MBN-101-201

Study to Assess Safety and Clinical Activity of Local MBN-101 in Treatment of Infected Bone Sites

NCT No.: NCT02436876

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APPENDIX 16.1.9: DOCUMENTATION OF STATISTICAL METHODS

(SAP)

A Phase 2a Randomized, Single-Blind, Placebo-Controlled, 12-week Escalating Dose Study to Assess the Safety, Tolerability and Clinical Activity of 3 Concentrations of Locally Applied MBN-101 to Infected Bone Sites

Protocol Number:	MBN-101-201
Development Phase:	2a
Sponsor:	Microbion Corporation 1102 West Babcock, Suite B Bozeman, MT 59715 USA
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SAP APPROVAL FORM

Document Title:	Statistical Analysis Plan
Protocol Number:	MBN-101-201
Study Title:	A Phase 2a Randomized, Single-Blind, Placebo-Controlled, 12-week Escalating Dose Study to Assess the Safety, Tolerability and Clinical Activity of 3 Concentrations of Locally Applied MBN-101 to Infected Bone Sites
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (Serum glutamic pyruvic transaminase [SGPT])
AST	Aspartate aminotransferase (Serum glutamic oxaloacetic transaminase [SGOT])
$AUC_{0-\infty}$	Area under the curve from time 0 to infinity
AUC_{0-t}	Area under the curve from time 0 to the time of the last measurable concentration
Bi	Bismuth, used as a surrogate in concentration and PK Analysis after MBN-101 administration
BisEDT	Bismuth-1,2-ethanedithiol
BMI	Body mass index
BUN	Blood urea nitrogen
CK	Creatinine kinase
CL/F	Apparent clearance after extravascular administration
CLSI	Clinical and Laboratory Standards Institute
C_{max}	Maximum observed concentration
CRF	Case report form
CRP	C-reactive protein
DRC	Data Review Committee
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mITT	Modified Intent-to-Treat
NCA	Non-compartmental (PK) analysis
PCS	Physical health domain score
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

SMFA	Short Musculoskeletal Function Assessment
SOC	System organ class
$T_{1/2}$	Apparent half-life after extravascular administration
TEAE	Treatment-emergent adverse event
T_{max}	Time of the maximal observed concentration
VAS	Visual Analog Scale
VR-12	Veterans Rand 12 Item Health Survey
V_z/F	Apparent volume of distribution after extravascular administration
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol MBN-101-201 (Version 5.0, 27 July 2017) and describes in detail the statistical methodology and the statistical Analysis to be conducted for the above-mentioned protocol.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of single escalating doses of locally administered MBN-101 or placebo as adjunct to standard of care antimicrobial and surgical therapy.

2.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the clinical activity of single escalating doses of locally administered MBN-101.
- To evaluate the pharmacokinetics of single escalating doses of locally administered MBN-101.

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a randomized, single-blind, placebo-controlled multi-center study to assess the safety and tolerability of escalating doses of MBN-101 applied directly to target structures within infected osteosynthesis sites during revision surgery with or without hardware removal and replacement for patients diagnosed with an apparent fracture site infection or to sites of chronic or acute-on-chronic osteomyelitis of the long bone extremities or residual amputated limbs. Three successive cohorts of 8 patients will be enrolled in this trial. Consecutive patients from each of the study sites will be screened for potential participation as they present to the orthopedic service for clinical care for their infections. Patients meeting all eligibility criteria on screening will be offered participation in the study.

Following baseline evaluation, patients will receive standard of care treatment for their postoperative fracture site infection or osteomyelitis that includes systemic antibacterial treatment per institutional standard of care guidelines and debridement/revision surgery with or without hardware removal and placement/replacement as indicated. A single application of MBN-101 or placebo, applied intraoperatively directly to target structures within infected bone sites, will be performed following the final irrigation and debridement procedure and immediately prior to definitive closure. In cases where original hardware is retained, MBN-101 will be applied to all accessible surfaces of hardware and adjacent bone (target structures). In cases where hardware is placed or replaced, or in cases of two-stage procedures, MBN-101 will be applied to all accessible surfaces of hardware and adjacent

bone (target structures) following implantation of hardware and immediately prior to definitive closure. In cases where hardware is not required, MBN-101 will be applied to affected areas of bone only prior to definitive closure. If wounds are left open, the investigational product will be applied immediately prior to definitive closure. The minimum amount of MBN-101 required to achieve a thin coat of the relevant target structures within the infected bone site will be used.

Patients will be randomized 3:1 (active:control) to three successive doses (0.025, 0.075, or 0.25 mg/mL w:v) of MBN-101 (up to 8 mL, for a dose of up to 0.2, 0.6, or 2.0 mg, respectively) or placebo (diluent). Enrollment to the next dose cohort will not commence until an evaluation by the Data Review Committee (DRC) of all available safety data on all patients through Week 6 of study supports escalation to the next cohort.

PK assessments will be performed predose and at nominal 1, 6, 12, 24, 36, 48 (Day 2), 60, 72 (Day 3), 96 (Day 4), and 336 (Day 14; Week 2) hours after administration of study drug.

Patients will undergo study visits at Hour 48 and Weeks 2, 6 and 12. All patients will be followed for a total of 12 weeks after surgery.

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Twenty-four adult male or female patients meeting protocol-specified eligibility criteria may participate in the study, with the objective of having a total of 6 patients per dose level in the MBN-101-treated group and 6 patients in a pooled placebo-treated group.

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Subjects will be randomized in a 3:1 (active:placebo) ratio up to 24 hours prior to surgery via a central randomization scheme.

