. 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 15, if the patient has a malignant solid tumor, indicate if it is metastatic or non-metastatic.

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

Product: MK-3415A

15

Protocol/Amendment No.: 001-00

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 and is associated with a positive stool test for toxigenic *C. difficile*.

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)

serum 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

absolute blood neutrophil 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

Product: MK-3415A

16

Protocol/Amendment No.: 001-00

urine creatinine clearance test
urine glucose test
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

Product: MK-3415A

17

Protocol/Amendment No.: 001-00

6.6 BIOMARKER EVALUATION IN THIS STUDY

Rationale for Biomarker Evaluations in this Study

A question of interest in the treatment of *C. difficile* infection 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. Assays will be performed on all patients for more standard procedures, and at designated Biomarker Substudy centers for more intensive assays. *The first 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-3415, 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-3415, 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-3415, MK-6072, or MK-3415A.*

Prior studies have yielded conflicting results regarding demographically- and clinically-based predictors of response. 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 *C. difficile* infection 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 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 *C. difficile* infection 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 for a long-range prediction (LRp) of 3.35. The 90% CI for LRp 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 for a LRp of 2.25. The 90% CI for LRp 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.: 001-00

In a separate study of hospitalized subjects, Garey, et al. examined the relationship between an IL-8 polymorphism and *C. difficile* infection 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 *C. difficile* infection 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 *C. difficile* infection 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
- Baseline anti-toxin A and anti-toxin B antibodies
- Serum dehydroepiandrosterone (DHEA)
- Gene (messenger RNA [mRNA]) expression

Blood that is collected within 24 hours prior to infusion on Day 1 in a subset of approximately 150 patients in the Biomarker Substudy group. The number of patients in the Biomarker Substudy may increase if 3 or more treatment groups continue after the interim analysis decision is communicated.

- 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 Week 1 visit in consenting patients

- 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)

Blood samples to assess gene (mRNA) expression will also be collected at predefined post-infusion visits *in a subset of approximately 150 patients (in the Biomarker Substudy group, which may increase in number of patients if 3 or more treatment groups continue after the interim analysis decision is communicated)*. In addition, in this same set of approximately 150 patients, additional stool samples will be collected at predefined post-infusion visits to further assess the gut flora diversity to assess changes after study drug

Product: MK-3415A

19

Protocol/Amendment No.: 001-00

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 the subset of patients who are part of the Biomarker Substudy (enrolled following the interim analysis decision). 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 in this substudy 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].

Inflammatory Cytokine Profiles

Serum samples will be collected within 24 hours prior to infusion on Day 1 for measurement of cytokines assessment in the subset of patients who are part of the Biomarker Substudy (enrolled following the interim analysis decision). 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

Product: MK-3415A

20

Protocol/Amendment No.: 001-00

model for prediction of risk of CDI recurrence. The assay to be used is the RulesBasedMedicine™ Human InflammationMAP™ Cytokine Panel.

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.

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 who are part of the Biomarker Substudy (enrolled following the interim analysis decision). Peripheral blood will be collected at Week 1, Week 2, 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.

Single Nucleotide Polymorphism (SNP) Genotyping

An optional blood samples will be collected from patients at the Week 1 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:

Product: MK-3415A

21

Protocol/Amendment No.: 001-00

- 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 who are part of the Biomarker Substudy (following the interim analysis decision of the study being communicated) at Week 1 (Day 4 ± 1 day), Week 2 (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 Substudy

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 analysis.

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

Product: MK-3415A

22

Protocol/Amendment No.: 001-00

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.

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.

Sensitivity, specificity, long-range prediction (LRp), 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 to determine if the primary hypothesis can be met.

While there are 3 different methods that may be considered for building the classification model, no multiplicity adjustment will be made since the objective of this sub-study 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 of a subset of subjects may confound some of the biomarker measurements. Specifically, those with liquid tumors or those on cytotoxic therapies will likely have different T- and B-cell populations, and possibly cytokine profiles, than other subjects. 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 Biomarker Substudy

The recurrence rate of CDI expected in the placebo group is 25% based on the analysis of data from a Phase II study. A total sample size of 150 patients in the placebo group (equaling 75 patients in the placebo group in each of 2 studies combined) with a CDI recurrence rate of 25%, a true sensitivity of 0.8, true LRp of 4, yields ~86% 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 ~72% power for the lower bound of the 90% CI

Product: MK-3415A 23

Protocol/Amendment No.: 001-00

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.: 001-00

6.7 HIGH RISK DEMOGRAPHIC AND CLINICAL IDENTIFIERS

An analysis to identify patients at high risk for CDI recurrence will be performed using the clinical trial data from this study and other Phase III studies. 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), 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.

Only patients in the placebo group of this trial will be used for this analysis. 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.

Univariate logistic regression analyses (with recurrent CDI (yes/no) as the outcome variable) will be conducted for each of the potential predictor variables. All variables that have a p-value <0.2 will be included in a multivariable logistic regression model along with any other variables thought to be potential confounders. The β coefficients (i.e., parameter estimates) from the multivariable logistic regression model will be used to compute the predicted probability of recurrent CDI for each patient. If the predicted probability of recurrent CDI is ≥ 0.5 for a given patient, then that patient will be classified as having a high risk for developing recurrent CDI.

Sensitivity, specificity, positive and negative predictive values of this classification will be evaluated. Accuracy will be measured 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.

3415A, Protocol 001-00 Issue Date: 20-Jul-2010

132

Product: MK-3415A 25**Protocol/Amendment No.:** 001-00

7. ATTACHMENTS

Merck & Co., Inc. Code of Conduct for Clinical Trials

Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research
Collected from Clinical Trials Sponsored by Merck & Co., Inc.: A Guideline for
Clinicians and Privacy Board Members

Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff

Merck & Co., Inc
Code of Conduct for Clinical Trials

I. Introduction**A. Purpose**

Merck & Co., Inc. ("Merck") 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 consistent with standards established by the Declaration of Helsinki and in compliance with all local and/or national regulations and directives.

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 and conduct of a study (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 and/or misconduct are suspected, the issue is investigated: when necessary, the clinical site will be closed and, if appropriate, the responsible regulatory authorities and ethics review committees notified.

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 local medical 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.

**Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research
Collected from Clinical Trials Sponsored by Merck & Co., Inc.
A Guideline for Clinicians and Privacy Board Members**

1. Principles and Introduction

It is now well recognized that information obtained from studying and testing clinical specimens (i.e., blood, body fluids and/or tissue) may provide important indicators not only of the presence or absence of disease, but also of responses to medical treatments. The study of the relationships between such test results and drug efficacy is a critical component of the scientific research objectives for clinical development programs at Merck & Co., Inc. (MERCK). MERCK recognizes that studying and testing clinical specimens offers unique opportunities to enhance our understanding of human disease and health and ultimately to aid in the discovery and development of novel, breakthrough medications targeted to populations with the greatest need.

MERCK also recognizes, however, that analyses of specimens derived from consenting patients, including for research purposes, must be undertaken with the utmost consideration for human dignity and privacy, as noted in the Declaration of Helsinki, US FDA Requirements (21 CFR 50.20, 50.25, and 50.27), the International Conference on Harmonization (ICH) E6 Good Clinical Practices Guideline, and the 1997 UNESCO Declaration on the Human Genome and Human Rights. This document outlines the approach of MERCK to privacy protection of optional specimens for genetic and other biomedical research.

2. Definitions

For the purposes of this document, the following terms will apply:

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.¹

Genomic Biomarkers are measurable DNA or RNA characteristics that are indicators of normal biological or pathogenic processes and/or a response to therapeutic or other intervention.²

Pharmacogenomics (PGx): the investigation of variations of DNA and RNA characteristics as related to drug response.² Also see http://www.i-pwg.org/cms/index.php?option=com_docman&task=cat_view&gid=81&Itemid=118 for guidance from the Industry – Pharmacogenomics Working Group (I-PWG) to Investigators, IRBs/IECs and Investigational Site Staff

Pharmacogenetics (PGt): the influence of variation in DNA sequence on drug response²

Patient-specific Identifiers: Generally defined as data fields alone or in combination that would reasonably allow a third party to identify who a patient is. Examples of these are: Patient/Subject names, date of birth, telephone #s.

Study Site: The local site of the investigation, where patients are actively screened, enrolled and studied as per the clinical protocol.

Coding of Specimens/Data: There are several categories of coding for clinical specimens and the data associated with them. See <http://www.ich.org/LOB/media/MEDIA3383.pdf> for additional detail on these categories. The standard method of coding used in clinical studies is single coding.

Central Laboratory/BioBank: The third-party entity that is responsible for accessioning, proper handling, and archiving clinical specimens.

3. Optional Specimens for Genetic and Other Biomedical Research: Data/Information associated with the specimen

Biomarkers, including genomic biomarkers, may be measured and analyzed by standard or novel methods to explore variations that may be related to the development and/or treatment of the diseases studied in clinical trials sponsored by Merck & Co., Inc. (Merck). The research that we would like to perform on the specimens is considered to be critical to further advance the Merck's scientific understanding of the disease and drug responses. The research will further enable Merck to:

- a) better understand disease and how to improve treatment of disease,
- b) better understand how drugs work in individuals and different patient populations,
- c) address emerging scientific questions that arise during the development of drugs and treatments, not known today, that would be very difficult to address if Merck did not collect a sample now, because it is not possible for the Merck, alone, to re-contact a patient directly to collect a tissue sample at a later date when the main study is finished,
- d) discover and understand biological markers (biomarkers) that can be used to help understand therapeutic treatments and disease,
- e) increase the chances that improved drugs may be commercially available by improving the risk benefit ratio of the treatment drug or similar drugs being developed to treat the disease in a patient or patient populations.

In order to realize and optimize the research that can be conducted with optional specimens, as described above, it is critical to link the patients' clinical information associated with the treatments in the protocol. In fact little or no research can be conducted without connecting the clinical study data to the specimen and it is unlikely the specimen would ever be used at all making any effort to collect it pointless to Merck and the patient. The clinical data allow specific analyses to be conducted for example a pharmacogenomic analysis might require knowing that specimens came from "men with type II diabetes between 20 and 50 years of age" or "children with asthma who did not respond to Drug X". In these instances, knowing gender, age and medical history and treatment outcomes are critical.

"Single coding is the current standard used in clinical research and offers additional safeguards to the subject's identifiers compared to the general healthcare confidentiality and privacy protection in everyday medical practice."² Consistent with this understanding, in clinical trials sponsored by Merck & Co., Inc., optional specimens and the data associated with them

will be single-coded, providing the same level of privacy for clinical research in general. In this model, the key that links the actual subject to their specimens and the data associated with them is maintained by study site personnel.

By exception, double-coding of the specifically-collected genetic specimen and/or related data analyses may be invoked. This option should only be used if there are local regulations **requiring** double-coding of genetic specimens and/or related data analyses. It is important to note that analyses may be double-coded, even if the specimen has not been double-coded. To request either of these options, complete the attached request form and submit it, along with written guidance supporting your local regulations, to your primary MERCK contact for the associated clinical trial.

4. Informed Consent

As per protocol procedures, patients/subjects should be presented with the consent form for Optional Specimens for Genetic and Other Biomedical Research at a designated visit. The consent should be administered in the standard manner, with special care to explain to the patient/subject that his/her privacy will be protected in the same way as it is provided for in the main study (unless double-coding is invoked, in which case there is slightly less risk of disclosure of the genetic research results). The individual administering consent should also carefully explain that the patient has the option to withdraw their specimens covered by the optional consent at a later date (See Section 6). Information pertaining to the administration and acquisition of the consent for Optional Specimens for Genetic and Other Biomedical Research will be captured in the Case Report Forms (CRFs) to assure that only appropriately-consented specimens are used for genetic and other biomedical research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

5. Assembly of Kits, Specimen Collection and Handling

A designated Central Laboratory will be responsible for assembling and distributing specimen collection kits and labels both for the main study specimens and for the optional specimens. The Central laboratory will also provide the instructions on how to obtain, label, process and ship the specimens. Upon receipt by the Central Laboratory (or its associated biobank), the specimens will be processed and/or stored as specified in the contract and consistent with each subject's actual consent. MERCK will routinely monitor the condition and disposition of specimens at the biobank so that each specimen may be used appropriately.

If double-coding is agreed upon for the specifically-collected genetic specimens, then those specimens or their derivatives will be transferred to another container that contains a second unique code number. The key that links the single code to the second code will be kept in a secure place with limited access. All analyses and clinical data related to the specimen or its derivatives will be linked to the second or other codes and specifically not to the original single code.

6. Specimen Destruction Procedures for Withdrawal of Consent

Patients who request their specimens to be withdrawn are instructed in the consent form to contact the Investigator *in writing*. 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), there will no longer be a link between the patient's personal information and their specimens. On this instance, the request for specimen destruction can not be processed. If medical records for the main study are available, the Investigator will contact MERCK using the supplied telephone contact (see Sponsor Contact Information section) and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. MERCK will identify specimens to be destroyed using an agreed upon form. After appropriate sign-off by both parties and affirmation of destruction, specimens will be retrieved from storage and incinerated or pyrolyzed such that DNA and other biomolecules are completely destroyed, i.e. rendered to a state such that the DNA is not able to be manipulated by standard molecular biological techniques (i.e. PCR). Any residual specimens or derivatives from the samples that have left the biobank and can be tracked will also be destroyed, but only after all main study testing is complete. A confirmatory letter will be sent from the biobank to MERCK and then later from MERCK to the investigator. It is the responsibility of the Investigator to inform the patient of completion of destruction. Any data that has been generated from the specimens before sample destruction will be maintained and can not be specifically deleted.

7. Conclusions

Merck recognizes both the tremendous potential, and the inherent responsibility that genetic and other biomedical research specimens provide to clinical studies. The procedures outlined in this document are intended to ensure that meaningful investigation of biomedical influences in disease and/or responses to therapies can be achieved while providing a high degree of privacy protection for patients in the study.

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**Request to Double-Code Specifically-Collected Genetic Specimens
Obtained from Clinical Trials Sponsored by Merck & Co., Inc.**

Instructions:

1. The Principal Investigator completes Section 1 of the form below and submits it, along with the specific regulatory guidance supporting the request, to the primary MERCK contact.
2. The primary MERCK contact submits the request to the head of the Molecular Profiling Leads for review and approval.
3. The head of the Molecular Profiling Leads reviews and approves the request by completing Section 2 and returns the completed form to the study site's primary MERCK contact, copying the MERCK liaison to the central laboratory and to the patient informed consent developers.
4. The study site's primary MERCK contact returns the completed form to Principal Investigator.
5. The MERCK liaison to the central laboratory informs them of the deviation from standard practice.
6. The patient informed consent developers document the deviation from standard practice.

Section 1 (To be completed by the Primary Investigator):

Compound Number:

Clinical Protocol Number:

Investigator Study Site Number:

Check only those requirements that apply:

I request double-coding of the specifically-collected genetic specimens obtained in the above-referenced study site because local regulations require this method of specimen labeling.

I request double-coding of any genetic data analyses related to the specifically-collected genetic specimens obtained in the above-referenced study site because local regulations require this level of privacy protection.

Attached is the local regulation supporting this request.

Principal Investigator's Name (printed):

Principal Investigator's Signature:

Date:

Section 2 (To be completed by Merck Research Laboratories):

Approval granted

Insufficient evidence of requirement, based on regulations submitted (In this instance, the Principal Investigator should provide additional information)

Approver's Name (printed): _____

Approver's Signature: _____

Approver's Title: _____

Date: _____

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.

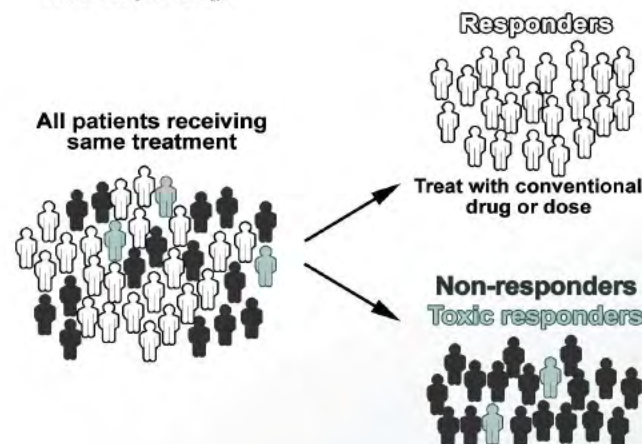
Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

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

1

Protocol/Amendment No.: 001-00

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

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 1

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the **SPONSOR** or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Administrative Binder.