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This study is a single blind study; however, knowledge of treatment assignment should remain limited to those directly involved with the patient's surgical procedure and other individuals on a need to know basis. In order to provide unblinding data in an emergency in the absence of an individual privy to treatment assignment, sites will be provided with a numbered unblinding envelope corresponding to each numbered test kit the site is delivered. These envelopes will be securely stored in the pharmacy. The unblinding envelope specifies the treatment group of the kit and should only be opened when absolutely necessary. For treatment of adverse events, it should be assumed that the patient has received study drug, thus avoiding the need to unblind the patient. However, in the event the Investigator determines the randomization assignment information is required to treat the patient for an adverse event, the Medical Monitor should be contacted. If the Medical Monitor cannot be reached, the blind may be broken by opening the envelope. The site should document the unblinding process in the patient's source documents.

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Table 1 presents the schedule of events of the study.

Table 1. Schedule of Events

Procedure	Screening	Baseline/ Day of Surgery	Hour 48- 60	Hour 72	Hour 96	Week 2	Week 6	Week 12, EOT	Early Term / Tx Failure
		Day 1	Day 2	Day 3	Day 4	Day 14 ±4 days	Day 42 ±8 days	Day 84 ±8 days	
Review of eligibility criteria	X	X							
Informed consent	X								
Randomization		X							
Surgery/Administration of the Investigational Product		X							
Medical history	X								
Physical exam	X								
Interval physical exam		X	X			X	X	X	X
Hematology	X		X				X	X	X
Serology		X				X	X	X	X
Serum chemistry	X		X				X	X	X
Urinalysis	X		X				X	X	X
Pregnancy test	X	X						X	X
BisEDT Blood levels[1]		X	X	X	X	X			
12-lead ECG	X	X	X					X	X
Vital signs	X	X	X	X	X	X	X	X	X
Patient-reported outcomes[2]	X					X	X	X	X
Surgical site signs and symptoms		X	X	X	X	X	X	X	X
Surgical site pain score		X	X	X	X	X	X	X	X
Microbiology		X	(X)[3]			(X)	(X)	(X)	(X)
Radiographic evaluation		X				X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X

[1] PK blood samples will be collected pre-dose and at nominal 1, 6, 12, 24, 36, 48 (Day 2), 60, 72 (Day 3), 96 (Day 4) and 336 (Day 14; Week 2) hours after administration of the investigational product
[2] Patient-reported outcomes include the Veterans Rand 12 Item Health Survey (VR-12) and Short Musculoskeletal Function Assessment (SMFA)
[3] Microbiology will be performed at any time that a new surgical intervention is required.

4. SAMPLE SIZE CONSIDERATIONS

Sample size (24) for this study was chosen empirically for the purpose of the study without any formal statistical hypothesis to be tested.

Six subjects will receive active drug in each dose cohort. With 6 subjects receiving active drug, the probability of observing at least one of 6 subjects in a dose cohort exhibiting an AE of a specific type is 95% if the true background incidence rate for that event-type were approximately 0.385 or greater. Hence, if an AE of a specific type is not observed in the study in a sample size of 6 subjects receiving active study drug at a given dose, one would "rule-out" this AE as having an incidence rate of more than 0.385 with 95% confidence.

Similarly, if a rare event of interest is not reported in the 18 subjects treated with the active study drug, one could conclude that the rate of the event would be 0.153 or less with 95% confidence.

5. STUDY ASSESSMENT

5.1. Efficacy Assessments

5.1.1. Surgical Site Signs and Symptoms

The following signs and symptoms of the surgical site will be evaluated:

- Local erythema extending beyond suture material or staples
- Induration
- Drainage from surgical incision
- Degree of healing of the surgical incision

Patients with non-healing or worsening status of their surgical site may be considered for additional standard of care treatment, but should be encouraged to remain in the study in order to complete study evaluations.

5.1.2. Serious Interventions

All interventions meeting the following criteria are serious interventions:

- Initiation of antibiotic treatment in patient not previously on antibiotics
- Change in the route of antibiotic administration from oral to intravenous for escalation of treatment
- Change in the type or dosage of antibiotic drug for escalation of treatment
- Readmission (exclusive of readmissions associated with a healed bone site)
- Reoperation (exclusive of reoperations associated with a healed bone site)

5.1.3. Microbiology

The microbiology of the index site will be assessed at baseline and at the time of any subsequent surgical procedure at the index site. The presence of viable microorganisms will

be determined by standard microbiological culture methods and include speciation and antimicrobial susceptibility testing of any bacterial isolates found.

5.1.3.1. Specimen Collection

Samples collected will include at least one tissue site (bone when possible; eraser head size, suitable for dividing into two samples) from the infected bone site (if accessed) or involved tissue adjacent to any implant(s), two swabs of the deep infection site, and two swabs of the superficial tissue/wound closure/sinus tract site. One set of specimens (i.e. 1 tissue specimen, 1 deep swab, 1 superficial swab) will be placed into local site transport vessels. The duplicate set of samples will be placed into transport vessels provided by the central laboratory (International Health Management Associates, Inc.; IHMA). One set of specimens will be delivered to the local site microbiology laboratory using the standard storage and transport procedures employed at each site. The duplicate set of specimens will be transported to IHMA.

5.1.3.2. Specimen Processing: Local Laboratory

The tissue site sample and swabs will be analyzed immediately in the local laboratory for the presence of infectious pathogens by Gram stain and microbiological culture for both aerobic and anaerobic bacteria. The specimens will be processed (primary isolation, identification to species level and susceptibility testing) per the standard methods of each local site microbiology laboratory. Following isolation and identification of each microorganism, the susceptibility of each to one or more standard antibacterial agents (but not including MBN-101), as specified by the surgeon or per local site standard procedures, will be determined. It is recognized that the local site laboratory may be using one of a variety of susceptibility test methods, and therefore, the susceptibility result may be reported as a specific Minimal Inhibitory Concentration (MIC) value or as a categorical result (i.e. Susceptible, Intermediate or Resistant). Susceptibility to MBN-101 will not be determined at the local site laboratory; the susceptibility results determined locally are for the use of the surgeon in the care of the patient.

5.1.3.3. Specimen Processing: IHMA (Central Laboratory)

The tissue site sample and swabs will be analyzed immediately in the central laboratory for the presence of infectious pathogens by microbiological culture for both aerobic and anaerobic bacteria. The specimens will be processed (primary isolation, identification to species level, and susceptibility testing) per the central laboratory methods, as described in the central laboratory study manual.

Following identification, the susceptibility of the isolates to MBN-101 and comparator agents will be determined using either the reference broth microdilution method (for aerobic/facultative bacteria) or the reference agar dilution method (for anaerobic bacteria) as detailed by the Clinical and Laboratory Standards Institute (CLSI). Susceptibility tests for aerobic/facultative bacteria will be quality-controlled as detailed by CLSI using reference quality control strains and previously-established ranges for MBN-101 and comparators. Susceptibility tests for anaerobic bacteria will also include CLSI reference quality control strains, however, since quality control ranges for anaerobic bacteria are not yet established, the MIC values for the quality control strains will be collected then retrospectively compared to the quality control ranges once they are available. Susceptibility testing will be conducted with

batches of study isolates as each study cohort is completed. Patient and specimen identifier and microbiology results will be recorded in the database.

5.1.3.4. Integration of Local Site Laboratory and Central Laboratory Primary Isolation and Identification Results

There may be instances where the organism(s) isolated from a given specimen may be different at the local site laboratory and the central laboratory. In this instance, the central laboratory will first confirm the identification of the archived isolate. If the identification is confirmed, the pathogens present in the specimen will be defined as the total number of pathogens recovered by the local site laboratory and the central laboratory. For example, if the local site laboratory were to recover S. aureus and the central laboratory recovered S. aureus and P. acnes, the specimen would be defined as containing both S. aureus and P. acnes following merger of the data.

It is possible that local site laboratory may perform susceptibility tests with agents that are also present in the central laboratory test panel. The MIC value (and interpretation) provided by the central laboratory supersedes the local site determination for the purposes of clinical trial data analysis and inclusion in the Clinical Study Report. The local site susceptibility test results are for use by the surgeon in the local care of the patient; however, these data will also be captured in the study database.

5.1.4. Radiographic Evaluation

Radiographic evaluation will be performed at baseline and Weeks 2, 6 and 12. Radiographs (at least two orthogonal views) will be reviewed for bone morphology and integrity, periosteal reaction, union, interval callus formation, loss or change in reduction, and hardware integrity/failure.

5.1.5. Pain Assessments

Pain related specifically to the surgical site (Surgical Site Pain Score) will be assessed via a Visual Analog Scale (VAS, 0-10 scale, where 0=no pain at all and 10 =the worst possible pain) utilizing a 24 hour recall at screening, baseline, Hour 48 and Weeks 2, 6 and 12.

5.1.6. Patient Reported Outcomes

Patient-reported outcomes will be collected using the Veterans Rand 12 Item Health Survey (VR-12) and Short Musculoskeletal Function Assessment (SMFA) at screening, Weeks 2, 6 and 12.

5.1.6.1. The Veterans RAND 12 Item Health Survey (VR-12) Questionnaire

The Veterans RAND 12 Item Health Survey (VR-12) is a brief, generic, multi-use, self-administered health survey comprised of 12 items. The instrument is primarily used to measure health related quality of life, to estimate disease burden and to evaluate disease-specific benchmarks with other populations. The 12 items in the questionnaire correspond to eight principal physical and mental health domains including general health perceptions; physical functioning; role limitations due to physical and emotional problems; bodily pain; energy-fatigue, social functioning and mental health.

5.1.6.2. The Short Musculoskeletal Function Assessment Questionnaire (SMFA)

The 46-item SMFA questionnaire comprises two parts: the dysfunction index with 34 items and the bother index with 12 items. The dysfunction index assesses the patient's perceptions of the amount of difficulty they have in the performance of certain functions (25 items) and how often the patients have difficulty when performing certain functions (9 items). The dysfunction items are grouped into four categories: daily activities, emotional status, function of the arm and hand, and mobility. Each item has a 5-point response format (1 point for good function and 5 points for poor function). The bother index asks the patients to assess how much they are bothered by problems in various areas of life (e.g., recreation, work, sleep and rest). These items also have a 5-point response format (1 point for not at all bothered and 5 points for extremely bothered).

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Blood samples will be obtained to measure blood concentrations of Bismuth (Bi) as a surrogate for BisEDT. A pre-dose sample will be collected prior to administration of the investigational product. Blood will be drawn for PK samples at nominal 1, 6, 12, 24, 36, 48 (Day 2), 60, 72 (Day 3), 96 (Day 4), and 336 (Day 14) hr after application of MBN-101 to the surgical site.

BisEDT levels in whole blood after MBN-101 administration will be assessed with a qualified Inductively Coupled Plasma Mass Spectrometry (ICP-MS) assay method using bismuth as a surrogate for BisEDT according to the schedule.

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Safety variables will be collected at regular scheduled intervals during the study as shown in the Schedule of Events (Table 1). These will include physical examinations, vital signs and laboratory assessments (as detailed below) and the assessment of AEs.

5.3.1. Adverse Events

An adverse event is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (e.g., diabetes) that occurs after initiation of the investigational study whether or not it is considered to be related to the investigational product. All adverse events (AEs) will be recorded throughout the study, beginning when the subject signs the Informed Consent Form. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.1).

5.3.2. Clinical Laboratory Evaluations

All clinical laboratory tests will be performed by the local clinical site laboratory. Blood and urine will be collected for hematology, serology, serum chemistry, urinalysis, and pregnancy testing (as indicated) according to the schedule.

Hematology	WBC, RBC, hemoglobin, hematocrit, platelet count, MCV, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, absolute basophils, PT, PTT.
Serologies	ESR, CRP.
Serum Chemistry	Sodium, potassium, chloride, carbon dioxide, BUN, glucose, creatinine, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), AST (SGOT), ALT (SGPT), GGT, creatinine kinase (CK), calcium, magnesium, Vitamin D.