TITLE:

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

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: III

US IND NUMBER: 12823

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

Product: MK-3415A Page 2
Protocol/Amendment No.: 001-03

TABLE OF CONTENTS

Table of Contents.....	2
SUMMARY OF CHANGES.....	7
PRIMARY REASON(S) FOR THIS AMENDMENT.....	7
ADDITIONAL CHANGE(S) FOR THIS AMENDMENT	10
1. SUMMARY.....	15
1.1 TITLE	15
1.2 INDICATION.....	15
1.3 SUMMARY OF RATIONALE.....	15
1.4 SUMMARY OF STUDY DESIGN	16
1.5 SAMPLE	17
1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN.....	18
1.7 STUDY FLOW CHART - BASE STUDY (DAY 1 TO WEEK 12).....	19
2. CORE PROTOCOL.....	23
2.1 OBJECTIVES AND HYPOTHESES	23
2.1.1 Primary (Interim Analysis).....	23
2.1.2 Primary (Final Analysis)	23
2.1.3 Secondary	24
2.1.4 Exploratory Objectives.....	26
2.2 PATIENT INCLUSION CRITERIA.....	26
2.3 PATIENT EXCLUSION CRITERIA.....	27
2.4 STUDY DESIGN AND DURATION.....	29
2.4.1 Summary of Study Design.....	29
2.4.2 Biomarker Assessments.....	31
2.4.3 Treatment Plan.....	31
2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS.....	34
2.5.1 Efficacy.....	34
2.5.1.1 Primary Objective (CDI Recurrence)	34
2.5.1.2 Other Efficacy Measures (Secondary/ Exploratory Objectives)	35
2.5.2 Endogenous Antibody Levels and Pharmacokinetics	35
2.5.3 Immunogenicity.....	35
2.6 LIST OF SAFETY MEASUREMENTS.....	36
2.7 STATISTICAL ANALYSIS PLAN SUMMARY	36
2.7.1 Efficacy Analyses.....	36
2.7.2 Safety Analyses	38
2.7.3 Power and Sample Size	38
2.7.4 Interim Analyses.....	40

Product: MK-3415A Page 3
Protocol/Amendment No.: 001-03

3. PROTOCOL DETAILS.....	41
3.1 RATIONALE	41
3.1.1 Rationale for This Study.....	41
3.1.2 Rationale for Dose Regimen	43
3.1.3 Rationale for Patient Population and Primary Endpoint	44
3.1.4 Rationale for Adaptive Study Design.....	44
3.1.5 Rationale for Biomarker Evaluations in This Study.....	45
3.1.6 Rationale for Optional Specimen Collection for Genetic and Other Biomedical Research.....	45
3.2 STUDY PROCEDURES	46
3.2.1 Concomitant Medication(s)/Treatment(s)	46
3.2.1.1 Standard of Care (SOC) Therapy for CDI	46
3.2.1.1.1 Metronidazole.....	47
3.2.1.1.2 Vancomycin.....	47
3.2.1.1.3 Fidaxomicin.....	47
3.2.1.2 Other Prior/ Concomitant Medication(s)/ Treatment(s).....	48
3.2.2 Diet / Activity / Other.....	49
3.2.2.1 Diet.....	49
3.2.2.2 Pregnancy and Contraception	49
3.2.3 Procedures	49
3.2.3.1 Informed Consent.....	49
3.2.3.1.1 General Informed Consent	49
3.2.3.1.2 Consent and Collection of Specimens for Genetic and Other Biomedical Research.....	50
3.2.3.2 Assignment of Baseline/Screening Number	51
3.2.3.3 Procedures Performed During the Pre-Infusion Phase	51
3.2.3.3.1 General Medical History	52
3.2.3.3.1.1 CDI History	52
3.2.3.3.1.2 Horn's Index	53
3.2.3.3.1.3 Charlson Index.....	53
3.2.3.3.2 Physical Examination.....	53
3.2.3.3.3 Vital Signs	53
3.2.3.3.4 Stool Sample Collection.....	53
3.2.3.3.5 Blood and Urine Sample Collection.....	54
3.2.3.4 Stratification.....	54
3.2.3.5 Randomization/Allocation	55
3.2.3.6 Nonrandomized Patients	56
3.2.3.7 Procedures Performed in Conjunction With Treatment – Infusion (Day 1)	56
3.2.3.7.1 Vital Signs Pre-Infusion	56
3.2.3.7.2 12-Lead Electrocardiogram Pre-Infusion.....	56
3.2.3.7.3 Dosage and Administration of Infusion	56
3.2.3.7.4 Unblinded Preparation of Infusion (Unblinded Pharmacist).....	57
3.2.3.7.5 Vital Signs During and Immediately Post-Infusion	58
3.2.3.7.6 Infusion Reactions During and Post-Infusion	58

Product: MK-3415A Page 4
Protocol/Amendment No.: 001-03

3.2.3.7.7	Blood Sample Post-Infusion.....	59
3.2.3.7.8	12-Lead Electrocardiogram Post-Infusion	60
3.2.3.8	Procedures Performed Post-Infusion (Day 1 through Week 12).....	60
3.2.3.8.1	Clinical Follow-up.....	60
3.2.3.8.1.1	Loose Stool Counts and Body Temperature.....	60
3.2.3.8.1.2	Phone/Visit Contact to Assess and Record Loose Stool Counts, SOC Compliance, and Body Temperature	61
3.2.3.8.1.3	Vital Signs	61
3.2.3.8.1.4	Physical Examination	61
3.2.3.8.2	Laboratory Follow-up.....	62
3.2.3.8.2.1	Stool Samples	62
3.2.3.8.2.2	Blood and Urine Samples	62
3.2.3.8.3	New Episode of Diarrhea/Unscheduled Visit	62
3.2.3.9	Blinding/Unblinding	63
3.2.3.10	Discontinuation/Withdrawal from Study	64
3.3	EFFICACY / PHARMACOKINETIC / IMMUNOGENICITY MEASUREMENTS.....	65
3.3.1	Clinical Measurements for Efficacy (Assessment of Primary, Secondary, and Exploratory Efficacy Endpoints)	65
3.3.2	Immunologic and Bacteriologic Measurements	67
3.3.2.1	Toxigenic <i>C. difficile</i> Testing in Stool Specimens (Local Assays Specified in Appendix 6.1)	67
3.3.2.2	Anaerobic Stool Culture.....	67
3.3.2.2.1	Toxigenic Strain Typing.....	67
3.3.2.2.2	Antibacterial Susceptibility Testing.....	68
3.3.2.3	Detection of MK-3415 and MK-6072 in Blood Samples	68
3.3.2.4	Detection of Endogenous Antibodies to Toxin A and Toxin B in Blood Samples	68
3.3.2.5	Detection of Anti-Drug Antibody (ADA) to MK-3415 or MK-6072	69
3.3.2.6	Neutralizing Antibody in Samples Positive for ADA.....	69
3.3.3	External Data Monitoring Committee (eDMC)	69
3.3.3.1	eDMC Membership.....	69
3.3.3.2	Summary of eDMC Responsibilities	70
3.3.3.3	eDMC Meeting at the Interim Analysis.....	71
3.4	SAFETY MEASUREMENTS	72
3.4.1	Clinical and Laboratory Measurements for Safety.....	72
3.4.1.1	Laboratory Safety Tests	72
3.4.2	Recording Adverse Experiences.....	73
3.4.3	Definition of an Overdose for This Protocol.....	73
3.4.3.1	Reporting of Overdose to SPONSOR.....	74
3.4.4	Reporting of Pregnancy to SPONSOR.....	74
3.4.5	Immediate Reporting of Adverse Experiences to the SPONSOR	74

03GGHO

Product: MK-3415A Page 6
Protocol/Amendment No.: 001-03

4.1.1	Confidentiality of Data	103
4.1.2	Confidentiality of Subject/Patient Records	103
4.1.3	Confidentiality of Investigator Information	103
4.2	COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT	104
4.3	COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS	105
4.4	QUALITY CONTROL AND QUALITY ASSURANCE	106
4.5	COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS	106
4.6	PUBLICATIONS	106
5.	LIST OF REFERENCES	108
6.	APPENDICES	115
6.1	ACCEPTABLE <i>C. DIFFICILE</i> DIAGNOSTIC METHODS	115
6.2	BRISTOL STOOL CHART	116
6.3	MODIFIED HORN'S INDEX	117
6.4	CHARLSON INDEX	118
6.5	LABORATORY SAFETY TESTS	120
6.6	BIOMARKER EVALUATION IN THIS STUDY	122
6.7	HIGH RISK DEMOGRAPHIC AND CLINICAL IDENTIFIERS	126
7.	ATTACHMENTS	128
8.	SIGNATURES	144
8.1	SPONSOR'S REPRESENTATIVE	144
8.2	INVESTIGATOR	144

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 7

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT

Section Number(s)	Section Title(s)	Description of Change(s)
1.6; 3.2.3.7.3	Dosage/Dosage Form, Route, and Dose Regimen; Dosage and Administration of Infusion	The infusion set filter pore size was changed to 5 micron or smaller based on recently completed compatibility studies. This change is to allow greater flexibility in the types of infusion materials that can be used.
1.7; 3.2.3.8.1.2	Study Flow Chart; Phone/Visit Contact to Assess and Record Loose Stool Counts and Body Temperature	These sections have been modified to add instruction that compliance with Standard of Care (SOC) antibiotic therapy administration is to be discussed with subjects during the daily contacts when the patient is still receiving SOC. Duration of SOC antibiotic therapy is important for the protocol definition of clinical cure. Addition of this daily question is expected to improve patient compliance as well as accuracy in recording of stop dates for therapy. Also updated the title of the section to include SOC Compliance.
1.7; 2.4.1	Study Flow Chart; Summary of Study Design	These sections were clarified to note that a stool sample is to be collected when recurrence of diarrhea occurs after SOC therapy has completed. It is not required to collect a sample if diarrhea resolves during SOC and resumes again before the end of SOC therapy.

Product: MK-3415A

Page 8

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
1.4; 1.8; 2.4.1; 2.5.2; 2.5.3; 3.2.3.1.3; 3.2.3.8.3; 3.2.3.8.4; 3.4.1.1; 3.4.5.1; 3.5.1; 3.5.10	Summary of Study Design: Study Flow Chart- Extended Follow-Up Period for Subset of Patients (Months 4 to 12); Summary of Study Design: Other Efficacy Measures (Secondary/ Exploratory Objectives): Endogenous Antibody Levels and Pharmacokinetics: Immunogenicity: Informed Consent for Additional 9-Month Extended Follow-up; New Episode of Diarrhea/ Unscheduled Visit: Responsibility for Analysis/In-House Blinding: Additional 9-Month Extended Follow-Up	The 9-month extended follow-up portion of the study has been removed. Upon review of the data needed for product registration and the rate of enrollment into the extension in Protocol 002, it was determined that it will be possible to enroll the required number of patients with Protocol 002 alone.
1.4, 2.2	Patient Inclusion Criteria	Inclusion Criterion # 2 has been clarified: A confirmed diagnosis of <i>C. difficile</i> infection (CDI) must have been made, but diarrhea does not need to be present on the day of the infusion. Also, the positive stool test for toxigenic <i>C. difficile</i> must be from a stool sample collected no more than 7 days before the study infusion. These clarifications provide important additional information to help the investigator determine which patients are eligible for study participation.

Product: MK-3415A

Page 9

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
2.3	Patient Exclusion Criteria	Exclusion Criterion # 1 has been clarified: A patient with an uncontrolled chronic diarrheal illness such that their normal 24-hour bowel movement habit is 3 or more loose stools (as defined by the Bristol Stool Chart Types 5, 6 or 7) should be excluded. In addition, patients with a history of inflammatory bowel disease who are controlled (i.e., had no recent active diarrhea prior to current <i>C. difficile</i> episode) may be enrolled if in the opinion of the investigator the symptoms are more likely due to CDI than a flare of the inflammatory bowel disease. These clarifications provide important additional information to help the investigator determine which patients with preexisting diarrheal illnesses are eligible for study participation.
2.3; 3.2.1.2	Patient Exclusion Criteria	Exclusion Criterion #6 has been expanded: A patient receiving a <i>C. difficile</i> vaccine or other experimental monoclonal antibody against <i>C. difficile</i> toxin A or B should be excluded. The enrollment period for this study spans 2 years and it is recognized that these therapies may reach clinical testing at some point during the recruitment period. These medications would be expected to decrease the chance that the patient would have a recurrence of CDI.
2.3; 3.2.1.2	Patient Exclusion Criteria; Other Prior/Concomitant Medication(s)/ Treatment(s)	Exclusion Criterion #10 has been changed to note the following (changes underlined): "Patient has received <u>more than a 24-hour regimen</u> of cholestyramine, <u>cholestimide</u> , rifaximin...." The duration of prior use was expanded because a single dose of these medications is not expected to interfere with the primary and secondary study endpoints. Cholestimide is an anion-exchange resin similar to cholestyramine which is available in some countries where the study is being conducted.
2.3; 3.2.1.2	Patient Exclusion Criteria; Other Prior/Concomitant Medication(s)/ Treatment(s)	Exclusion Criterion #11 has been clarified: "Patient plans to take medications which are given to decrease <u>gastrointestinal</u> peristalsis..." This change is important to acknowledge that all medications used to treat diarrhea are not excluded, but rather only those given to decrease gastrointestinal peristalsis as their mechanism of action would lead to exclusion.
2.3; 3.2.1.2	Patient Exclusion Criteria; Other Prior/Concomitant Medication(s)/ Treatment(s)	Exclusion Criterion #12 was expanded: Patients who plan to receive fecal transplantation therapy or any other therapies that have been demonstrated to decrease CDI recurrence at any time following infusion (Day 1) and through the completion of the 12-Week study period should be excluded. The criterion was further clarified to state that all such therapies would be allowed if recurrence occurs after study therapy/SOC have completed. The exclusion of these treatments is being added because they may interfere with the primary and secondary study objectives.

Product: MK-3415A

Page 10

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
2.3	Patient Exclusion Criteria	Exclusion Criterion #13 was clarified to be consistent with Section 3.2.1.2: "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 with an investigational agent during the 12-Week study period."
2.4.1; 3.2.1.1	Summary of Study Design; Standard of Care (SOC) Therapy for CDI	These sections now provide clarifications as to when the duration of SOC therapy can be longer than 14 days. The clarification addresses 2 situations where a change in therapy occurs before randomization and there is a medically plausible reason why treatment should be extended: 1) when the total daily dose prior to randomization was below that mandated by the protocol; 2) lack of efficacy was noted pre-randomization with a prior regimen. In these two situations, it would not be appropriate to classify the patient's clinical response to study SOC as a clinical failure solely because the duration of the pre-randomization therapy plus the duration of the new therapy were > 14 days.
2.7.1; 3.5.3.1; 3.5.5.1	Efficacy Analyses; Efficacy Endpoints; Statistical Methods for Efficacy Analyses	The definition of the clinical cure endpoint was modified with regard to the duration of standard of care (SOC) medication: a 14 day regimen is defined as treatment spanning no more than 16 calendar days. A patient prescribed a 14-day regimen could actually take the medication for 16 calendar days depending on when during the first day they start the regimen and/or if they "take until finished" but miss a few doses. For this reason, a patient who has resolved their diarrhea will not be considered a failure for the clinical cure endpoint unless they receive more than 16 calendar days of medication.
2.7.1; 3.5.4.1	Efficacy Analyses; Efficacy Analysis Populations	The definition of the FAS population was modified to add an additional exclusion criterion of failure to receive protocol defined SOC therapy within a 1 day window of the infusion. Those patients without documented SOC antibiotic therapy within this window will not be included in the primary efficacy population.
3.2.3.3.4	Stool Sample Collection	This section was modified to allow use of a stool sample collected prior to enrollment for microbiological assessments performed by the central laboratory.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT

Section Number(s)	Section Title(s)	Description of Change(s)
Title page	Title	With this amendment, the new study number is MK-3415A PN001-03.
1.4	Summary of Study Design	Clarified definition on loose stools in Figure 1 by adding the appropriate Bristol Stool Chart types.

Product: MK-3415A

Page 11

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
1.4; 2.4.1; 3.2.1.1	Summary of Study Design; Standard of Care Therapy for CDI	These sections were clarified to note that patients enrolled in this study should be <u>prescribed</u> a SOC regimen for a minimum duration of 10 days and a maximum duration of 14 days.
1.6; 2.4.1; 3.2.3.7.4	Dosage/Dosage Form, Route, and Dose Regimen; Summary of Study Design; Unblinded Preparation of Infusion (Unblinded Pharmacist)	These sections were modified to add that the infusion is to be prepared by an Unblinded Pharmacist or <u>qualified designee</u> . This allows for consistency with wording in Section 3.6.1 of the protocol.
1.7	Study Flow Chart	The approximate blood draw volumes collected at the main study visits have been updated in this section. This change has been made based on updated information received from the central laboratory to reflect more accurate amounts of blood needed per visit.
1.7	Study Flow Chart	A clarification has been added to the flowchart footnote that medical history should be reviewed <u>prior to or on Day 1</u> .
1.7; 3.2.1.1; 3.2.1.2	Study Flow Chart; Standard of Care (SOC) Therapy for CDI; Other/Prior Concomitant Medication(s)/ Treatment(s)	A correction was made to the flowchart footnote that antimicrobial therapies should be recorded for the <u>28</u> days prior to study medication infusion. For all other medications, the period is 14 days prior to study medication infusion. This correction is needed to ensure consistency with other study documents (i.e., case report form [CRF] entry guidelines).
1.7; 3.2.3.1.1; 3.2.3.1.2; 3.2.3.3.4; 3.2.3.8.2.2; 6.6	Study Flow Chart; General Informed Consent; Consent and Collection of Specimens for Genetic and Other Biomedical Research; Stool Sample Collection; Biomarker Evaluation in This Study	These sections were modified to remove the specific method for conducting genetic analyses. Also, these sections have removed reference to the method for deep sequencing of gut flora. These deletions were made to allow for the use of other available technologies. These sections were also modified to remove language that samples would be retained for no more than 10 years. Sample storage information is specified in the GBRC consent.
1.7; 3.2.3.3; 3.2.3.3.1.	Study Flow Chart; Procedures Performed During the Pre-Infusion Phase; CDI History	The description of the information to be reported regarding the patient's CDI history and the presenting episode of CDI was updated in these sections. The question regarding whether the patient has an appendix will also be added to the appropriate CRF. Clarified that the review of a patient's medical history will include reviewing occurrences of CDI in the past 12 months. These corrections provide for consistency with other study documents (CRF).