Other	Urine analysis Serum pregnancy test for women of childbearing potential

5.3.3. Vital Signs

Vital signs include blood pressure, pulse, respiratory rate and body temperature; vital signs will be assessed according to the schedule.

5.3.4. 12-Lead ECG

Testing will be conducted at screening, baseline, and 48 hours. The ECG trace will be stored at the investigational sites as source document; clinical interpretation, including normal, abnormal but not clinically significant, and abnormal and clinically significant, will be determined by the investigator.

5.3.5. Physical Examination

A comprehensive physical examination will be performed on all patients at Screening, including assessments of height, weight, head, ears, eyes, nose, throat, chest, heart, abdomen, and skin. Interval physical exams will be performed at all subsequent study visits according to the schedule and will focus on the surgical site, with assessments of local erythema, induration, drainage and degree of healing.

5.4. Prior and Concomitant Medications

All patients will receive their usual concomitant medications for any underlying medical conditions without interruption. Patients will also receive standard of care treatment for their infection that includes systemic antibacterial treatment per prevailing standard of care guidelines (i.e., national, institutional, or physician preference) and other indicated postoperative medications, including pain medications.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD March 2015).

5.5. Medical History

A comprehensive medical history will be taken on all patients at Screening, including but not limited to past medical history, past surgical history, current medications, allergic history and psychosocial history.

6. STUDY ENDPOINTS

6.1. Safety Endpoints

The safety and tolerability of locally administered MBN-101 will be assessed by:

- Treatment-emergent adverse events.
- Treatment-emergent serious adverse events.
- Changes in clinical laboratory tests (clinical chemistry, hematology, and urinalysis).

- Changes in vital signs (blood pressure, pulse, respiratory rate and body temperature).
- Changes in physical exams.
- Clinical findings of 12-lead electrocardiograms.

6.2. Efficacy Endpoints

Clinical activity of locally administered MBN-101 will be assessed by:

- Proportion of treatment failures. A treatment failure defined as a subject with non-healing or worsening status of their surgical site requiring serious intervention by Week 12.
- Cumulative number of serious interventions at Week 12.
- Time to first serious intervention, time to readmission and time to reoperation, exclusive of serious interventions, readmissions, and reoperations associated with a healed bone site.
- Number of subjects undergoing removal of stabilizing orthopedic hardware due to a healed bone site by Week 12.
- Time to removal of orthopedic hardware due to a healed bone site.
- Incidence and intensity of surgical site signs and symptoms, including local erythema, induration, drainage and degree of healing.
- Change from baseline in patient-reported outcomes at each post baseline time point. Patient-reported outcomes will include Veterans Rand 12 Item Health Survey (VR-12) and Short Musculoskeletal Function Assessment (SMFA).
- Surgical site pain score and change from baseline in pain score at each post baseline time point. Pain intensity at the surgical site will be assessed by Visual Analog Scale (VAS, 0-10 scale).
- Findings of microbiology evaluations at the surgical site. Microbiologic success is assessed by clearance of infection.
- Findings of radiographic evaluations at the surgical site. Radiographic success is assessed by healing on radiologic examination.
- Change in serologic markers CRP and ESR at each post baseline time point.

6.3. Pharmacokinetic Endpoints

Whole blood concentrations of Bismuth (Bi) will be measured after administration of single escalating doses of MBN-101 (bismuth as a surrogate for BisEDT) and will be used to calculate pharmacokinetic parameters (i.e., T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{1/2}$, CL/F, V_z/F).

7. ANALYSIS POPULATIONS

The following analysis datasets will be identified for the purpose of analysis.

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All Screened Subjects will include all subjects who signed informed consent for the study.

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Intent-to-Treat (ITT) Population will include all subjects who were randomized in the study. A randomized subject may or may not be treated with the assigned study drug.

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Safety Population will include all subjects who received any amount of study drug (active or placebo). All treated subjects will be included in the safety analysis.

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Modified Intent-to-Treat (mITT) Population will include the ITT subjects who received any amount of study (active or placebo) and have at least one post-treatment assessment. The mITT Population is the primary population for efficacy analysis. Post-treatment assessment includes any post-treatment assessment in any study data collected, for example, lab, vital sign, etc.

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PK Concentration Population will include all subjects with any measurable bismuth blood concentrations.

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PK Evaluable Population will include all subjects providing sufficient measurable bismuth blood concentrations to facilitate determination of PK parameters.

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Summary statistics will be presented by treatment group. For continuous variables, the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum will be provided. For categorical variables, the frequency and percentage in each category will be displayed.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g. standard deviation) will be displayed to two decimal places greater than the original value. All Analysis will be performed using SAS® Version 9.3.

All safety and efficacy endpoints will be tabulated with descriptive statistics; data from all placebo subjects (2 per cohort; 6 subjects in total) will be pooled. Data from BisEDT treated subjects will be presented by dose (6 subjects per dose) and combined (a total of 18 subjects). If data permits, differences between the treatment groups and 95% confidence intervals for the difference will be presented.

In the event that a subject received study drug treatment that is not the assigned/randomized

treatment group, the subject has a major protocol deviation. The subject, however, will be included in the analysis for safety and efficacy in the actual treatment group received.

8.2. Handling of Dropouts/Missing Data

For the efficacy endpoint, proportion of treatment failures, subjects who discontinued from the study or died by week 12 will be considered as treatment failures for the efficacy analysis.

For the missing data of SMFA, in the case of the dysfunction index, unanswered items in a category are replaced by the individual's mean score for that category, as long as more than 50 percent of the items in that category have been answered. If $\leq$ 50% of the items in that category have been answered, the missing data will not be imputed.

In the cases of missing or incomplete dates (e.g. AE and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data Analysis and summaries.