Product: MK-3415A

Page 12

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
2.4.1; 3.2.1.1	Summary of Study Design; Standard of Care (SOC) Therapy for CDI	These sections were clarified to note that a switch in SOC therapy can be made at any time for an adverse experience related to the SOC. This clarification is to ensure that investigators are aware that it is not necessary to wait 3 days before switching the SOC medication if the patient has an adverse reaction to the SOC therapy.
3.2.1.1	Standard of Care (SOC) Therapy for CDI	This section has been clarified to note that treatment with SOC therapy for longer than 14 days is not a protocol violation if this was not the intent at the time of randomization (e.g., treatment duration increase due to persistent diarrhea). A clarification was also added that the choice of treatment(s) and duration of therapy is not restricted after the patient meets the primary endpoint of CDI recurrence.
3.2.1.1	Standard of Care (SOC) Therapy for CDI	Text that noted that SOC therapy is not being provided by SPONSOR has been removed. This is because reimbursement by Merck for one or more SOC therapies is required in some countries.
3.2.1.2	Other Prior/ Concomitant Medication(s)/ Treatment(s)	Text was added to state that the use of any other treatments not currently specified in the protocol that have been shown to decrease CDI recurrence should not be given unless the patient has a recurrence during the study following the completion of study therapy/SOC.
3.2.2.2; 3.4.4	Pregnancy and Contraception; Reporting of Pregnancy to SPONSOR	The collection of information if the partner of a patient enrolled in the study becomes pregnant has been added, where appropriate, to correct an inconsistency between eligibility criteria and description of data to be collected in the event of a partner pregnancy.
3.2.3.2	Assignment of Baseline/ Screening Number	The following change has been made to align with a change in the actual process that is being used for this study: Each patient will receive a unique baseline/screening number, generated by the <u>site</u> .
3.2.3.3.1; 3.2.3.3.5	General Medical History; Blood and Urine Sample Collection	A clarification has been added that patients with renal disease and patients who do not produce urine are not excluded from the protocol. This was added to address a frequently asked question regarding inclusion of patients with advanced renal disease and to waive the requirement for urine samples from these patients.
3.2.3.3.1.2; 6.3	Horn's Index; Modified Horn's Index	A clarification was added to note that the Modified Horn's Index assessment is to be completed by a physician at the time of study entry. It was also clarified that the answers to the questions will be based on review of information obtained during screening.
3.2.3.7.3; 3.2.3.7.4	Dosage and Administration of Infusion; Unblinded Preparation of Infusion (Unblinded Pharmacist)	A clarification was added that the dosage of monoclonal antibody is based on <u>actual</u> patient weight.

Product: MK-3415A

Page 13

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
3.2.3.7.6	Infusion Reactions During and Post-Infusion	This section describes infusion reactions caused by other monoclonal antibodies; there is limited human experience to date for the monoclonal antibodies (MK-3415, MK-6072) under study. A sentence was added describing the monoclonal antibodies under study in this protocol and that they may be less likely to cause some of these reactions.
3.2.3.7.6; 3.2.3.8.1.2; 3.4.1	Infusion Reactions During and Post-Infusion; Phone/Visit Contact to Assess and Record Loose Stool Counts and Body Temperature; Clinical and Laboratory Measurements for Safety	A clarification was added about the timing and topics for the follow-up telephone contacts with the patients.
3.2.3.8.1.1	Loose Stool Counts and Body Temperature	The section was modified to note that there are no protocol-specific criteria which will require a patient to be withdrawn prematurely from the study and that patients who receive study infusion should continue to record daily loose stool counts.
3.2.3.8.1.1	Loose Stool Counts and Body Temperature	This section was modified to note that stool count logs and other source documents containing information obtained from the patient should be maintained as source documents at the end of the study.
3.2.3.8.3	New Episode of Diarrhea/ Unscheduled Visit	This section has been clarified to note that at the time of diarrhea recurrence, an unscheduled visit should occur and a stool sample is to be collected for local and central laboratory testing for toxigenic <i>C. difficile</i> , even if there is another plausible diagnosis for the diarrhea.
3.3.2.2; 3.3.2.2.1	Anaerobic Stool Culture; Toxigenic Strain Typing	A statement was added to clarify that the results of anaerobic stool culture and toxigenic strain typing would not be available to inform patient management/treatment decisions.
3.3.2.2.1	Toxigenic Strain Typing	A clarification was added that additional typing methods may be considered to differentiate relapse versus reinfection of CDI, if necessary and/or as the science evolves.
3.4.1.1	Laboratory Safety Tests	This section has been clarified to note that blood will also be collected for a limited panel of safety laboratory tests at unscheduled visits for a new episode of diarrhea during the 12-week study period.
3.4.3	Definition of an Overdose for This Protocol	The dose of each antibody (MK-3415, MK-6072) that is considered an overdose for this study has been increased to 20 mg/kg, since this is the highest dose studied in man to date. This dose was well tolerated in healthy male and female volunteers.

Product: MK-3415A

Page 14

Protocol/Amendment No.: 001-03

Section Number(s)	Section Title(s)	Description of Change(s)
3.4.5.2	Selected Nonserious Adverse Experiences	A clarification was included to note that liver function test values that meet the events of clinical interest (ECI) criteria, but are present at baseline, are not considered ECI for the study. Also a patient whose values meet the criteria at baseline will only meet the criteria post-baseline if the values worsen.
3.5.5.1	Statistical Methods for Efficacy Analyses	Text was added to describe the planned sensitivity analysis of CDI recurrence.
3.5.5.1	Statistical Methods for Efficacy Analyses	Text was added to specify the planned sensitivity analyses for clinical cure.
3.5.5.4; 6.6	Other Analyses; Biomarker Evaluation in This Study	Text was added to note that these various biomarker analyses are not expected to be necessary for marketing authorization and therefore will not be reported in the Clinical Study Report describing the analyses for the primary, secondary, and exploratory objectives.
3.5.9.2	Safety Interim Analysis	Modified text in this section to clarify that eDMC will review safety at time of efficacy interim analysis and not at regular intervals (unless safety signal was identified).
6.1	Acceptable <i>C. difficile</i> Diagnostic Methods	Two new assays have been added to the list of acceptable commercial available assays.
6.4	Charlson Index	Charlson Index is a comorbidity index; several past conditions which are to be included as “present” for this assessment have been clarified.
6.5	Laboratory Safety Tests	Text has been added to note that the central laboratory will be reporting percent counts as well as absolute counts for neutrophils, basophilic leukocytes, eosinophilic leukocytes, lymphocytes, and monocytes.
Multiple	Multiple	General formatting and spelling errors were corrected.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 15

1. SUMMARY

1.1 TITLE

A Phase III, Randomized, Double-Blind, Placebo-Controlled, Adaptive Design Study of the Efficacy, Safety, and Tolerability of a Single Infusion of MK-3415 (Human Monoclonal Antibody to *Clostridium difficile* toxin A), 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 I)

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).

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 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. 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 A and toxin B. 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 1:1:1:1 ratio into 1 of 4 treatment groups. On Day 1 (day of study therapy infusion), patients will receive MK-3415, MK-6072, MK-3415A, or placebo. Investigators are encouraged to enroll 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 be prescribed a SOC regimen for a minimum duration of 10 days and a maximum duration 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

Product: MK-3415A

Page 17

Protocol/Amendment No.: 001-03

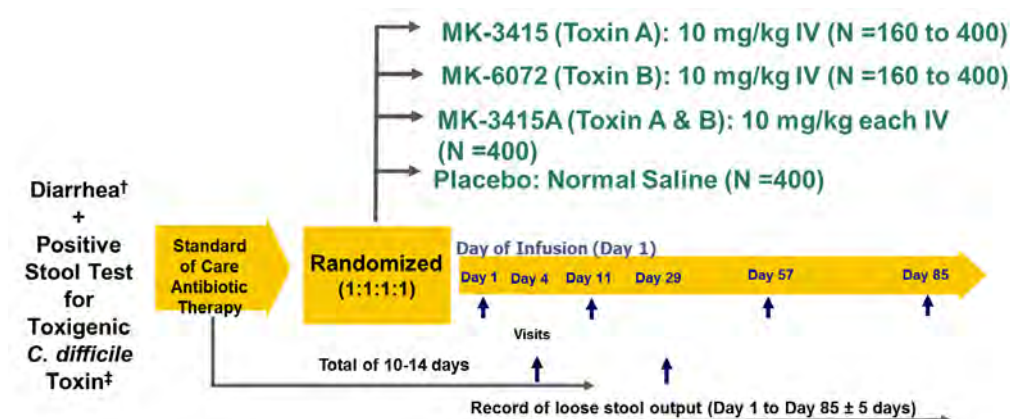
and laboratory adverse experiences in the 4 treatment groups through Week 4 (Day 29 \pm 3 days), hereafter referred to as Week 4.

This study has an adaptive design whereby one or both of the *individual* monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped based on the results of a single interim analysis if there is a significant difference in the reduction of CDI recurrence when compared to MK-3415A (i.e., MK-3415A is significantly better than MK-3415 and/or MK-3415A is significantly better than MK-6072). The interim analysis will be conducted by an independent, external Unblinded Statistician and reviewed by an independent, external Data Monitoring Committee (eDMC).

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)



[†] Diarrhea: 3 or more loose stools in 24 or fewer hours (types 5, 6 and/or 7 per Bristol Stool Chart)

[‡] Positive stool test for toxigenic *C. difficile* (stool sample must have been collected no more than 7 days prior to infusion)

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 up to 400 patients in each treatment group (to a maximum sample size of 1,600 patients). Actual enrollment will depend on the results of the interim analysis, as one or both of the *individual* monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped at the time of the interim analysis (Section 3.3.3 and 3.5.9). Thus, total enrollment will ultimately range from 1,120 patients (if only 2 groups are continued after the interim analysis) to 1,600 patients (if all 4 groups are continued after the interim analysis).

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Patients will be randomized at study onset in a 1:1:1:1 ratio into 1 of 4 treatment groups to receive one of the following:

- A single infusion of the MK-3415 (10 mg/kg of monoclonal antibody to *C. difficile* toxin A only), or
- 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 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 or qualified designee, will be administered as a single 250 mL total infusion volume in 0.9% sodium chloride. The total infusion volume for all patients, regardless of dose or treatment group (i.e., whether receiving placebo, an individual monoclonal antibody [MK-3415 or MK-6072], or both monoclonal antibodies [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-3415, MK-6072, and MK-3415A versus placebo, all 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 5 micron or smaller 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.: 001-03

Page 19

1.7 STUDY FLOW CHART - BASE 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 (\pm 1 day)	Day 11 (\pm 2 days)	Week 4 (Day 29 \pm 3 days)	Week 8 (Day 57 \pm 7 days)	Week 12 (Day 85 \pm 5 days)	Day 1 to Week 12 (Day 85 \pm 5 days)
CDI Diagnosis (local laboratory stool test for toxigenic <i>C. difficile</i>) [†]	X						X
Written Informed Consent	X						
Genetic and Other Biomedical Research Informed Consent	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	

Confidential

15-May-2013

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 20

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 anaerobic stool culture and other ancillary microbiological assessments (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 Week 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						
CLINICAL SEROLOGY & BIOMARKER SAMPLES							
Blood Sample for messenger RNA (mRNA) Profiling Sample ^{††††}	X						
Stool Sample for Deep sequencing of gut flora ^{§§§§}	X						
Blood Sample for Genetic and Other Biomedical Research		X (Optional to all patients)					

Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 21

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)
<p>NOTE: The following approximate blood draw volumes will be collected during the main study (not including optional GBRC sample): Visit 1 = 38.5 mL, Visit 2 = 14 mL, Visit 3 = 14 mL, Visit 4 = 24 mL, Visit 5 = 12 mL, Visit 6 = 16 mL, and UNS = 14 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 after SOC treatment has completed 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. After SOC treatment has completed, a stool sample for toxigenic <i>C. difficile</i> testing must be collected for each separate, new episode of diarrhea.</p> <p>‡ Medical history should be reviewed prior to or on Day 1 to confirm study eligibility, and all medical conditions present within the last 12 months should be recorded. The onset date of each prior CDI episode occurring within the last 12 months should be recorded. The number of prior CDI episodes occurring in the patient's lifetime will also be recorded. Relative to the presenting case of CDI, the patients' current and recent (3 months) hospitalization status, patients' location at the time of onset of CDI and treatment location; presence of nasogastric tube in the past month; endoscopic evidence of pseudomembranous colitis (if performed); signs and symptoms consistent with toxic megacolon, bowel perforation, or ileus; whether the patient had a colectomy or other surgical procedure to treat the presenting case of CDI; and whether the patient has an appendix should be recorded. An assessment of underlying disease severity by modified Horn's Index (see Appendix 6.3) must be performed by a physician. 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> <p> 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 approximately 30 minutes after the start 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.</p> <p>¶ 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.</p> <p># Prior antimicrobial medication use should be recorded for the 28 days prior to study entry and all other medications 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>, rifaximin, and nitazoxanide) should be recorded for the full 12-Week study period.</p> <p>†† 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.</p> <p>‡‡ 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.</p> <p>§§ 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.</p>							

Confidential

15-May-2013

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 22

	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 before infusion, if possible. However, in the event the patient no longer has diarrhea at the time of infusion, 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 after SOC treatment for the presenting episode is completed, 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). After SOC treatment for the presenting episode has completed, 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, body temperature, and compliance with SOC medications and to ensure they are being recorded on the log. Thereafter, study personnel will contact the patient twice weekly Week 3 through Week 12. The information communicated by the patient during the contact is to be recorded in the source documentation
\$\$\$	Study personnel will record the number of loose stools (defined by Bristol Chart Type 5 through Type 7, as per Appendix 6.2) for each day 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 at scheduled study visits per protocol schedule and at unscheduled visits at the time of a new episode of diarrhea
##	Blood sample will be collected within 24 hours prior to infusion for dehydroepiandrosterone (DHEA) levels
+++	Blood sample will be collected within 24 hours prior to infusion for CMV IgG titers
+++	Blood samples (2.5 mL into a PAXGENE tube) will be collected within 24 hours prior to infusion for mRNA expression profiling
\$\$\$	The stool sample for deep sequencing of gut flora is collected prior to infusion
	Blood sample (10 mL) will be collected from subjects who have signed the Genetic and Other Biomedical Research Informed Consent only. The sample may be collected at a later visit if necessary.

Confidential

15-May-2013

03GGHQ

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary (Interim Analysis)

Primary Objective #1: 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-3415 or MK-6072) 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 MK-3415 given with SOC therapy.

Primary Hypothesis #1b: 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 MK-6072 given with SOC therapy.

(NOTE: Primary Objective #1 will be tested at the interim analysis.)

2.1.2 Primary (Final Analysis)

Primary Objective #2: 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-3415 or MK-6072) with SOC therapy.

Primary Hypothesis #2a: 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 MK-3415 given with SOC therapy.

Primary Hypothesis #2b: 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 MK-6072 given with SOC therapy.

(NOTE: Primary Objective #2 will be tested at the final analysis. This objective will only evaluate MK-3415A relative to those individual monoclonal antibody treatment groups, if any, that remain following the interim analysis.)

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 24

Primary Objective #3: To determine if treatment with a single infusion of monoclonal antibody therapy with SOC therapy (*combined* monoclonal antibody therapy [MK-3415A] and possibly the separate *individual* monoclonal antibody therapy [MK-3415 and/or 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 #3a: 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 #3b: Treatment with a single infusion of MK-3415 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 #3c: 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.

(NOTE: Primary Objective #3 will be formally tested at the final analysis. This analysis will be evaluated for the MK-3415A group and any individual monoclonal antibody treatment groups remaining following the interim analysis.)

Primary Objective #4: To evaluate the safety profile in patients receiving a single infusion of monoclonal antibody therapy (either as MK-3415, 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 #4: Administration of a single infusion of monoclonal antibody therapy (either as MK-3415, 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.

2.1.3 Secondary

NOTE: *The various secondary efficacy objectives (Secondary Objectives #1 through #4 below) are focused on the comparison of MK-3415A versus placebo. However, these secondary efficacy objectives may also include the individual monoclonal antibody treatment groups (either MK-3415 or MK-6072) provided one (or both) of these regimens are not found to be different from MK-3415A for the second primary hypothesis AND demonstrate superiority versus placebo for the third primary hypothesis (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.

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 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 (either as MK-3415, MK-6072, or MK-3415A) with SOC therapy as compared to the treatment group receiving a single placebo infusion with SOC therapy.

2.1.4 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 groups (either MK-3415 or MK-6072) provided one (or both) of these regimens are not found to be different from MK-3415A for the second primary hypothesis AND demonstrate superiority versus placebo for the third primary hypothesis (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 $<101^{\circ}\text{F}$ [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 confirmed diagnosis of *C. difficile* infection (CDI) as defined by:
 - a. Diarrhea (passage of 3 or more loose stools in 24 or fewer hours [16]),

AND

- b. A positive stool test for toxigenic *C. difficile* from a stool samples collected no more than 7 days before the study infusion (allowed stool test methods and kits are listed in Protocol Appendix 6.1)

NOTE: Diarrhea is not required to be present on the day of infusion.

Product: MK-3415A

Page 27

Protocol/Amendment No.: 001-03

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 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.

2.3 PATIENT EXCLUSION CRITERIA

1. Patient with an uncontrolled chronic diarrheal illness such as, but not limited to, uncontrolled ulcerative colitis or Crohn's disease or with a condition such that their normal 24-hour bowel movement habit is 3 or more loose stools as defined by the Bristol Stool Chart Types 5, 6, and/or 7 (see Appendix 6.2). Patients with a history of

Product: MK-3415A

Page 28

Protocol/Amendment No.: 001-03

inflammatory bowel disease who are controlled (i.e, had no recent active diarrhea prior to current *C. difficile* episode) may be enrolled if in the opinion of the investigator the symptoms are more likely due to CDI than a flare of the inflammatory bowel disease.

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, has previously received MK-3415 or MK-6072 (either alone or in combination), has received a *C. difficile* vaccine, or has received any other experimental monoclonal antibody against *C. difficile* toxin A or B.
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. Patient 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 more than 24 hour regimen of cholestyramine, cholestimide, 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 which are given to decrease gastrointestinal peristalsis, such as loperamide (Imodium™) or diphenoxylate hydrochloride/atropine sulfate (Lomotil™) 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* or receive fecal transplant therapy, or any other therapies that have been demonstrated to decrease CDI

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 29

recurrences at any time following infusion (Day 1) and through the completion of the 12-Week study period (all such therapies would be allowed if recurrence occurs after study therapy/SOC has completed see Section 3.2.1.2).

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 with an investigational agent 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 adaptive design study evaluating the efficacy, safety, and tolerability of monoclonal antibodies to *C. difficile* toxin A and/or toxin B 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 4 treatment groups for the reduction of CDI recurrence:

- A single infusion of the MK-3415 (10 mg/kg of monoclonal antibody to *C. difficile* toxin A only)
- 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 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 1:1:1:1 ratio into 1 of 4 treatment groups. An Unblinded Pharmacist or

Product: MK-3415A

Page 30

Protocol/Amendment No.: 001-03

qualified designee 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 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 be prescribed an SOC regimen for a minimum duration of 10 days and a maximum duration 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/mm. Emergence of an adverse experience due to the inability of a patient to tolerate their current SOC therapy also warrants an SOC switch; this switch can be made at any time. 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 be prescribed 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), unless the switch occurs prior to or at the time of randomization for one of the following reasons: the prescribed antibiotic was (1) given at a total daily dose below that mandated by the protocol (see Sections 3.2.1.1.1 to 3.2.1.1.3 for description of required dose amounts and regimens for the allowed SOC therapies; or (2) the patient continued to have symptoms of CDI while on protocol allowed SOC regimen that was switched because it was deemed ineffective (e.g., switch from oral metronidazole to oral vancomycin).

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.

Following the completion of SOC therapy, 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). 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 of MK-3415 and MK-6072, and limited safety laboratory tests (as outlined in Appendix 6.5) should be collected at this unscheduled visit.

This study has an adaptive design whereby treatment groups may be dropped based on the results of a single interim analysis. When approximately 640 enrolled patients (40% of the targeted patient population) have completed the 12-Week study period or discontinued prior to Week 12, an interim analysis will be conducted. This interim analysis will be conducted by an independent, external Unblinded Statistician and reviewed by an independent eDMC to evaluate the efficacy (and safety) of each individual monoclonal antibody treatment group (MK-3415 or MK-6072) relative to the combined monoclonal antibody therapy (MK-3415A) in the reduction of CDI recurrence. If there is a significant difference between treatment groups in the reduction of CDI recurrence (i.e., MK-3415A is significantly better than MK-3415 and/or MK-3415A is significantly better than MK-6072), then the less effective monoclonal antibody treatment group(s) (MK-3415 and/or MK-6072) will be dropped from the study, and the other study groups will continue until the total patient population is enrolled (i.e., ~400 patients are fully enrolled in each remaining treatment group). Enrollment will continue in the 4 treatment groups until the results of the interim analysis are available. The patients enrolled during this time will not be included in the interim analysis and their data will have no bearing on the decisions made at the interim analysis.

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 among placebo-treated patients. Please refer to Appendix 6.6 for additional information.

2.4.3 Treatment Plan

Overall, the study plans to enroll up to 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 treatment group. Overall enrollment will depend on the results of the interim analysis, as one or both of the individual monoclonal antibody treatment groups (MK-3415 and/or MK-6072) may be dropped at the time of the interim

Product: MK-3415A

Page 32

Protocol/Amendment No.: 001-03

analysis. Thus, total enrollment will ultimately range from 1,120 patients (if only 2 groups are continued after the interim analysis) to 1,600 patients (if all 4 groups are continued after the interim analysis).

Table 2-1 describes the treatment plan at study onset. If results at the interim analysis indicate that no treatment groups will be dropped, then the treatment plan will remain as in Table 2-1. Table 2-2 and Table 2-3 describe the potential treatment plans following the interim analysis where one or two treatment groups are respectively dropped.

Table 2-1

Treatment Plan At Study Onset

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-3415	10 mg/kg
		MAb	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Metronidazole	Inpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Fidaxomicin (includes patients receiving both oral fidaxomicin and intravenous metronidazole concurrently)	Inpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAB	MK-3415	10 mg/kg
		MAB	MK-6072	10 mg/kg
		MAB	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 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
Protocol/Amendment No.: 001-03

Page 33

Table 2-2

Treatment Plan Following Interim Analysis
(Assuming Continuation of 3 Treatment Groups)

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-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAb	MK-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Metronidazole	Inpatient	MAb	MK-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAb	MK-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
Fidaxomicin (includes patients receiving both oral fidaxomicin and intravenous metronidazole concurrently)	Inpatient	MAb	MK-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 10 mg/kg of MK-6072
		Placebo	Placebo	N/A
	Outpatient	MAb	MK-3415 or MK-6072	10 mg/kg
		MAb	MK-3415A	10 mg/kg of MK-3415 <u>and</u> 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
Protocol/Amendment No.: 001-03

Page 34

Table 2-3

Treatment Plan Following Interim Analysis
 (Assuming Continuation of 2 Treatment Groups)

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

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 ± 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

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 35

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 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 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).

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 (\pm 1 day), Day 11 (\pm 2 days), Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), Week 12 (Day 85 \pm 5 days) and at an unscheduled visit for a new episode of **diarrhea**.

2.5.3 Immunogenicity

A blood sample collected within 24 hours prior to infusion and at Week 4 (Day 29 \pm 3 days), Week 8 (Day 57 \pm 7 days), and Week 12 (Day 85 \pm 5 days) 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 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**. 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.

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, interim analyses, 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 2-4 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 ± 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).

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 37

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 day regimen 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 -day regimen 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.

Individual monoclonal antibody therapies (MK-3415 and MK-6072) will be compared separately to the combined monoclonal antibody therapy (MK-3415A), and the various active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared separately to placebo. Under the global null hypothesis that the four therapies (three 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-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)
- Failure to receive protocol defined SOC therapy within a 1 day window of the infusion

Table 2-4

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 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 events; these analyses will be performed using the Miettinen and Nurminen method (1985) [17], an unconditional, asymptotic method.

2.7.3 Power and Sample Size

This study has a planned sample size of 1600 patients to be randomized in a 1:1:1:1 ratio to each of the four treatment groups (MK-3415A, MK-3415, MK-6072, and placebo).

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 39

The following power calculations are based on a two group chi-square test for comparing independent proportions.

Primary Endpoint - CDI Recurrence (Interim and Final Analyses)

An interim analysis is planned when approximately 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12). The purpose of this interim analysis is to evaluate if treatment with combined monoclonal antibody therapy (MK-3415A) is superior to treatment with either of the individual monoclonal antibody therapies (MK-3415 or MK-6072). If MK-3415A is found to be superior to MK-3415 or MK-6072, then further enrollment in one or both of these respective groups will be stopped. These two comparisons will be performed at a 1-sided alpha level of 0.0001, as described in Section 3.5.6.

At the interim analysis, it is anticipated that 160 patients per group will be in the analysis population for the CDI recurrence endpoint. This will provide approximately 80% power to detect the following differences in the incidence of CDI recurrence between combined monoclonal antibody therapy (MK-3415A), π_1 , and the individual monoclonal antibody therapies (MK-3415 or MK-6072), π_2 :

π_1	π_2	Difference	Power
.08	.274	.194	80%
.09	.289	.199	80%
.10	.304	.204	80%

At the final analysis, 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 0.0125. 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	.171	.091	95%
.09	.184	.094	95%
.10	.198	.098	95%

Secondary Endpoint - Global Cure - (Final Analysis)

At the final analysis, 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
Protocol/Amendment No.: 001-03

Page 40

Secondary Endpoint - CDI Recurrence in Subset of patients with Clinical Cure - (Final Analysis)

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%

2.7.4 Interim Analyses

One interim analysis will be performed in this study. Results will be reviewed by an eDMC. The endpoint, timing, and purpose of the interim analysis are summarized in Table 2-5 below. The decision rule and other statistical details are further described in Section 3.5.9.

Table 2-5

Summary of Interim Analysis Strategy

Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
CDI Recurrence	After approximately 640 patients (40% of planned total number of randomized patients) have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12).	Futility Analysis Adapt study design by dropping individual monoclonal antibody groups (MK-3415 and/or MK-6072)

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

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 vancomycin and metronidazole. 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*

Product: MK-3415A

Page 43

Protocol/Amendment No.: 001-03

infection 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

The 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, the results from the recent Phase I study (Protocol 005) suggest that the pharmacokinetics of MK-3415 and MK-6072 administered in a 250-mL 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-3415 and/or MK-6072 is planned for this study.

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 Adaptive Study Design

Results from the Phase II study of MK-3415A support its efficacy as a combination of monoclonal antibodies for toxin A and toxin B. However, the clinical efficacy data for each individual component of MK-3415A (i.e., MK-3415 and MK-6072) is limited. The current study will be performed using an adaptive design. This approach represents an efficient method to evaluate the contribution of individual monoclonal antibody components (MK-3415 [10 mg/kg of monoclonal antibody to *C. difficile* toxin A] and MK-6072 [10 mg/kg of monoclonal antibody to *C. difficile* toxin B] relative to the combined product, MK-3415A (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]) by using the results of an interim analysis (conducted when approximately 40% of the

targeted patient population have been enrolled and have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12). This approach allows for 1 or both of the individual monoclonal antibody treatment groups (MK-3415 and/or MK-6072) to be dropped at the interim analysis if the results are not comparable to those seen in the combination monoclonal antibody group (MK-3415A), thereby allowing for effective use of resources for the portion of the study conducted following the interim analysis. In recognition of the unmet medical need for new therapies to address the growing *C. difficile* epidemic, the adaptive design should provide the most efficient way to determine the optimal therapeutic approach. Importantly, an independent external Data Monitoring Committee (eDMC) will review the results of the interim analysis. The eDMC will use the guidelines proposed in Table 3-5 (Statistical Evaluation Plan and Multiplicity Strategy) and in Section 3.5.9 to make recommendations about modifications to the study design.

The interim analysis uses a one-sided p-value of 0.0001 to provide evidence that the individual monoclonal antibody therapy groups (MK-3415 and/or MK-6072) could be dropped relative to the combination group (MK-3415A). With this approach, the potential of dropping individual monoclonal antibody treatment groups inappropriately in the face of no true differences relative to combination monoclonal antibody (MK-3415A) treatment group remains very low. Available preclinical data from multiple sources have demonstrated that a combination monoclonal antibody product (MK-3415A) was associated with better responses in CDI as compared to the individual monoclonal antibody treatment groups (MK-3415 or MK-6072). Additionally, as previously summarized in Section 3.1.1, available clinical data from the prior Phase II study have demonstrated that a combination monoclonal antibody product (MK-3415A) was associated with a statistically significant difference relative to placebo in the prevention of CDI recurrence [15]. Finally, available clinical data from an earlier Phase II study have demonstrated no numerical difference between individual monoclonal antibody therapy (MK-3415) as compared to placebo [37].

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 with assays performed on samples collected at study entry. Please refer to Appendix 6.6 for additional information.

3.1.6 Rationale for Optional Specimen Collection for Genetic and Other Biomedical Research

As part of this study, Merck Research Laboratories would like to conduct genetic and other biomedical research on specimens routinely and specifically collected during this clinical study. Genetic and other biomedical research on such fluids and specimens may

include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Conduct of genetic and other biomedical research that is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) may only be obtained from appropriately consented patients as an optional procedure (refer to “Consent and Collection of Specimens for Genetic and Other Biomedical Research” section). The objective of collecting specimens for future 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 patients receive the correct dose of the correct drug at the correct time.

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, or 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 the infusion or within a few hours following the infusion.

Patients enrolled in this study should be prescribed an SOC regimen for a minimum duration of 10 days and a maximum duration of 14 days. 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) unless the switch occurs prior to or at the time of randomization for one of the following reasons: the prescribed antibiotic was (1) given at a total daily dose below that mandated by the protocol (see Sections 3.2.1.1.1 to 3.2.1.1.3 for description of required dose amounts and regimens for the allowed SOC therapies); or (2) the patient continued to have symptoms of CDI while on a protocol allowed SOC regimen that was switched because it was deemed ineffective (e.g., switch from oral metronidazole to oral vancomycin). Additionally, treatment with SOC therapy longer than 14 days is not a protocol violation if this was not the intent at the time of randomization (e.g., treatment duration increase due to persistent diarrhea).

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/mm³. Emergence of an adverse experience due to the inability of a

patient to tolerate their current SOC therapy also warrants an SOC switch; this switch can be made at any time. 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 in the source documents and via the appropriate eCRF for instances when administered in the 28 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 in the source documents and on the appropriate eCRF. Duration of all SOC therapy regimens will be calculated based on the dates provided.

NOTE: The defined agents, dosages, and treatment durations for SOC medications are mandatory 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.

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.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 48

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 and below. The following medications are excluded:

- Receipt of immune globulin within 6 months prior to receipt of the infusion or administration of immune globulin prior to the completion of the 12-Week study period.
- Receipt of MK-3415 and/or MK-6072 or other experimental monoclonal antibody against *C. difficile* toxin A or B, or receipt of *C. difficile* vaccine.
- Receipt of more than a 24-hour regimen of cholestyramine, cholestimide, 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.
- Receipt of medications which are given to decrease gastrointestinal peristalsis, such as loperamide (Imodium™) or diphenoxylate hydrochloride/atropine sulfate (Lomotil™), 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* or fecal transplantation therapy at any time following infusion (Day 1) and through the completion of the 12-Week study period.
- Use of any other treatments not currently specified in the protocol that have been shown to decrease CDI recurrence should not be given during the 12-week study period, unless they are given after the patient has met the primary endpoint of recurrence.
- Receipt of another investigational study agent within the previous 30 days or intended receipt of an investigational agent during the 12-Week study period.

The use of the above excluded therapies is allowed if given to treat a new episode of CDI that has an onset during the 12-week follow-up period.

All antibiotic therapies given 28 days prior to infusion and at any time during the 12-Week follow-up period are to be recorded on the appropriate eCRF. All anti-diarrheal medications and excluded medications/therapies (e.g., cholestyramine, cholestimide, *S. boulardii*, rifaximin, nitazoxanide, and fecal transplantation therapy (see Section

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 49

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 ± 3 days) following the infusion should also be recorded on the appropriate eCRF(s). All medication given within 14 days prior to onset of an SAE and used to treat an SAE are also to be recorded on the appropriate eCRF through Week 12 (85 ± 5 days).

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 or a partner of 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.

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), biomarkers (includes serum dehydroepiandrosterone [DHEA] level, cytomegalovirus [CMV] IgG titer, and mRNA profiling), and blood chemistry and hematology (as part of safety monitoring). 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 deep sequencing of gut flora in all patients per protocol. Providing consent allows these samples to be obtained from all patients.

3.2.3.1.2 Consent and Collection of Specimens for Genetic and Other Biomedical Research

During this study, a separate signed informed consent will be administered to cover the conduct of genetic and other biomedical research, including 1) optional blood specimen(s) and 2) specimens remaining after the main study is completed (e.g., blood, body fluids and/or tissue).

Review committees (IRBs/ERCs) and/or individual sites may choose not to participate, and in some cases local regulations may prevent conduct of genetic and other biomedical research on collected specimens. Under such circumstances, this information should be communicated to Merck Research Laboratories by the local study representative of the associated agencies and/or IRBs/ERCs, when initial submission takes place. Such declaration will not lead to protocol amendment. However, a Protocol Clarification Letter could be issued by the MRL clinical team.

Only those patients who have consented to allow the genetic and other biomedical research may have additional, optional blood specimen(s) drawn. The investigator or designate is responsible for explaining the optional nature of the conduct of genetic and other biomedical research and that participation in the associated clinical study is not dependent upon giving consent or additional samples for such research. The investigator or designate is also responsible for verifying the patient's written consent before obtaining any additional blood specimens for such research. Collection of the additional specimens may occur at any visit after the corresponding consent has been signed.