8.3. Baseline Definition

Baseline pathogen(s) are determined from all specimens collected prior to the first dose of study drug.

For all other efficacy and safety endpoints, the baseline value is defined as the last measurement or assessment prior to the first dose of study drug.

8.4. Subject Disposition

Subject disposition will be summarized for the ITT Population for each treatment group and in total. The following subject disposition categories will be included in the summary for all randomized subjects:

- Subjects who were randomized,
- Subjects who were treated,
- Subjects who were not treated,
- Subjects who completed the study, and
- Subjects who did not complete the study.

For subjects who did not complete the study, a summary will be provided by reason for discontinuation. The total number of subjects in each defined analysis population will be tabulated.

In additional, a summary of screen failures and the reason will also be tabulated for All Screened Subjects.

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Demographic and baseline characteristics such as age, age group (<65 and ≥65), gender, race, ethnicity, height, weight, BMI, and surgery site characteristics (type of injuries, method of fraction fixation, surgical site location), time from previous surgery to study enrollment, and type of previous treatment and current surgery characteristics (area of the osteosynthesis or osteomyelitis site, hardware removal, new hardware replacement, and method of wound closure) will be summarized with appropriate descriptive statistics (the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables; number and percentage for categorical variables) by treatment group and overall.

Baseline characteristics summaries will be based on the Safety Population and repeated for the mITT and PK Concentration Populations.

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Distribution of Pathogens Isolated at Baseline will be tabulated by treatment group and overall for the mITT Population with any baseline pathogens.

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Medical History (Connective tissue disease/Autoimmune disease, HIV/AIDS, Renal disease, and Diabetes Mellitus) will also be summarized descriptively by treatment group and in total for the Safety and mITT Populations.

All medical histories will be listed by subject.

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Prior medications are medications used before the first dose of study drug. Concomitant medications are medications that were taken on or after first dose of study drug.

The prior and concomitant medications will be summarized with the number and percentages by ATC class and preferred term for each treatment group and overall for the Safety and mITT Populations. Concomitant systemic antibiotic administered for treatment of the infected osteosynthesis/arthrodesis surgical site will also be summarized in the same manner. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more preferred terms in the same classification.

All prior and concomitant medications and procedures will be listed by subject.

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All efficacy analysis will be based on the mITT Population.

8.9.1. Treatment Failure

The number and percent of subjects with treatment failure during the study will be tabulated by treatment group. If data permit, the difference in proportion of treatment failures between each treatment dose group and placebo group and the corresponding 95% exact confidence intervals for the difference will be presented. The Exact confidence interval will be calculated using the Clopper Pearson method.

Sensitivity Analysis for Treatment Failure

An 'as assigned' analysis will be performed on the mITT subjects as a sensitivity analysis for treatment failure. In this analysis, subjects who received a treatment that is not the assigned treatment will be included in the 'assigned' treatment group for this analysis.

8.9.2. Incidence of Serious Interventions, Readmission, and Reoperation

The number and percent of subjects with at least one serious intervention, readmissions and reoperations (exclusive of serious interventions, readmissions, and reoperations associated with a healed bone site) and total number of serious interventions, readmissions and reoperations will be tabulated by treatment group for the following periods:

- duration of the study,
- within the first 4 weeks after the surgery,
- from week 4 to week 8; and
- from week 8 to week 12.

If data permit, the difference in proportion of the above incidences between each treatment dose group and placebo group and the corresponding 95% exact confidence intervals for the difference will be presented. The Exact confidence interval will be calculated using the Clopper Pearson method.

8.9.3. Time-to-Event Efficacy Endpoints

The following time-to-event efficacy endpoints will be summarized descriptively using the Kaplan-meier estimatorby treatment group:

- Time to the first serious intervention exclusive of serious interventions, readmissions, and reoperations associated with a healed bone site
- Time to readmission (exclusive of readmissions associated with a healed bone site)
- Time to reoperations (exclusive of reoperations associated with a healed bone site)
- Time to removal of hardware due to a healed bone site

Time to first serious intervention will be calculated as the number of study days from the study surgery date to the event onset date plus 1. Subjects who do not have any serious intervention will be censored to the last observation date.

Time to readmission will be calculated as the number of study days from the initial hospital discharge date to the hospital readmission date plus 1. Subjects who do not have any readmission will be censored to the last observation date.

Time to reoperation will be calculated as the number of study days from the study surgery date to reoperation date plus 1. Subjects who do not have any reoperation will be censored to the last observation date.

Time to removal of hardware will be calculated as the number of study days from the study surgery date to the event date plus 1. Subjects who do not have any removal of hardware will be censored to the last observation date.

The number and percentage of subjects with the event and subjects censored will be tabulated by treatment group. Subjects who do not have the event will be considered censored. The Kaplan-Meier estimate of Q1, Q3, and the median time to the event and the associated 95% confidence interval will be presented for each treatment group. The Kaplan-Meier plot for each endpoint will be provided.

8.9.4. Surgical Site Signs and Symptoms

The number and percentage of subjects with surgical site signs and symptoms including local erythema, induration, drainage and degree of healing will be summarized descriptively by treatment group at baseline and each scheduled post-baseline time point. The intensity of the signs and symptoms will be summarized as well. For each symptom, the difference in proportion of the above incidences between each treatment dose group and placebo group and the corresponding 95% exact confidence intervals for the difference will be presented. The Exact confidence interval will be calculated using the Clopper Pearson method.

8.9.5. Patient-Report Outcomes

8.9.5.1. The Veterans RAND 12 Item Health Survey (VR-12) Questionnaire

VR-12 total score, physical health domain score (PCS), and mental health domain score (MCS) at each scheduled visit and change from baseline will be summarized descriptively by treatment group.