In some cases, the approval of this consent form and the associated protocol procedures (e.g., collection of blood specimens) may proceed independently from the associated main clinical study through review (by Agencies, IRBs/ERCs, Independent Ethical Committees, Privacy Committees, etc.). In such cases, the Clinical Study approval should not be delayed by the consent approval process for the optional specimen collection for genetic and other biomedical research. If the latter consent is denied, additional blood specimens for genetic and other biomedical research will not be

collected and main study specimens will not be used for that purpose. If the consent for optional specimen collection for genetic and other biomedical research is delayed, the additional blood specimens must not be collected and main study specimens will not be used for genetic and other biomedical research until approval is granted. In either event, specimen testing defined as part of the main study would not be affected by the consent process for genetic and other biomedical research.

For additional background information, see Attachments "Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research Collected from Clinical Trials Sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.: A Guideline for Clinicians and Privacy Board Members," and "Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff."

For stool samples remaining after the study is completed, additional testing for other bacteria/organisms (e.g., other organism types and counts) as well as toxigenic *C. difficile* testing may be performed. These stool samples may also be used to better characterize the microbiota in the stool at the time of the initial CDI episode or during the follow-up period. For blood samples remaining after the study is completed, additional testing for anti-toxin antibody levels may be performed. The same measures to maintain confidentiality and privacy will be applied to leftover samples as those applied when these samples are used in the main study.

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, generated by the site for identification purposes during the study. Baseline/screening numbers are 9-digits in length with a 4-digit site number followed by a 5-digit sequential number with leading zeros, if necessary. 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 number.

Patients can be rescreened multiple times for the study. Once determined that a patient will not participate in the study, the patient should be recorded as screen-failed in IVRS.

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 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 12 months, the patient's overall history of CDI, Horn's Index, and Charlson Index), review of prior and current medications, physical

Product: MK-3415A

Page 52

Protocol/Amendment No.: 001-03

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 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.

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. In addition, patients with renal disease, including those that receiving chronic dialysis therapy, are not excluded from the protocol. 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 in the source documentation and 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.

The dates of all prior episodes of CDI which occurred in the past 12 months should be documented separately on the appropriate eCRF. If the patient had at least one prior event, but it has been longer than 12 months since the patient had an episode, the date of the most recent event should be recorded instead. Additionally, the following information will be recorded in the eCRF: overall number of episodes of CDI in the patient's lifetime; the patient's current and recent (previous 3 months) hospitalization status; patient's location at the time of onset of CDI and treatment location; presence of nasogastric tube in the past month; endoscopic evidence of pseudomembranous colitis (if endoscopy performed); whether the subject had signs and symptoms consistent with toxic megacolon, bowel perforation, or ileus; whether the subject had a colectomy or other surgical procedure to treat the presenting case of CDI; and whether the patient has an appendix.

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 Modified Horn's index is a measure of the physician's clinical judgment of the patient's overall condition. At the time of study entry, the investigator, or another physician involved in the patient's care, is to select the score associated with the best description of the patient's overall condition using their clinical judgment. See 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.

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 in the source documentation 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. Collections of vital signs, at other times during the study, are 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.

The same stool sample or a second **stool sample must also be collected** and sent to a central laboratory **for anaerobic culture and other ancillary microbiological assessments (including microbial identification, toxigenic strain typing, and antibacterial susceptibility testing). This is an absolute requirement for this study.** This sample should be optimally collected before infusion, if possible. However, in the event the patient no longer has diarrhea, this stool sample may be collected up to within 72 hours after infusion.

Product: MK-3415A

Page 54

Protocol/Amendment No.: 001-03

In all patients, the pre-infusion (Day 1) stool sample will also undergo deep sequencing of gut flora. 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. Visit 1 laboratory safety assessments are for baseline values only and results are not required for patient entry into the study. All blood samples will be tested by designated central laboratories.

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. Patients who do not produce urine (i.e., advanced renal disease receiving regular dialysis treatments), can be enrolled and a urine sample is not necessary. Urine samples will be tested by a designated central laboratory. 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 metronidazole [alone] vs. oral vancomycin [alone or concurrently with intravenous metronidazole] 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.

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). Stratification by these factors at study entry will continue following the interim analysis.

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 1:1:1:1 ratio into 1 of the 4 treatment groups as previously described.

Following the interim analysis (See Sections 3.3.3 and 3.5.9), randomization into the study may adjust to a 1:1:1 ratio into 1 of 3 treatment groups or a 1:1 ratio into 1 of 2 treatment groups if the results of the interim analysis conclude that 1 or 2 of the individual monoclonal antibody treatment groups (MK-3415 or MK-6072) can be dropped. However, if the results at the interim analysis indicate that no treatments groups are dropped, then a 1:1:1:1 randomization ratio will be maintained to the completion of the study. Enrollment will continue in the 4 treatment groups until the results of the interim analysis are available (see Section 2.4.1).

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

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 56

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 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 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-3415, MK-6072, MK-3415A) and placebo will be administered as a single 250-mL intravenous infusion in 0.9% sodium chloride through a sterile 5 micron or smaller 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, an individual monoclonal antibody [MK-3415 or MK-6072], or both monoclonal antibodies [MK-3415A]) is to be 250 mL. However, if the patient's underlying medical condition

Product: MK-3415A

Page 57

Protocol/Amendment No.: 001-03

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-3415 (toxin A antibody)	10 mg MK-3415/kg of actual patient weight	Single infusion of 250 mL
MK-6072 (toxin B antibody)	10 mg MK-6072/kg of actual patient weight	Single infusion of 250 mL
MK-3415A (toxin A antibody and toxin B antibody)	10 mg MK-3415/kg of actual patient weight and 10 mg MK-6072/kg of actual 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.		

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 or qualified designee will be responsible to prepare and account for the monoclonal antibodies (MK-3415, 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 actual 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-3415 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.

Product: MK-3415A

Page 58

Protocol/Amendment No.: 001-03

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-3415, 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.

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.

Since MK-3415 and MK-6072 contain only human protein sequences and no murine components, allergic reactions may be less likely to occur than those seen with murine, chimeric, or humanized monoclonal antibodies. Please refer to the IB for a full assessment of the available clinical data for this compound.

All patients should be evaluated for infusion-specific reactions for 24 hours following the start of the infusion. If the patient is an outpatient, the study staff is to contact the patient approximately 24-hours post infusion to inquire about post-infusion reactions. Patients are to be instructed to call the site staff if an adverse reaction occurs within the first 24 hours. 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

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 59

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.

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>
<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]</p>	

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

Product: MK-3415A

Page 60

Protocol/Amendment No.: 001-03

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 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 log 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, caregiver, nurse, family member or friend) is permitted to aid the patient in filling out the log. There are no protocol-specific criteria which will require a patient to be withdrawn prematurely from the study. All patients who receive the study infusion should remain in the study and continue to record daily loose stool counts until the Week 12 visit, unless it is not in the best interest of the patient to continue.

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 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. At the end of the study, the stool count log and other source documents containing information obtained from the patient should be maintained as source documents.

3.2.3.8.1.2 Phone/Visit Contact to Assess and Record Loose Stool Counts, SOC Compliance, 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. Compliance with SOC medication administration should also be discussed during the daily contacts. 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**. Study personnel do not need to contact the patient on weekends or holidays, unless the 24-hour infusion follow-up assessment for infusion-specific reactions occurs on one of these days. It is important that the study personnel record the information communicated by the patient during the phone call/contact in the source documents. This includes recording information for the day of the call as well as the information for each day since the previous contact.

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

3.2.3.8.2.1 Stool Samples

Stool samples should be collected for all new episodes of diarrhea at the time of an Unscheduled visit (See Section 3.2.3.8.3). 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.

3.2.3.8.2.2 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 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), Week 12 (Day 85 ± 5 days) and at an Unscheduled Visit, 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), Week 12 (Day 85 ± 5 days) and at an Unscheduled visit, as described in the Study Flow Chart (Section 1.7).

Additionally, blood samples will be tested for ADA (including neutralizing antibody) at 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, for patients consenting to samples for optional genetic testing, there will be blood drawn at Day 4 (± 1 day) or any subsequent visit for Genetic and Other Biomedical Research.

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, 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, even if there is another plausible diagnosis for the diarrhea. At the time there is a new episode of **diarrhea**, a stool sample should 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).**

Stool samples should not be collected by rectal swab throughout the 12-Week study period when there is a new episode of **diarrhea**. 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 also 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. Non-serious adverse experiences will be recorded if the unscheduled visit occurs up to Week 4 of the study. SAEs will be recorded through Week 12 of the study. See Section 3.4 for details on reporting adverse experiences. Results should be recorded on the appropriate eCRF

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-3415, 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

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 64

assignment or the preparation of the infusion. Due to slight differences in appearance between monoclonal antibodies (MK-3415, 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.

Additional information regarding maintenance of blinding for the interim analysis is found in Sections 3.3.3. and 3.5.9.

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.

Patients who optionally donate blood, body fluids and/or tissue for genetic and other biomedical research analyses may request that their specimen(s) be removed from storage and destroyed in accordance with the terms outlined in the associated consent form. Patients should be informed that withdrawal from the main study does not cause the

withdrawal and destruction of the optional specimens for genetic and other biomedical research. Requests for withdrawal and destruction of the optional specimens for genetic and other biomedical research should be made in writing to the investigator. In turn, the investigator must promptly inform MRL so that appropriate follow-up can be initiated. The investigator will be informed when the associated specimens are destroyed and should notify the patient that specimen destruction is complete.

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 \pm 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 recorded in the source document during the telephone/in-person contacts and 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 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.

Product: MK-3415A

Page 66

Protocol/Amendment No.: 001-03

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*.
- 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

Product: MK-3415A

Page 67

Protocol/Amendment No.: 001-03

Week 12 (Day 85 ± 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 ± 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 $\text{WBC} > 10,000 \text{ cells/mm}^3$ at baseline and $\leq 10,000 \text{ cells/mm}^3$ 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 of those with an elevated temperature ($\geq 101^\circ\text{F}$ [38.4°C]) at baseline and resolution of this elevated temperature ($< 101^\circ\text{F}$ [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 in the US and in other countries. 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. Results of the anaerobic stool culture will not be available to inform investigators regarding patient management/treatment decisions.

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. Results of the anaerobic stool culture will not be available to inform investigators regarding patient management/treatment decisions.

Product: MK-3415A

Page 68

Protocol/Amendment No.: 001-03

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 ribosomal 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.

Following REA and/or PCR Ribotyping analysis, gene amplification for binary toxin may be performed for selective isolates. As the science continues to evolve in this field, additional typing methods may be considered if necessary to differentiate relapse vs. reinfection.

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 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.

3.3.2.4 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
Protocol/Amendment No.: 001-03

Page 69

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

3.3.2.5 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 methods. 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).

3.3.2.6 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.

3.3.3 External Data Monitoring Committee (eDMC)

An independent, unblinded eDMC will be appointed and responsible for the review of the interim efficacy data for this study. The eDMC will also review the accumulated safety data from the study, in conjunction with the scheduled interim efficacy review. The responsibilities of the eDMC are described in the subsections that follow. Refer to Sections 3.5.1 and 3.5.9 for further details pertaining to the interim analysis.

The roles and responsibilities of the eDMC and logistical details will be summarized in an eDMC Charter.

3.3.3.1 eDMC Membership

The eDMC will be comprised of 3-7 independent (i.e., non-SPONSOR) experts in operational, medical, and biostatistical aspects of clinical trials, specifically including senior national (and possibly international) healthcare leaders, clinicians, and/or statisticians. One member of the eDMC will serve as Chairperson. No member of the eDMC may participate as a primary investigator, a member of the Scientific Advisory Committee (SAC), or be involved in any other way with the conduct of the study. Only the independent external Unblinded Statistician and the eDMC will be aware of the treatment-level results of the interim analysis. The independent external Unblinded Statistician must adhere to the same confidentiality requirements as the eDMC members.

3.3.3.2 Summary of eDMC Responsibilities

Efficacy Data Review

A primary responsibility of the eDMC is to evaluate the efficacy data from this study *at the interim review only*. The purpose of the interim analysis is to evaluate whether the individual monoclonal antibody groups (MK-3415 and MK-6072) meet success criteria related to Primary Objective #1 of the study (relative to the combined monoclonal antibodies, MK-3415A). The interim analysis is planned to be performed when approximately 640 enrolled patients (40% of the targeted patient population) have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12). The accumulated data will be summarized and analyzed according to the analysis plan for Primary Objective #1 of the study, as described in Section 3.5.9. An independent external Unblinded Statistician will be responsible for preparing the unblinded interim summary of efficacy data for this study. The independent, external Unblinded Statistician will present a report of the treatment-level unblinded results to the eDMC.

Enrollment will continue into the 4 treatment groups until the interim analysis decision is communicated. Following the eDMC review of the data and recommendation, enrollment may continue in 4 treatment groups or be adjusted to randomize patients equally into 2 or 3 treatment groups. The eDMC may reserve the authority to request summaries of any other efficacy data that the committee determines to be of interest. The need for additional reports at the interim analysis will be assessed by the eDMC.

The eDMC will formally meet at least once to review the data as prepared by the independent, external Unblinded Statistician. Following their meeting, the eDMC Chairperson will be responsible for reporting post-meeting decisions and/or recommendations (e.g., discontinuation of specific treatment group(s)) to a steering committee comprised of Merck Senior Management members (Merck Senior Management Committee, or MSMC). The MSMC may discontinue the study in the event of efficacy concerns reported by the eDMC. The treatment-level results will not be provided to the MSMC unless there is concern that the study should be stopped.

Safety Data Review

Another primary responsibility of the eDMC is to evaluate the safety data from this study at the interim analysis (coinciding with the efficacy interim analysis). Specifically, at the time of the interim analysis, the independent, external Unblinded Statistician will provide the eDMC with the following:

- **Serious Adverse Experiences:** A listing of serious adverse experiences that have occurred during the study, including allocation number, adverse experience term, and date (relative to infusion) will be provided. These will also be grouped based on treatment group, and categorized by whether they were drug-related or led to death or study discontinuation.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 71

- **Most Common Adverse Experiences:** Counts of the most common (≥ 4 of patients in any treatment group) adverse experiences will be provided by treatment group, sorted by adverse experience term. These will also be grouped based on drug relationship and seriousness.
- **Infusion-specific Reactions:** Counts of all infusion-specific reactions, as defined in Section 2.6, will also be provided. All infusion-specific reactions will be presented by treatment group, sorted by term. These will also be grouped based on drug relationship and seriousness.

The eDMC may reserve the authority to request summaries of any other safety data that the committee determines to be of interest. The need for additional reports at the interim analysis will be assessed by the eDMC. In the event that at the interim review a significant safety signal is identified in a treatment group, the eDMC may recommend that the treatment group be discontinued.

3.3.3.3 eDMC Meeting at the Interim Analysis

Prior to the interim review, the eDMC will be oriented to the protocol and the details of data collection and analysis in order to plan for this interim review. This introduction to the study will be an open session involving blinded members of the SPONSOR protocol team.

A formal face-to-face or teleconference meeting of the eDMC will be scheduled for the predefined interim analysis. This meeting will incorporate a closed session for eDMC members and the independent, external Unblinded Statistician to strictly maintain the blinding of data. The eDMC and the independent, external Unblinded Statistician will keep all interim study results (both efficacy and safety) strictly confidential.

All eDMC members should be present for the interim review. The independent, external Unblinded Statistician will provide the report of efficacy and safety results at the interim and the eDMC will make a recommendation to the MSMC. This may include a recommendation to discontinue an individual monoclonal antibody treatment group (MK-3415 and/or MK-6072) in relation to Primary Objective #1 (per Section 3.5.9). Additionally, if a significant safety signal is observed in a treatment group, the eDMC may recommend discontinuation of the treatment group.

After the interim analysis meeting, it is the role of the eDMC to notify the MSMC in writing regarding its recommendations. The actual results for the various treatment groups will not be provided to the MSMC, the investigator, study site staff, or blinded SPONSOR personnel. In the event that the eDMC recommends that further enrollment in one or both of the individual monoclonal antibody therapy groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the group(s) to be stopped. It will be the responsibility of the MSMC to implement the recommendations of the eDMC and to ensure the investigators and the respective Institutional Review Boards (IRBs)/Independent Ethical Committees (IECs) are properly notified. The MSMC will inform the protocol team of modifications to the

protocol. The investigator, study site staff, and blinded SPONSOR personnel will remain strictly blinded to specific patient treatment group assignments until the study has ended.

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-3415, 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 minutes 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. If the patient is an outpatient, the study staff is to contact the patient approximately 24-hours post infusion to inquire about post-infusion reactions. Patients are to be instructed to call the site staff if an adverse reaction occurs. Post-infusion reactions 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.

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

Product: MK-3415A

Page 73

Protocol/Amendment No.: 001-03

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 (\pm 1 day), Day 11 (\pm 2 days), and Week 4 (Day 29 \pm 3 days). Appendix 6.5 provides a complete list of laboratory safety tests at these defined visits.

Blood will be also 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** during the 12-week main study (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.

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 highest dose studied in man to date (i.e., >20 mg/kg of monoclonal antibody against toxin A [MK-3415] and/or >20 mg/kg of monoclonal antibody against toxin B [MK-6072]).

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 74

No specific information is available on the treatment/management of overdose of MK-3415, 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 Sharp & Dohme Corp., a subsidiary of 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 pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 14 days of completing the 12-week (85 ± 5 days) follow-up period. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

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 the 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.

Product: MK-3415A

Page 75

Protocol/Amendment No.: 001-03

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 post baseline laboratory test values that meet the following criteria:

- 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 in a patient with baseline values that did not meet these criteria, or if baseline values were elevated, there is a clinically significant worsening.*

*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.: 001-03

Page 76

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	
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?	
Relationship to test drug	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

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15-May-2013

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 77

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

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15-May-2013

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

Planned interim analyses are described in Section 3.5.9. Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Patient-level unblinding will be restricted to an independent external statistician who will be preparing the interim analysis and who will have no other responsibilities associated with the study. Treatment-level results of the interim analysis will be provided by the independent external statistician to the eDMC.

The eDMC will serve as the primary reviewer of the results of the interim analysis and will make recommendations for modification to an executive committee (MSMC) of the SPONSOR. The treatment-level results will not be provided to the MSMC unless there is concern that the study should be stopped. In the event that the eDMC recommends that

further enrollment in one or both of the individual monoclonal antibody therapies treatment groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the treatment groups(s) to be stopped. No additional information (e.g., summary statistics or p-values) will be shared with the SPONSOR. Additional logistical details will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 3.5.9.

Prior to final study unblinding, the independent, external statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses.

3.5.2 Hypotheses

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

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).

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 80

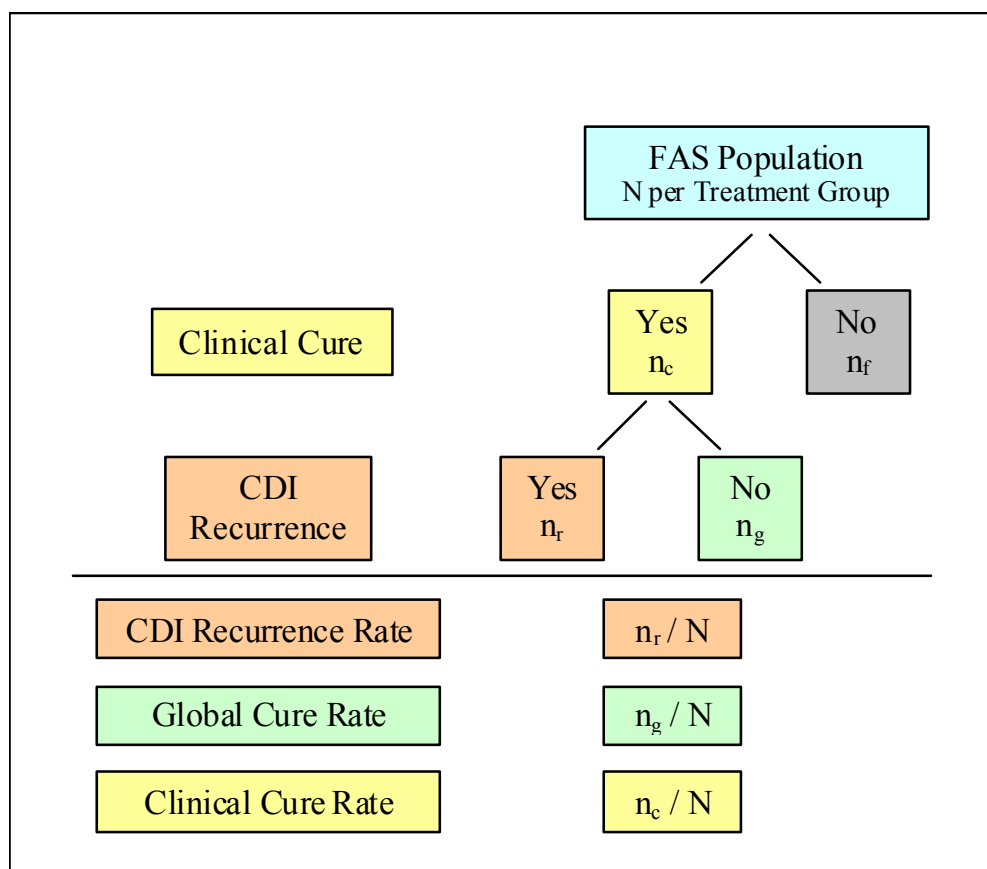
Global Cure: Defined as clinical cure of the initial CDI episode AND no CDI recurrence through Week 12. The proportion of patients with global cure will be assessed as a secondary efficacy endpoint.

Clinical Cure: Defined as patient received ≤ 14 day regimen 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 a >14 day **regimen** 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 their SOC window 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.

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.

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)
- Failure to receive protocol defined SOC therapy within a 1 day window of the infusion.

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 substantially 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. 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. Details regarding the decision to stop enrollment in MK-3415 and/or MK-6072 treatment groups at the interim analysis, and the multiplicity adjustments that will be applied to control the overall rate of declaring any of the active treatment groups superior to placebo under the null hypothesis at 1.25%, are provided in Section 3.5.6.

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.

A sensitivity analysis that treats those subjects with missing CDI recurrence information as failures (i.e., having CDI recurrence) and a sensitivity analysis that treats subjects with no post-randomization endpoint data subsequent to infusion of study medication as having CDI recurrence will be provided.

Finally, the impact of study medication on the course and resolution of CDI recurrent episodes will be explored by comparing factors such as, but not limited to, need for rehospitalization, whether or not the recurrence lead to death, need for additional antibiotic treatment for the episode, and time to resolution of diarrhea from the start of the recurrent episode.

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.

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 day regimen 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. For the purposes of the clinical cure endpoint, a 14-day regimen of SOC therapy is defined as treatment spanning no more than 16 calendar days. 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.

Additional sensitivity analyses will be conducted with alternative definitions of clinical cure which relax the maximum number of days SOC therapy the patient is able to receive and still be considered a clinical cure (and as such expand the number of patients who would be in the "risk set" for recurrence). One such planned sensitivity analysis will define the numerator for clinical cure as the number of patients from the FAS population who have received SOC therapy for ≤ 28 calendar days (vs. 14-day regimen in the primary definition) and have no diarrhea for two consecutive days following completion of SOC therapy. Other sensitivity analyses will investigate the effect of relaxing the duration of SOC therapy to 42 calendar days or removing the restriction on the duration of SOC therapy entirely for the purposes of defining clinical cure. The effect of these changes to the clinical cure definition on the CDI recurrence and global cure endpoints will also be explored.

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 their SOC window (≤ 16 calendar days as defined above for Clinical Cure) 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.

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) comparisons between active monoclonal antibody therapies (MK-3415, 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 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

Product: MK-3415A

Page 87

Protocol/Amendment No.: 001-03

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 SOC [‡] (incidence ≥ 4 of patients in one of the treatment groups)		X	X
Tier 3	Specific adverse experiences or SOC [‡] (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.				

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. These analyses are not expected to be necessary for marketing authorization and therefore will not be reported in the Clinical Study Report describing the analyses for the primary, secondary, and exploratory objectives outlined in Section 2.1.

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. 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 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 multiple treatment comparisons at two analysis times (one interim analysis and a final analysis). Treatment comparisons have been grouped into two families. In Family 2, individual monoclonal antibody therapies (MK-3415 and MK-6072) will be compared separately to the combined monoclonal antibody therapy (MK-3415A). In Family 1, the various active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared separately to placebo. The multiplicity strategy has been designed to provide strong control of the studywise Type 1 error at 0.025 (1-sided) for the primary endpoint of CDI recurrence. Several types of multiplicity adjustment are required to control the Type I error rate. The initial adjustment employs an alpha allocation scheme to divide the studywise Type 1 error of 0.025 (1-sided) evenly between the two families described above: 0.0125 (1-sided) per family.

Under the global null hypothesis that the four therapies (three active treatments and placebo) are equal, the overall probability of making a false claim of superiority for any of the experimental treatments (Family 1) is controlled at level 0.0125, one-sided. Under the global null hypothesis that the three active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) are equal and are all superior to placebo, the overall probability of making a false claim of superiority for the combined monoclonal antibody therapy over either of the individual monoclonal antibody therapies (Family 2) is also controlled at level 0.0125, one-sided.

Further multiplicity adjustments within each of the families are described below and the entire evaluation plan and multiplicity strategy is presented in Table 3-5, Figure 3-2, and Figure 3-3. Simulation results presented in Section 3.5.7 provide further information regarding the overall probability of making a Type I error.

Combined Monoclonal Antibody Therapy (MK-3415A) vs. Individual Monoclonal Antibody Therapies (MK-3415 or MK-6072) - Family 2 Comparisons

Family 2 treatment comparisons (MK-3415A vs. MK-3415; MK-3415A vs. MK-6072) will be performed at the interim analysis (Stage 2) and, conditionally, at the final analysis (Stage 3). Overall Type 1 error is controlled at 0.0125 (1-sided) for Family 2.

The first adjustment employs Dunnett's method for comparing multiple treatments to a single control to divide the overall alpha of 0.0125 across the two treatment comparisons such that Type 1 error is controlled at 0.0067 (1-sided) per comparison. The second adjustment further divides the Type I error for the group sequential design using a Haybittle-Peto boundary. The p-value cutoff at the interim analysis will be 0.0001 (1-sided) and the p-value cutoff at the final analysis will be 0.0066 (1-sided). A significant finding for either of these two comparisons at either analysis time will result in that individual monoclonal antibody treatment group (MK-3415 and/or MK-6072) being dropped from further evaluation. Further enrollment in one or both of these groups will be stopped if a significant finding for either of these two comparisons occurs at the interim analysis.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 90

Active Monoclonal Antibody Therapy (MK-3415, MK-6072, MK-3415A) vs. Placebo - Family 1 Comparisons

Family 1 treatment comparisons (MK-3415A vs. placebo; MK-3415 vs. placebo; MK-6072 vs. placebo) will be performed at the interim analysis (Stage 1) and at the final analysis (Stage 4). Overall Type 1 error is controlled at 0.0125 (1-sided) for Family 1.

At Stage 1 of the interim analysis, a test of futility will be performed to assess the likelihood of declaring MK-3415A to be superior to placebo for the primary endpoint of CDI recurrence. The non-binding stopping boundary for the futility analysis will be based on the Hwang-Shih-DeCani (or gamma) spending function with $\gamma = -1.529$. Assuming the futility analysis is performed with 40% of the planned total sample size, the criteria for stopping the study for futility would be met if the CDI recurrence rate for the MK-3415A group exceeds that of the placebo group (1-sided p-value greater than 0.5). Futility analyses are generally associated with a loss in overall study power, however; as this is a conservative futility bound (very little Type 2 error spent at the interim), the impact on final study power is insignificant. The study will not be stopped early for efficacy for MK-3415A over placebo. As a result, the futility analysis will not inflate the overall Type I error for the study.

At Stage 4 of the final analysis, all remaining monoclonal antibody therapy groups (i.e., those that have not been dropped from further evaluation based on the criteria described above) will be compared to placebo. The combination of a sequentially rejective testing approach and Dunnett's methodology will be employed to control the overall probability of making a false claim of superiority for any of the experimental treatment groups at 0.0125 (1-sided).

The first test in the sequence will be the evaluation of MK-3415A versus placebo with a p-value cut-off of 0.0125 (1-sided). If this is significant, then the remaining monoclonal antibody therapy groups (MK-3415 and/or MK-6072) will be compared to placebo simultaneously. The p-value cut-off will be 0.0125 (1-sided) if only one group remains and 0.0067 (1-sided) if two groups remain. Based on Dunnett's method, a p-value cutoff of 0.0067 for these comparisons will control the overall probability of a Type I error at level 0.0125. A p-value that is >0.0125 for the MK-3415A versus placebo comparison will not be considered statistically significant and will halt further testing in the sequence.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 91

Table 3-5

Statistical Evaluation Plan and Multiplicity Strategy

Analysis	Stage	Comparison(s)	Multiplicity Strategy	p-Value cut-off for individual comparisons (1-sided)	Purpose
Interim [†]	1	MK-3415A vs. PBO	No alpha spend	>0.5	Futility Analysis (non-binding) Will not stop for efficacy success No impact on Type I error
	2	MK-3415A vs. MK-6072	Dunnnett's & Haybittle-Peto [‡]	≤ 0.0001	Decision to stop enrollment in MK-3415 and/or MK-6072 arms
Final	3	MK-3415A vs. MK-3415		≤ 0.0066	Decision to stop further testing of MK-3415 and/or MK-6072 arms in Stage 4
	4	MK-3415A vs. PBO MK-6072 vs. PBO [§] MK-3415 vs. PBO [§]	Fixed Sequence & Dunnnett's ^{‡‡}	≤ 0.0125 (≤ 0.0067)	Evaluate effectiveness of remaining MAb arms

MK-3415A is the combined administration of monoclonal antibodies (MAbs) to Toxins A and B.
MK-3415 is MAb to Toxin A only; MK-6072 is MAb to Toxin B only; PBO is placebo.
[†] Interim analysis is planned when 40% of planned patient enrollment have completed the 12-Week post-infusion study period.
[‡] Stages 2 and 3 of the analysis involve comparisons of individual monoclonal antibody therapies to the combined monoclonal antibody therapy (Family 2). Overall Type 1 error is controlled at 0.0125 (1-sided) for Family 2. The first adjustment employs Dunnnett's method to divide the overall alpha of 0.0125 across the two treatment comparisons (Type 1 error controlled at 0.0067 per comparison). The second adjustment further divides the Type I error for the group sequential design using a Haybittle-Peto boundary.
^{‡‡} Stage 4 of the analysis involves comparisons of monoclonal antibody therapies to placebo (Family 1). Overall Type 1 error is controlled at 0.0125 (1-sided) for Family 1 using a combination of a sequentially rejective procedure and Dunnnett's method. The first test in the sequence will be the evaluation of MK-3415A vs. placebo with a p-value cut-off of 0.0125 (1-sided). If significant, then MK-3415 and/or MK-6072 will be compared to placebo simultaneously. The p-value cut-off will be 0.0125 (1-sided) if only one treatment group remains and 0.0067 (1-sided) if two treatment groups remain (Dunnnett's method to control overall probability of a Type I error at level 0.0125).
[§] If remaining after testing in Stage 2 and Stage 3.

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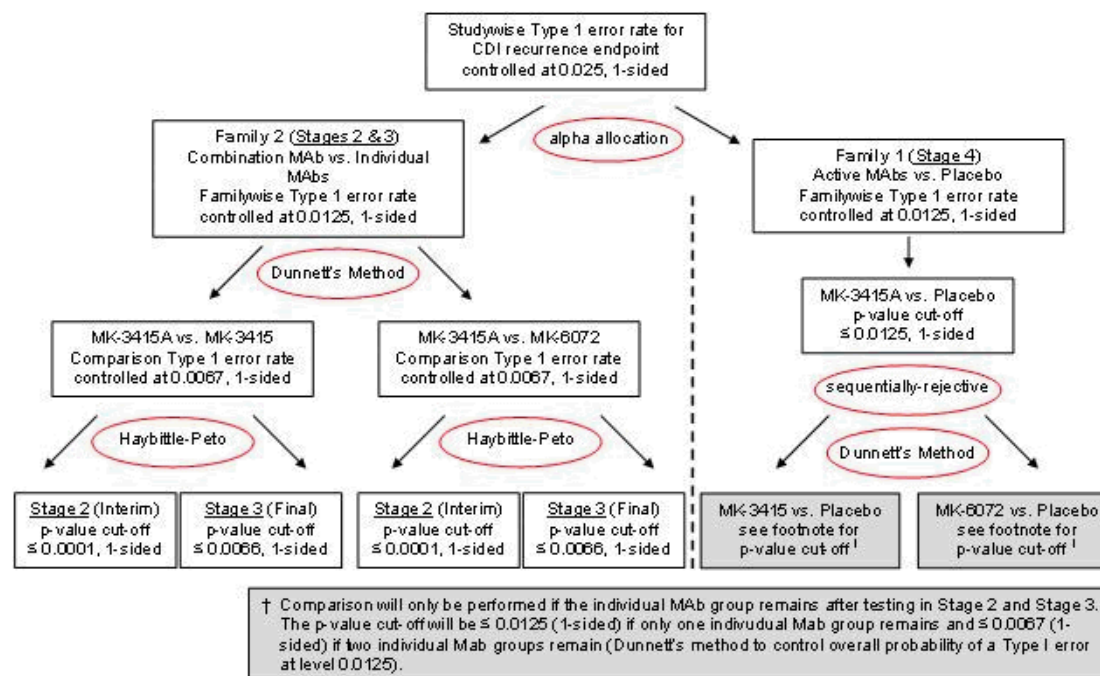
15-May-2013