8.9.5.2. The Short Musculoskeletal Function Assessment Questionnaire (SMFA)

SMFA results include the scores of the dysfunction and the bother indices, which are calculated by summing up the responses to the items and then transforming the scores according to the formula: (actual raw score - lowest possible raw score)/(possible range of raw score) ×100.

SMFA results and change from baseline will be summarized by visit and treatment group with descriptive statistics.

8.9.6. Pain Assessments

Surgical site pain score (VAS) and change from baseline will be summarized descriptively by treatment group at baseline and each scheduled post-baseline time point.

8.9.7. Microbiology

Microbiological success is assessed by clearance of infection, which is defined as eradication of all baseline pathogens.

The number and percentage of subjects with microbiological success will be tabulated descriptively by treatment group and time point. The difference in proportion of microbiological success between each treatment dose group and placebo group and the corresponding 95% exact confidence intervals for the difference will be presented. The Exact confidence interval will be calculated using the Clopper Pearson method.

8.9.8. Radiographic Evaluation

Radiographic success is assessed by healing on radiographic examination.

The number and percentage of subjects with radiographic success will be tabulated descriptively by treatment group and time point.

8.9.9. Serologic Markers

Serologic marker CRP and ESR values and the change from baseline for each scheduled visit will be summarized with descriptive statistics by treatment group.

The number and percentage of subjects with normal, abnormal clinically significant, and abnormal not clinically significant for each serologic marker will be tabulated by treatment group at each scheduled visit.

8.9.10. Subgroup Analysis for Treatment Failure

If data permit, the following selected subgroups may be performed for subgroup analysis of treatment failure.

1. Area of the infected site
2. Method of fracture fixation
3. Type of infection (per identified microorganism)
4. Anatomic location of the surgery site
5. Hardware retention status (retained vs. exchanged)
6. Type of injuries
7. Method of wound closure
8. Osteomyelitis vs. non-osteomyelitis

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All safety Analysis will be presented using descriptive statistics and the Safety Population. No inferential statistics will be reported.

8.10.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE starting after the first dose of the investigational agent or placebo is administered. If the AE is present prior to the administration of the first dose of the investigational agent or placebo but increases in severity, it will also be considered a TEAE.

An overview of adverse events will be provided which summarizes the number and percentage of subjects and the number of events for the following:

- All TEAEs,
- Drug-related TEAEs,
- Maximum severity of TEAEs,
- Deaths,
- Serious adverse events (SAEs), and
- Discontinuation due to AEs.

The number and percentage of subjects with at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAE, all SAEs and all AEs leading to study discontinuation, pre-specified local TEAEs will be summarized in the same manner. In the case of multiple occurrences of the same AE within the same subject, each subject will be counted only once for each SOC and preferred term.

Summaries will be provided by maximum severity and relationship to study drug for the number and percentage of subjects with TEAEs by system organ class and preferred term. Maximum severity for pre-specified local TEAEs will be summarized in the same manner. For this summary, subjects with multiple adverse events will be counted only once by the maximum severity with in an SOC and preferred term.

Subject listings of SAEs and of AEs causing discontinuation of the study will be provided. All adverse events will be listed.

8.10.2. Clinical Laboratory Evaluations

Laboratory test results (hematology and serum chemistry) at each scheduled visit and change from baseline will be summarized by treatment group.

Laboratory data will be tabulated using counts and percentages based on the following result class by each scheduled visit and treatment group.

- Normal: result is within the local lab normal range
- Abnormal: result is either higher or lower than the normal range

The number and percentage of subjects with the following potentially clinically significant (PCS) abnormal liver function tests will be summarized:

- ALT ≥3×ULN
- AST ≥3×ULN
- ALT or AST ≥3×ULN
- Total bilirubin ≥1.5×ULN and ≥2×ULN
- ALP ≥1.5×ULN and ≥3×ULN
- ALT or AST ≥3×ULN and Total bilirubin ≥2×ULN
- Potential Hy's Law cases: ALT or AST ≥3×ULN, Total bilirubin ≥2×ULN, and ALP ≤ 2×ULN

A listing of patients with any post baseline abnormal liver function tests will be presented.

All clinical laboratory data will be listed. Values outside the normal ranges will be flagged.

8.10.3. 12-Lead ECG

Descriptive statistics will be provided for 12-lead ECG findings (PR, QRS, QT, and RR) and changes from baseline for each scheduled visit.

All abnormal values will be assessed for clinical significance; clinical significance will be captured in the case report form. Number and percent of subjects within each result class (normal, abnormal but not clinically significant, and abnormal and clinically significant) will be presented by time point and treatment group.

Shift tables will be used to summarize individual subject changes from baseline to each post baseline time point using the following categories; normal, abnormal but not clinically significant, and abnormal and clinically significant.

All 12-lead ECG findings will be listed by subject.

8.10.4. Vital Signs

Descriptive statistics will be provided for the vital signs (blood pressure, pulse, respiratory rate, and temperature) and changes from baseline for each scheduled visit.

Vital sign results will also be tabulated based on the following result class.

- Normal: result is within the normal range
- Abnormal: result is either higher or lower than the normal range

All abnormal values will be assessed for clinical significance; clinical significance will be captured in the case report form. Number and percent of subjects within each result class (normal, abnormal but not clinically significant, and abnormal and clinically significant) will be presented by time point and treatment group.

Additionally, shift tables, showing individual subject changes from baseline to each post baseline time point, by treatment group, will be presented for each vital sign parameter using the following categories: normal, abnormal but not clinically significant, and abnormal and clinically significant.

A listing of all vital signs will be provided by subject.

8.10.5. Physical Examination

Shift tables for physical examination overall assessment will be used to summarize individual subject changes from baseline to each post baseline time point using the following categories; normal, abnormal but not clinically significant, and abnormal and clinically significant.

Physical examination findings will be listed by subject.

8.11. Pharmacokinetic Analysis

Bismuth (Bi) concentration data will be analyzed by noncompartmental analysis (NCA) with Phoenix™ WinNonlin® Version 6.4 or higher, using an extravascular administration model

and actual sampling times. The PK parameters will be calculated and analyzed by another vendor and reported separately.

Summary statistics [N, mean, standard deviation (SD), minimum (Min), median (Med), maximum (Max), percent coefficient of variability (% CV)] for the PK concentration data will be presented by treatment group and time point.

A listing of the PK concentrations by subject will be provided.

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Interim Analysis are planned for this study for the purpose of DRC. The purpose of the interim analysis is to allow the DRC to review the data and to make recommendation to the Sponsor on whether or not the next cohort of the subjects should be studied as planned.

Data Review Committee (DRC) Charter

A Phase 2a Randomized, Single-Blind, Placebo-Controlled, 24-week Escalating Dose Study to Assess the Safety, Tolerability and Clinical Activity of 3 Concentrations of Locally Applied MBN-101 to Infected Osteosynthesis Sites

Protocol Number:	MBN-101-201
Sponsor of Protocol:	Microbion Corporation
Date of Document:	28 April 2015
Version:	1.0

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REVISION HISTORY OF THE DOCUMENT

The DRC Charter is currently in Version 1.0. (A Chair will be selected, and upon specification, the Version will be revised to Version 1.1).

INTRODUCTION

This Charter is for the Data Review Committee (DRC) for protocol MBN-101-201 titled **A Phase 2a Randomized, Single-Blind, Placebo-Controlled, 24 week Escalating Dose Study to Assess the Safety, Tolerability and Clinical Activity of 3 Concentrations of Locally Applied MBN-101 to Infected Osteosynthesis Sites.**

This Charter defines the scope, roles and responsibilities, operating procedures, and membership of the DRC. The DRC membership consists of independent medical experts with expertise relevant to the proposed clinical indication.

PRIMARY RESPONSIBILITIES OF THE DRC

The primary responsibility of the DRC is to protect the safety of trial participants.

The DRC will serve in an advisory capacity to the Sponsor. The DRC may make recommendations to the Sponsor regarding:

- Continuation of the trial without modification.
- Continuation of the trial with modification to the Protocol, Informed Consent and/or Investigator's Brochure.
- Suspension or termination of patient enrollment.
- Termination of the trial.

The DRC will be responsible for written documentation including the rationale of any recommendations. In all situations, the final decision to act upon any DRC recommendation will rest with the Sponsor.

In order to execute its responsibilities, the DRC membership will have read and be familiar with the Protocol, Investigator's Brochure, Informed Consent, and Safety Monitoring Plan. The DRC membership will also have read and approved this Charter.

Safety Monitoring

The DRC will exercise its primary responsibility by the periodic review of accumulating study data including: trial recruitment, retention, and safety data. Additional DRC responsibilities include:

1) Dose escalation recommendations – determining when subjects may be enrolled into the next higher dose cohort.
2) Recommendations regarding re-starting enrollment should the threshold of the protocol stopping rules be reached.

Efficacy Data and Interim Analyses

The DRC will not be responsible for reviewing efficacy data or making recommendations on the basis of efficacy since the trial's primary objective is safety. Since the study is not adequately powered for statistical tests of hypotheses, no formal statistical interim analysis of efficacy data is planned. However, the DRC may request to review ongoing efficacy data from the study in an effort to better understand the evolving benefit/risk relationship of the investigational product in the proposed indication.

Publications

The DRC will not have any special role in publications resulting from the study.

Confidentiality

All materials, discussions and proceedings of the DRC are considered confidential. The DRC membership will protect the integrity of the trial by maintaining confidentiality regarding the trial data and trial execution. All DRC members will be held to the same confidentiality requirements. Any communication of confidential information outside of the DRC will be fully documented.

MEMBERSHIP OF THE DRC

Members

The DRC is a multidisciplinary group consisting of three voting members. All three members are independent of the Sponsor and the clinical trial. At least one member is an infectious diseases specialist.

Contact List

DRC Member #1: Redacted

DRC Member #2: Redacted

DRC Member #3: Redacted

Role of the DRC Members

- Protect the safety of study participants.
- Review and be familiar with the protocol, informed consent, investigator's brochure, and the safety monitoring plan, as well as any amendments to these documents.
- Review and approve the DRC charter.
- Participate in DRC meetings and review any materials provided.
- Evaluate the accumulating safety data on a regular periodic basis as well as an *ad hoc* basis. It is anticipated that the DRC will hold formal meetings via teleconference approximately 4-5 times over the course of the study.
- Review study performance including recruitment, accrual and other factors that might be relevant to study safety.
- Engage in open debate and discussion.
- Make recommendations to the Sponsor regarding study conduct.
- Ensure the confidentiality of the study data.
- Discharge itself from its duties when the study is complete.

Role of the DRC Chair

The DRC Chair will be appointed by the Sponsor and the CRO. The DRC Chair will be responsible for:

- Co-chairing the DRC Orientation meeting.
- Preparing the DRC agendas.
- Chairing and facilitating the DRC meetings.
- Reviewing Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI) on an ongoing basis to determine if an ad hoc meeting of the DRC is required.
- Scheduling ad hoc DRC meetings.
- Scheduling DRC meetings at milestone time points such as dose cohort escalation decisions.
- Ensuring that attendance of the full DRC membership is present at each DRC meeting.
- Reviewing DRC minutes prior to release to the general DRC membership for approval.
- Ensuring the DRC minutes are reviewed and approved by the DRC membership.
- Serving as the lead liaison between the DRC and the Sponsor.
- Ensuring that any DRC recommendations to the Sponsor are made in a timely manner.

Sponsor

The Sponsor is responsible for:

- Choosing the DRC membership.
- Appointing the DRC Chair.
- Scheduling and Co-Chairing the Orientation Meeting.
- Ensuring that the DRC has the information needed to execute its responsibilities.
- Responding to the DRC in a timely manner with regard to any DRC recommendations, questions, or requests.
- Informing the DRC in a timely manner of any changes to the clinical protocol, informed consent, Investigator Brochure or any other relevant regulatory documents related to the clinical trial.