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 92

Figure 3-2

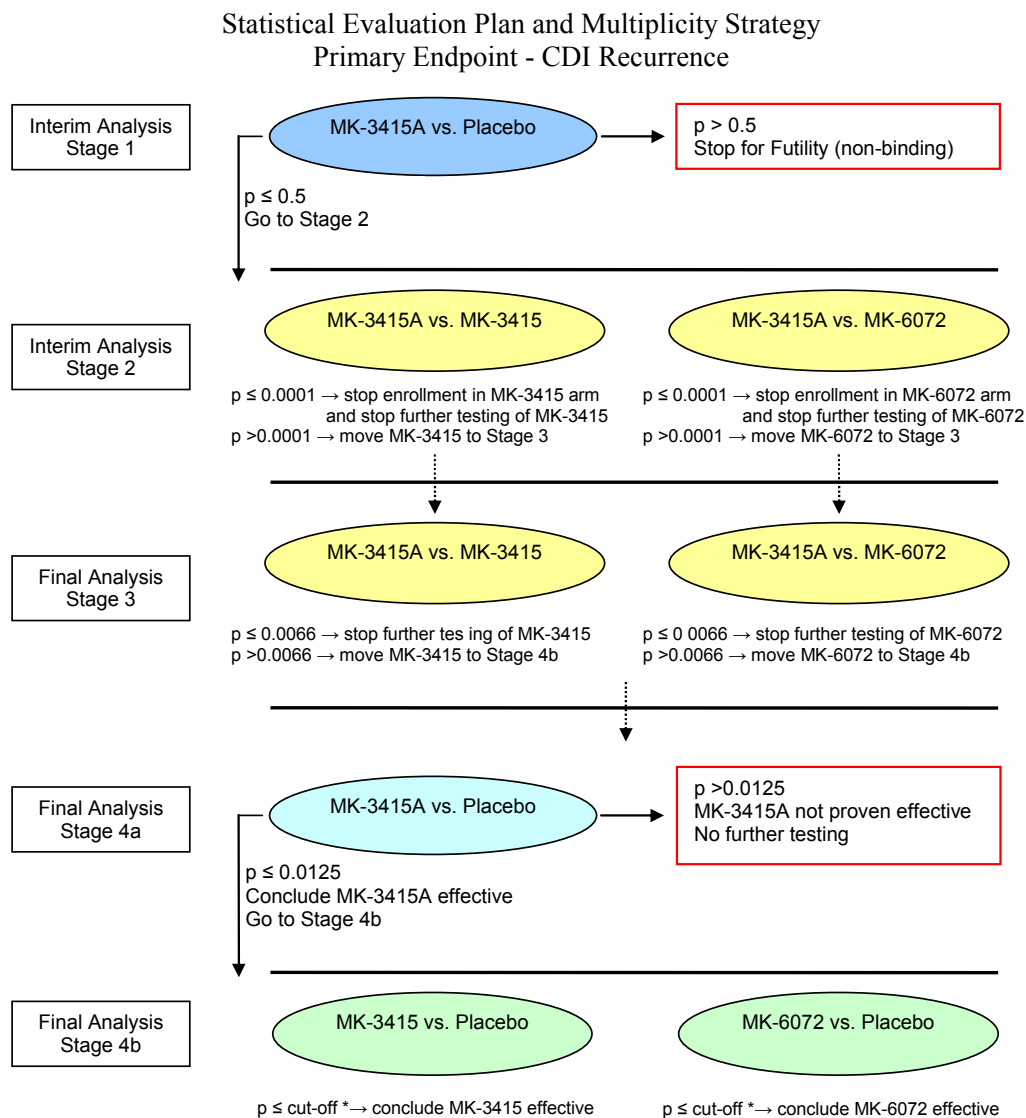
Multiplicity Adjustments to Control Studywise Type 1 Error



Confidential

15-May-2013

Figure 3-3



Notes:

- 1) All p-values cut-offs are 1-sided.
- 2) Stage 4b comparisons to be performed only if a specific individual MAb group remains after testing in Stages 2 and 3. The p-value cut-off will be ≤ 0.0125 if only one individual MAb group remains (MK-6072 or MK-3415) and ≤ 0.0067 if two individual MAb groups remain (MK-6072 and MK-3415).

3.5.7 Sample Size and Power Calculations

This study has a planned sample size of 1600 patients to be randomized in a 1:1:1:1 ratio to each of the four treatment groups (MK-3415A, MK-3415, MK-6072, 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 (26.0% 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 (Interim and Final Analyses)

An interim analysis is planned when approximately 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12). The purpose of this interim analysis is to evaluate if treatment with combined monoclonal antibody therapy (MK-3415A) is superior to treatment with either of the individual monoclonal antibody therapies (MK-3415 or MK-6072). If MK-3415A is found to be superior to MK-3415 or MK-6072, then further enrollment in one or both of these respective groups will be stopped. These two comparisons will be performed at a 1-sided alpha level of 0.0001, as described in Section 3.5.6.

At the interim analysis, it is anticipated that 160 patients per group will be in the analysis population for the CDI recurrence endpoint. This will provide approximately 80% power to detect the following differences in the incidence of CDI recurrence between combined monoclonal antibody therapy (MK-3415A), π_1 , and the individual monoclonal antibody therapies (MK-3415 or MK-6072), π_2 :

π_1	π_2	Difference	Power
.08	.274	.194	80%
.09	.289	.199	80%
.10	.304	.204	80%

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 95

At the final analysis, 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 0.0125. 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	.171	.091	95%
.09	.184	.094	95%
.10	.198	.098	95%

Secondary Endpoint - Global Cure - (Final Analysis)

At the final analysis 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).

Secondary Endpoint - CDI Recurrence in Subset of Patients with Clinical Cure - (Final Analysis)

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%

Simulation Results - CDI Recurrence - Interim and Final Analyses

Table 3-6 provides the results of a simulation study examining the operating characteristics of the tests for CDI recurrence within the design. A 100,000 replication simulation was performed to estimate Type 1 error under the two null hypotheses and to estimate power for eight different alternative hypotheses.

Product: MK-3415A

Page 96

Protocol/Amendment No.: 001-03

For the primary endpoint of CDI recurrence, individual monoclonal antibody therapies (MK-3415 and MK-6072) will be separately compared to combined monoclonal antibody therapy (MK-3415A) (Family 2 comparisons) **and** active monoclonal antibody therapies (MK-3415, MK-6072, and MK-3415A) will be compared to placebo (Family 1 comparisons).

Under the global null hypothesis (Null #1) that the four therapies (three active and placebo) are equal, a multiplicity strategy is designed to control at 1.25% the probability of falsely concluding that one or more of the active monoclonal antibody therapies is effective.

Under the global null hypothesis (Null #2) that the three active monoclonal antibody therapies are equal and are all superior to placebo, a multiplicity strategy is designed to control at 1.25% the probability of falsely concluding that combined monoclonal antibody therapy is superior to one or both of the individual monoclonal antibody therapies. Under this null hypothesis, the conclusion that one or more of the active monoclonal antibody therapies is effective is not a Type I error.

The simulation results show that Type 1 error for each family of treatment comparisons is controlled as 1.25% under both null hypotheses. The simulation also indicates that the design provides sufficient power to select an effective treatment regimen. Under a variety of alternative scenarios, the overall probability of demonstrating effectiveness with at least one experimental arm exceeds 99%. The probability of dropping an individual monoclonal antibody arm (MK-3415 or MK-6072) ranges from about 2% when the difference is 6 percentage points versus the combined monoclonal antibody (MK-3415A) to about 36% when the difference is 13 percentage points versus the combined monoclonal antibody (MK-3415A).

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 97

Table 3-6

Simulation Study (100,000 Replications) of Operating Characteristics for CDI Recurrence Endpoint

	CDI Recurrence Rates				Superiority to PBO for at least one MAb	Drop MK-3415 at interim	Drop MK-6072 at interim	Drop both MK-3415 & MK-6072 at interim	Drop either MK-3415 or MK-6072 at either analysis
	Placebo	MK-3415	MK-6072	MK-3415A					
Null 1	21%	21%	21%	21%	1.25% [†]	0.01%	0.02%	<0.01%	1.28%
Null 2	21%	8%	8%	8%	>99%	0.01%	0.01%	<0.01%	1.22% [†]
Alternative 1	21%	18%	8%	8%	>99%	14.0%	0.01%	0.01%	97.1%
Alternative 2	21%	18%	14%	8%	>99%	14.0%	1.86%	1.09%	97.6%
Alternative 3	21%	18%	18%	8%	>99%	14.0%	14.1%	5.4%	>99%
Alternative 4	21%	14%	14%	8%	>99%	1.85%	1.86%	0.32%	77.3%
Alternative 5	21%	21%	8%	8%	>99%	35.6%	0.01%	0.01%	>99%
Alternative 6	21%	21%	14%	8%	>99%	35.6%	1.86%	1.55%	>99%
Alternative 7	21%	21%	18%	8%	>99%	35.6%	14.1%	9.7%	>99%
Alternative 8	21%	21%	21%	8%	>99%	35.6%	35.4%	19.8%	>99%

[†] Type 1 error estimated (≤ 0.0125) using simulation with 100,000 replicates.

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15-May-2013

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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 (stratification variable)
- SOC therapy (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 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

The eDMC will carefully monitor the formal safety and efficacy interim results of this trial. A description of the structure, function, and guidelines for decision-making by the eDMC will also be outlined in the eDMC charter.

3.5.9.1 Efficacy Interim Analyses

There is one planned interim efficacy analysis that will be performed during the course of the blinded portion of this study. The purposes of the interim analysis are: 1) to perform a futility analysis to assess the likelihood of declaring MK-3415A to be superior to placebo and 2) 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 will be stopped.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 99

The interim analysis will be conducted by an independent, external unblinded statistician who will have no other responsibilities with respect to this study. The independent, external unblinded statistician will review the results from this interim analysis with the eDMC. The eDMC will use the guidelines proposed in Table 3-5 (Statistical Evaluation Plan and Multiplicity Strategy) to make recommendations about modifications to the study design.

In the event that the eDMC recommends that further enrollment in one or both of the individual monoclonal antibody therapy groups (MK-3415 or MK-6072) be stopped, the eDMC will communicate to the SPONSOR ONLY the identity of the group(s) to be stopped. No additional information (e.g., treatment group summary statistics or p-values) will be shared with the SPONSOR.

The interim efficacy analysis is planned when approximately 640 enrolled patients (40% of planned total) have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12). The patient population for this interim analysis will be those patients who have concluded follow-up (i.e., completed the 12-Week study period or discontinued prior to Week 12) at the time of the interim analysis database lock. Study enrollment will be ongoing at the time of this interim analysis. It is recognized that additional patients will have been randomized and will be ongoing in the study at the time of database lock for the interim analysis. These patients will not be included in the formal interim analysis (i.e., p-value calculations) and their data will have no bearing on the decision criteria for the interim analysis. However, the eDMC will be provided with listings of important demographic, efficacy, and safety data for these ongoing patients. Data collected from these patients will also be included in a summary listing in the final CSR, but a separate analysis combining these patients together with the patients included in the interim analysis is not planned.

3.5.9.2 Safety Interim Analyses

The eDMC will also review the safety data of the trial at the formal interim analysis. At this time, safety data will be summarized by blinded treatment groups and will be provided by the independent, external statistician. If, during their review at the time of the interim analysis, the eDMC observes a potential safety signal, the eDMC may request additional reviews of the safety data. Further, if through blinded medical monitoring, the SPONSOR observes a potential safety signal, the SPONSOR may also request the eDMC to review unblinded safety data outside of the planned interim analysis.

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 1600 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
Protocol/Amendment No.: 001-03

Page 100

3.6.2 Product Descriptions

Investigational clinical materials will be provided by the SPONSOR as summarized in Table 3-7.

Table 3-7

Product Descriptions

Product Name & Potency	Dosage Form	Comments
MK-3415 toxin A antibody (25 mg/mL)	Injectable Solution - Vial	MK-3415 combined with MK-6072 is MK-3415A
MK-6072 toxin B antibody (25 mg/mL)	Injectable Solution - Vial	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-3415, MK-6072, and MK-3415A infusions.

Other clinical supplies (oral metronidazole; oral vancomycin; intravenous metronidazole, 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 3-8 below.

Table 3-8

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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3.6.4 Secondary Packaging and Labeling Information (kit)

There will be no secondary packaging.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 101

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.

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) 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. U.S. 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 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.

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 Page 104
Protocol/Amendment No.: 001-03

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, 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

Page 105

Protocol/Amendment No.: 001-03

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 Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of 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.

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

Page 107

Protocol/Amendment No.: 001-03

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.

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Product: MK-3415A

Page 109

Protocol/Amendment No.: 001-03

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Product: MK-3415A

Page 112

Protocol/Amendment No.: 001-03

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Product: MK-3415A

Page 114

Protocol/Amendment No.: 001-03

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Product: MK-3415A

Page 115

Protocol/Amendment No.: 001-03

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
DRG Diagnostics	<i>Clostridium difficile</i> Toxin A+B	EIA	100
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
R-Biopharm	RIDASCREEN <i>Clostridium difficile</i> Toxin A/B	EIA	96.8
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.			

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

6.3 MODIFIED HORN'S INDEX

Modified Horn's Index^{1,2}

The Modified Horn's Index^{3,4} is a measure of a physician's clinical judgment of the patient's overall condition. At the time of study entry, the investigator, or another physician involved in the patient's care, is to select the score associated with the best description of the patient's overall condition using their clinical judgment as follows:

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.

³ 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

⁴ 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.

6.4 CHARLSON INDEX

The Charlson Index is a comorbidity index. In general, only conditions that are present at the time of enrollment into the study should have an answer of “yes”. There are a few exceptions: (1) for myocardial infarction, answer “yes” if the patient had a definite or probable myocardial infarction diagnosis at any time in the past; (2) ulcer disease includes patients who have required treatment for gastrointestinal ulcer disease at any time in the past; (3) any tumor refers to a patient with a solid tumor without documented metastases, and initially treated within the previous 5 years.

Answer the following questions based on review of the patient’s medical history obtained during screening or from a review of the patient chart.

Indicate YES or NO for Questions 1-13.

- | | |
|----------------------------------|--|
| 1. AIDS? | <input type="radio"/> Yes <input type="radio"/> No |
| 2. Cerebrovascular disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 3. Chronic pulmonary disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 4. Congestive heart failure? | <input type="radio"/> Yes <input type="radio"/> No |
| 5. Connective tissue disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 6. Dementia? | <input type="radio"/> Yes <input type="radio"/> No |
| 7. Hemiplegia? | <input type="radio"/> Yes <input type="radio"/> No |
| 8. Leukemia? | <input type="radio"/> Yes <input type="radio"/> No |
| 9. Malignant lymphoma? | <input type="radio"/> Yes <input type="radio"/> No |
| 10. Peripheral vascular disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 11. Ulcer disease? | <input type="radio"/> Yes <input type="radio"/> No |
| 12. Myocardial infarction | <input type="radio"/> Yes <input type="radio"/> No |
| 13. Any tumor | <input type="radio"/> Yes <input type="radio"/> No |

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

- | | |
|------------------------|--|
| 14. Diabetes mellitus? | <input type="radio"/> None |
| | <input type="radio"/> Without end organ damage |
| | <input type="radio"/> With end organ damage |

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

- | | |
|--------------------|--------------------------------|
| 15. Liver disease? | <input type="radio"/> None |
| | <input type="radio"/> Mild |
| | <input type="radio"/> Moderate |
| | <input type="radio"/> 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
Protocol/Amendment No.: 001-03

Page 119

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
Protocol/Amendment No.: 001-03

Page 120

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 and percent blood neutrophil count
absolute and percent blood basophilic leukocyte count
absolute and percent blood eosinophilic leukocyte count
absolute and percent blood lymphocyte count
absolute and percent 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

Product: MK-3415A

Page 121

Protocol/Amendment No.: 001-03

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

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. Assays will be performed on all patients. *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.*

Prior studies have yielded conflicting results regarding demographically- and clinically-based predictors of response. 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 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 for a long-range prediction (LRp) of 3.35. The 90% CI for LRp 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 for a LRp of 2.25. The 90% CI for LRp 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.

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

Blood that is collected at Week 1 visit (or subsequent visit) in consenting patients

- Genetic and Other Biomedical Research

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

- Gut flora diversity (using deep sequencing). (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).

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 [56, 57, 58] and premature aging [59]. 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.

mRNA profiling

Gene expression profiling has successfully discriminated between patients with different acute infections [60], those with acute versus chronic hepatitis B infection [61], patients with chronic fatigue syndrome [62], and those with sepsis versus systemic inflammatory response syndrome [63]. 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 [64]. 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 mRNA profiling on Day 1 (prior to infusion) in all patients. Affymetrix arrays or other technology platforms will be used to examine associations between baseline mRNA signatures, CDI recurrence risk and other clinical outcome measurements.

Genetic Variation

A portion of the GBRC DNA blood sample will be used to explore genetic associations and correlations with *C. difficile* disease, clinical study outcomes, and measurements. These explorations will include, but are not limited to the following:

- Genetic variation that is associated with disease outcomes, treatment outcomes, gut flora diversity, quantitative gene expression measurements, and epidemiology of *C. Difficile* infection.
- Known IL-8 polymorphisms as IL-8 is known to be involved in leukocyte trafficking to the gut and colonic inflammation [65, 66, 67, 68, 69, 70, 71, 72, 73]; 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 [74].
- Genetic variation will be measured using multiple different technology platforms. The remaining portion of the GBRC sample may be used as described in GBRC section of this protocol.

Dehydroepiandrosterone (DHEA)

Levels of dehydroepiandrosterone (DHEA) are known to decline with age [75, 76], and the correlation of endocrinesenescence with immunosenescence has been recently described in a number of inflammatory conditions [77, 78, 79, 80]. It has been considered as an adjuvant to enhance vaccine responsiveness in aging adults with limited success [81, 82, 83]. 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.

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 CDI (i.e., the more rapid the recovery, the less risk of recurrence). As a result, stool samples will be collected for deep sequencing of gut flora at baseline (Day 1) from all patients. Baseline diversity, at time of administration of SOC antibiotics, may serve as a pre-monoclonal antibody biomarker of risk of recurrence. A diversity index for each patient will be calculated based on the distribution of species found by sequencing.