CONFLICTS OF INTEREST

The DRC membership consists of independent medical experts. Any member reporting or developing a conflict of interest during the course of the clinical trial will report this conflict to the DRC Chair and the Sponsor such that a replacement member of the DRC may be identified and established with minimal disruption to the roles and responsibilities of the DRC.

TIMING AND PURPOSE OF THE DRC MEETINGS

The DRC will determine the schedule and timing of its meetings at its Orientation Meeting. This Charter will be amended at that time.

The purpose of the DRC meetings will include the general review of safety data. Meetings of the DRC need not be face-to-face. It is anticipated that DRC meetings will be conducted via conference call, and the group will meet approximately 4-5 times during the conduct of the study.

DRC Quorum

The presence and participation of all three DRC voting members will be considered a quorum. At any particular meeting, a DRC quorum will be considered necessary and sufficient to conduct DRC business.

Types of DRC Meetings

It is anticipated that all DRC meetings will consist of an open session followed by a closed session followed by a second open session. During this second open session, recommendations of the DRC will be made directly to the Sponsor or Sponsor's representative.

Schedule of Meetings

The DRC will determine the schedule and timing of its meetings at its Orientation Meeting. In general, the DRC will meet for the following purposes:

- Milestone meetings required to trigger specific protocol events such as dose cohort escalation.
- Ad hoc meetings called by the DRC Chair, any DRC member, the Sponsor, or the Study Team.

Voting

All members of the DRC will be considered voting members.

Orientation Meeting

The DRC Chair will schedule an Orientation meeting which will be co-chaired by both the DRC Chair and the Sponsor. The purpose of the orientation meeting is to:

- Introduce and enable Q & A between the DRC, Sponsor and Study Team Members.
- Review the development program and proposed clinical trial for MBN-101.
- Discuss, approve and amend the DRC Charter.
- Outline DRC operating procedures and expectations.

Masking Policy

The DRC will review unblinded data. The DRC will exercise caution when providing recommendations to or otherwise communicating with the sponsor not to provide any recommendations or communications that might result in unblinding of the sponsor to the any data from the clinical trial.

Contract Research Organization/Data Analysis Center

The Contract Research Organization will be responsible for:

- Providing the necessary data listings and administrative information for each DRC data review meeting.
- Facilitating SAE and AESI review by the DRC Chair as these events occur.
- Providing additional information as requested by the DRC and approved by the Sponsor.

Formal Interim Analysis Meetings

No statistical interim analyses will be conducted. The study is expected to continue until its completion barring any unforeseen safety issue.

PROCEDURES TO ENSURE CONFIDENTIALITY & PROPER COMMUNICATION

Open and Closed Sessions

It is anticipated that all DRC meetings will consist of an open session followed by a closed session followed by a second open session. During this second open session, recommendations of the DRC will be made directly to the Sponsor or Sponsor's representative.

Minutes of the DRC Meeting

The DRC will generate both open and closed session minutes for each meeting. The DRC Chair will be responsible for transferring the DRC closed session meeting minutes to a secured server provided by the CRO to ensure confidentiality until completion of the study. The DRC Chair will also be responsible for providing open session minutes to both the Sponsor and the CRO as soon as they are available. DRC open and closed session minutes should be distributed to and approved by the DRC membership within 3 working days of the DRC meeting.

Retention of DRC Minutes

Minutes recorded from DRC meeting will be retained as long as the study data is retained.

Recommendations to the Sponsor

The DRC will make recommendations to the Sponsor orally during the open session and in writing.

STATISTICAL MONITORING GUIDELINES

CONTENT OF THE DRC'S OPEN AND CLOSED REPORTS

Given the exploratory nature and small sample size of the current Phase 2a trial, there are no statistical monitoring guidelines considered. The protocol does have stopping rules based on clinical guidelines which will be monitored throughout the study.

RESIGNATION, TERMINATION AND REPLACEMENT OF DRC MEMBERS

It is anticipated that DRC members will continue their membership until the study is completed and the DRC is discharged. However, in the event that a DRC member must be replaced, the DRC Chair should be notified of the pending departure and notify the Sponsor and other DRC members. The replacement of the DRC member will be at the discretion of the Sponsor.

TABLES/LISTINGS TO BE REVIEWED DURING DRC MEETINGS

The DRC will be provided with raw data listings for review directly from the Clinical Trial Database (CTDB). Aggregate data will not be provided. As the DRC will be reviewing safety data on an accumulating basis, it is recognized that the data will be a mix of "clean" and "dirty" data residing in the CTDB at any given time. All "dirty" data will be cleaned and available to the DRC for all subsequent meetings.

Administrative Data

The Contract Research Organization will provide a summary of the following information for each data review meeting:

- The number of subjects failing screening.
- The number of subjects enrolled.
- The amount of follow-up time for subjects enrolled.
- The amount of data entered into the Clinical Trial Database.
- The amount of data "cleaned".
- Date of last coding of AEs and Con Meds.
- The cutoff date corresponding to the data listings provided to the DRC. For example, all data entered into the CTDB as of a certain date.

Data Listings

The following data listings will be provided. For each data listing the repeating key subject information should be provided.

- Medical History
- Surgical History
- Eligibility/Exclusion Deviations
- Physical Exam including surgical site exam
- Vital Signs
- Adverse Events
- Serious Adverse Events
- Concomitant Medications, including concomitant antibiotics and pain medications
- Labs – Out of Range Values Only
    - Hematology
    - Serum Chemistry
    - Serologies
    - Urinalysis

Efficacy Data

If requested by the DRC, line listings of the number of treatment failures, serious interventions, readmissions and/or reoperations, as well as microbiology, radiographic and serologic marker analyses, will be provided.

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