Analyses Performed for Biomarkers

These analyses are not expected to be necessary for marketing authorization and therefore will not be reported in the Clinical Study Report describing the analyses for the primary, secondary, and exploratory objectives outlined in Section 2.1. 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 analysis.

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.

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.

Sensitivity, specificity, long-range prediction (LRp), 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 to determine if the primary hypothesis can be met.

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.

6.7 HIGH RISK DEMOGRAPHIC AND CLINICAL IDENTIFIERS

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 and other Phase III studies. 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.

Only patients in the placebo group of this trial will be used for this analysis. 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.

Univariate logistic regression analyses (with recurrent CDI (yes/no) as the outcome variable) will be conducted for each of the potential predictor variables. All variables that have a p-value <0.2 will be included in a multivariable logistic regression model along with any other variables thought to be potential confounders, based on published literature and input from expert *C. difficile* consultants. The β coefficients (i.e., parameter estimates) from the multivariable logistic regression model will be used to compute the predicted probability of recurrent CDI for each patient. If the predicted probability of recurrent CDI is ≥ 0.5 for a given patient, then that patient will be classified as having a high risk for developing recurrent CDI.

Based on a sample size of 400 placebo patients, CDI recurrence rate of 0.25, an alpha=0.05, and a 2-sided hypothesis test, the power to detect underlying odds for CDI recurrence was calculated as follows:

Odds Ratio	Power (Based on Continuous Predictor)	Power (Based on Dichotomous Predictor)
1.1	0.13	0.06
1.2	0.35	0.12
1.3	0.62	0.21
1.4	0.83	0.33
1.5	0.93	0.45
2.0	1.0	0.90
2.5	1.0	0.99
3.0 or greater	1.0	1.0

Product: MK-3415A

Page 127

Protocol/Amendment No.: 001-03

Sensitivity, specificity, positive and negative predictive values of this classification will be evaluated. Accuracy will be measured 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. Similar to the remainder of the clinical trial data, missing data will be handled using the Data as Observed (DAO) approach.

Product: MK-3415A Page 128
Protocol/Amendment No.: 001-03

7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research
Collected from Clinical Trials Sponsored by Merck Sharp & Dohme Corp., a subsidiary
of Merck & Co., Inc.: A Guideline for Clinicians and Privacy Board Members

Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 129

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 trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials 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 trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, 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, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial 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 trials it conducts. Some early phase or pilot trials 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 trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 130

III. Subject 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 subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

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

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial 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 subject 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. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

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 trials. Merck does not pay incentives to enroll subjects 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 subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

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 trial. 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 trials 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 appendix to the trial 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."

Privacy Protection of Optional Specimens for Genetic and Other Biomedical Research
Collected from Clinical Trials Sponsored by Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.:
A Guideline for Clinicians and Privacy Board Members

1. Principles and Introduction

It is now well recognized that information obtained from studying and testing clinical specimens (i.e., blood, body fluids and/or tissue) may provide important indicators not only of the presence or absence of disease, but also of responses to medical treatments. The study of the relationships between such test results and drug efficacy is a critical component of the scientific research objectives for clinical development programs at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (MERCK). MERCK recognizes that studying and testing clinical specimens offers unique opportunities to enhance our understanding of human disease and health and ultimately to aid in the discovery and development of novel, breakthrough medications targeted to populations with the greatest need.

MERCK also recognizes, however, that analyses of specimens derived from consenting patients, including for research purposes, must be undertaken with the utmost consideration for human dignity and privacy, as noted in the Declaration of Helsinki, US FDA Requirements (21 CFR 50.20, 50.25, and 50.27), the International Conference on Harmonization (ICH) E6 Good Clinical Practices Guideline, and the 1997 UNESCO Declaration on the Human Genome and Human Rights. This document outlines the approach of MERCK to privacy protection of optional specimens for genetic and other biomedical research.

2. Definitions

For the purposes of this document, the following terms will apply:

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.¹

Genomic Biomarkers are measurable DNA or RNA characteristics that are indicators of normal biological or pathogenic processes and/or a response to therapeutic or other intervention.²

Pharmacogenomics (PGx): the investigation of variations of DNA and RNA characteristics as related to drug response.²

Also see http://www.i-pwg.org/cms/index.php?option=com_docman&task=cat_view&gid=81&Itemid=118 for guidance from the Industry – Pharmacogenomics Working Group (I-PWG) to Investigators, IRBs/IECs and Investigational Site Staff **Pharmacogenetics (PGt):** the influence of variation in DNA sequence on drug response²

Patient-specific Identifiers: Generally defined as data fields alone or in combination that would reasonably allow a third party to identify who a patient is. Examples of these are: Patient/Subject names, date of birth, telephone #s.

Study Site: The local site of the investigation, where patients are actively screened, enrolled and studied as per the clinical protocol.

Coding of Specimens/Data: There are several categories of coding for clinical specimens and the data associated with them. See <http://www.ich.org/LOB/media/MEDIA3383.pdf> for additional detail on these categories. The standard method of coding used in clinical studies is single coding.

Central Laboratory/BioBank: The third-party entity that is responsible for accessioning, proper handling, and archiving clinical specimens.

3. Optional Specimens for Genetic and Other Biomedical Research: Data/Information associated with the specimen

Biomarkers, including genomic biomarkers, may be measured and analyzed by standard or novel methods to explore variations that may be related to the development and/or treatment of the diseases studied in clinical trials sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck). The research that we would like to perform on the specimens is considered to be critical to further advance the Merck's scientific understanding of the disease and drug responses. The research will further enable Merck to:

- a) better understand disease and how to improve treatment of disease,
- b) better understand how drugs work in individuals and different patient populations,
- c) address emerging scientific questions that arise during the development of drugs and treatments, not known today, that would be very difficult to address if Merck did not collect a sample now, because it is not possible for the Merck, alone, to re-contact a patient directly to collect a tissue sample at a later date when the main study is finished,
- d) discover and understand biological markers (biomarkers) that can be used to help understand therapeutic treatments and disease,
- e) increase the chances that improved drugs may be commercially available by improving the risk benefit ratio of the treatment drug or similar drugs being developed to treat the disease in a patient or patient populations.

In order to realize and optimize the research that can be conducted with optional specimens, as described above, it is critical to link the patients' clinical information associated with the treatments in the protocol. In fact little or no research can be conducted without connecting the clinical study data to the specimen and it is unlikely the specimen would ever be used at all making any effort to collect it pointless to Merck and the patient. The clinical data allow specific analyses to be conducted for example a pharmacogenomic analysis might require knowing that specimens came from "men with type II diabetes between 20 and 50 years of age" or "children with asthma who did not respond to Drug X". In these instances, knowing gender, age and medical history and treatment outcomes are critical.

"Single coding is the current standard used in clinical research and offers additional safeguards to the subject's identifiers compared to the general healthcare confidentiality and privacy protection in everyday medical practice."² Consistent with this understanding, in clinical trials sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., optional specimens and the data associated with them will be single-coded, providing the same level of privacy for clinical research in general. In this model, the key that links the actual subject to their specimens and the data associated with them is maintained by study site personnel.

By exception, double-coding of the specifically-collected genetic specimen and/or related data analyses may be invoked. This option should only be used if there are local regulations **requiring** double-coding of genetic specimens and/or related data analyses. It is important to note that analyses may be double-coded, even if the specimen has not been double-coded. To request either of these options, complete the attached request form and submit it, along with written guidance supporting your local regulations, to your primary MERCK contact for the associated clinical trial.

4. Informed Consent

As per protocol procedures, patients/subjects should be presented with the consent form for Optional Specimens for Genetic and Other Biomedical Research at a designated visit. The consent should be administered in the standard manner, with special care to explain to the patient/subject that his/her privacy will be protected in the same way as it is provided for in the main study (unless double-coding is invoked, in which case there is slightly less risk of disclosure of the genetic research results). The individual administering consent should also carefully explain that the patient has the option to withdraw their specimens covered by the optional consent at a later date (See Section 6). Information pertaining to the administration and acquisition of the consent for Optional Specimens for Genetic and Other Biomedical Research will be captured in the Case Report Forms (CRFs) to assure that only appropriately-consented specimens are used for genetic and other biomedical research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

5. Assembly of Kits, Specimen Collection and Handling

A designated Central Laboratory will be responsible for assembling and distributing specimen collection kits and labels both for the main study specimens and for the optional specimens. The Central laboratory will also provide the instructions on how to obtain, label, process and ship the specimens. Upon receipt by the Central Laboratory (or its associated biobank), the specimens will be processed and/or stored as specified in the contract and consistent with each subject's actual consent. MERCK will routinely monitor the condition and disposition of specimens at the biobank so that each specimen may be used appropriately.

If double-coding is agreed upon for the specifically-collected genetic specimens, then those specimens or their derivatives will be transferred to another container that contains a second unique code number. The key that links the single code to the second code will be kept in a secure place with limited access. All analyses and clinical data related to the specimen or its derivatives will be linked to the second or other codes and specifically not to the original single code.

6. Specimen Destruction Procedures for Withdrawal of Consent

Patients who request their specimens to be withdrawn are instructed in the consent form to contact the Investigator *in writing*. 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), there will no longer be a link between the patient's personal information and their specimens. On this instance, the request for specimen destruction cannot be processed. If medical records for the main study are available, the Investigator will contact MERCK using the supplied telephone contact (see Sponsor Contact Information section) and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. MERCK will identify specimens to be destroyed using an agreed upon form. After appropriate sign-off by both parties and affirmation of destruction, specimens will be retrieved from storage and incinerated or pyrolyzed such that DNA and other biomolecules are completely destroyed, i.e. rendered to a state such that the DNA is not able to be manipulated by standard molecular biological techniques (i.e. PCR). Any residual specimens or derivatives from the samples that have left the biobank and can be tracked will also be destroyed, but only after all main study testing is complete. A confirmatory letter will be sent from the biobank to MERCK and then later from MERCK to the investigator. It is the responsibility of the Investigator to inform the patient

Product: MK-3415A Page 133
Protocol/Amendment No.: 001-03

of completion of destruction. Any data that has been generated from the specimens before sample destruction will be maintained and cannot be specifically deleted.

7. Conclusions

Merck recognizes both the tremendous potential, and the inherent responsibility that genetic and other biomedical research specimens provide to clinical studies. The procedures outlined in this document are intended to ensure that meaningful investigation of biomedical influences in disease and/or responses to therapies can be achieved while providing a high degree of privacy protection for patients in the study.

8. References

1. From National Cancer Institute: <http://www.cancer.gov/dictionary/?searchTxt=biomarker>
2. From 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 Page 134
Protocol/Amendment No.: 001-03

**Request to Double-Code Specifically-Collected Genetic Specimens Obtained from
Clinical Trials Sponsored by Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc.**

Instructions:

1. The Principal Investigator completes Section 1 of the form below and submits it, along with the specific regulatory guidance supporting the request, to the primary MERCK contact.
2. The primary MERCK contact submits the request to the head of the Molecular Profiling Leads for review and approval.
3. The head of the Molecular Profiling Leads reviews and approves the request by completing Section 2 and returns the completed form to the study site's primary MERCK contact, copying the MERCK liaison to the central laboratory and to the patient informed consent developers.
4. The study site's primary MERCK contact returns the completed form to Principal Investigator.
5. The MERCK liaison to the central laboratory informs them of the deviation from standard practice
6. The patient informed consent developers document the deviation from standard practice.

Section 1 (To be completed by the Primary Investigator):

Compound Number:

Clinical Protocol Number: Investigator Study Site Number:

Check only those requirements that apply:

- ☐ I request double-coding of the specifically-collected genetic specimens obtained in the above-referenced study site because local regulations require this method of specimen labeling.
- ☐ I request double-coding of any genetic data analyses related to the specifically-collected genetic specimens obtained in the above-referenced study site because local regulations require this level of privacy protection.

Attached is the local regulation supporting this request.

Principal Investigator's Name (printed): _____

Principal Investigator's Signature: _____

Date: _____

Section 2 (To be completed by Merck Research Laboratories):

- ☐ Approval granted
- ☐ Insufficient evidence of requirement, based on regulations submitted (In this instance, the Principal Investigator should provide additional information)

Approver's Name (printed): _____

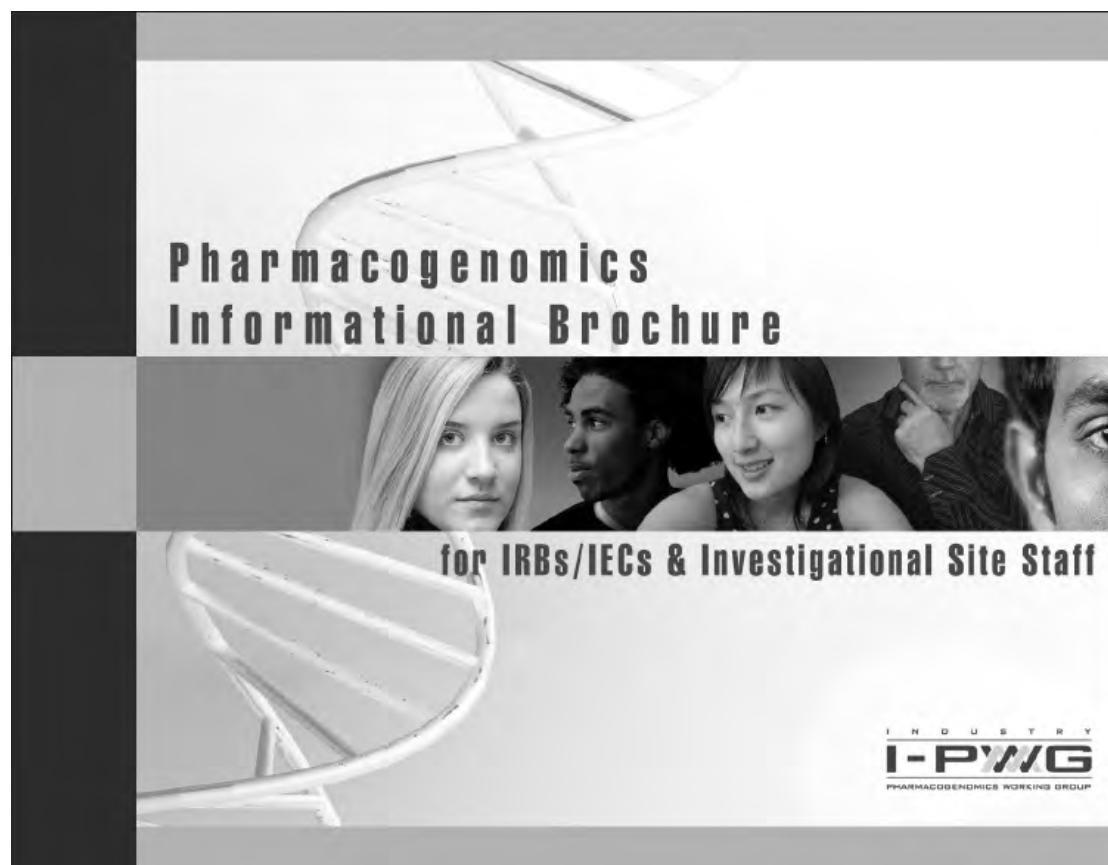
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Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 135



Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 136

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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Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 137

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:
www.fda.gov/Drugs/Research/Research/Pharmacogenetics/ucp0025573.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.

2

I-PWG
International Pharmacogenomics Working Group

Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 138

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 studies³. 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, 2008⁴.

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.

I-PWG

Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 139

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.

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 140

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, 2, 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>.

I-PWG
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Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 141

Glossary	References
<p>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).</p> <p>Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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).</p>	<ol style="list-style-type: none">1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories, April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98th/FDA-2006-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3363.pdf)2. Anderson DC, Gomez-Manolita B, Spear BB, et al. Elements of informed consent for pharmacogenetic research: perspective of the pharmacogenetics working group. <i>Pharmacogenomics Journal</i> 2002;2(5):284-92.3. ICH E6(R1) - Guideline for Good Clinical Practice, June 1996. (Accessed at: http://www.ich.org/LOB/media/MEDIA432.pdf)4. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. <i>Bioethics</i> 2006;20(1):24-36.5. Genetic Information Nondiscrimination Act (GINA); 2007-2008. (Accessed at: http://www.genome.gov/24518651)6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times—the Genetic Information Nondiscrimination Act of 2008. <i>New England Journal of Medicine</i> 2008;358(25):2561-3.7. EMEA CHMP Reflection Paper on Pharmacogenomics in Oncology – Draft, 2008. (Accessed at: http://www.emea.europa.eu/dfs/human/phaarmacogenetics/12843508s0001.pdf)8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics, June 2003. (Accessed at: http://www.tga.health.gov.au/dccs/pdf/euguide/emea/307001en.pdf)9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products, May 2007. (Accessed at: http://www.emea.europa.eu/dfs/human/phaarmacogenetics/12851708s001n.pdf)10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings, November 2006. (Accessed at: http://www.emea.europa.eu/pdfs/human/phaarmacogenetics/2022704en.pdf)

Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 142

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I-PWG
Pharmacogenomics Working Group

Confidential

15-May-2013

03GGHQ

Product: MK-3415A

Page 143

Protocol/Amendment No.: 001-03



Confidential

15-May-2013

03GGHQ

Product: MK-3415A
Protocol/Amendment No.: 001-03

Page 144

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME

SIGNATURE

DATE

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 NAME

SIGNATURE

DATE
