Study Assessing Safety & Effectiveness of a Catheter Lock Solution in Dialysis Patients to Prevent Bloodstream Infection

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NCT02651428

Statistical Analysis Plan

A Phase 3, prospective, multicenter, double-blind, randomized, active control study to demonstrate the safety and effectiveness of Neutrolin® in preventing catheter-related bloodstream infections in subjects receiving hemodialysis therapy as treatment for end stage renal disease

LOCK-IT-100

Sponsored by:

CorMedix Inc.

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1 Study Description

This study has been implemented to evaluate the efficacy and safety of Neutrolin® as a catheter lock solution (CLS) when used for the prevention of catheter-related bloodstream infection (CRBSI) in patients receiving hemodialysis (HD) for the treatment of End Stage Renal Disease (ESRD).

1.1 Objectives

The primary objective of this study is to demonstrate the efficacy and safety of Neutrolin® as a catheter lock solution (CLS) for prevention of catheter-related bloodstream infection (CRBSI) in subjects receiving hemodialysis (HD) for the treatment of End Stage Renal Disease (ESRD) when compared with heparin 4,000 USP Units/4 mL (1,000 USP Units/mL). The study will demonstrate whether Neutrolin® is superior to the active control heparin in reducing the incidence of CRBSI.

1.2 Study Design

This is a randomized, double-blind, active control, parallel-arm, multicenter study. Approximately 900 subjects will be randomized in a 1:1 ratio to receive either Neutrolin® or the active control heparin (Heparin sodium USP 1,000 units/mL, Benzyl alcohol 9.45 mg/mL and Sodium chloride 9.0 mg/mL) as a CLS. Neutrolin® or heparin will be instilled into central venous HD catheters at the discontinuation of all dialysis sessions and will be withdrawn prior to the initiation of the next dialysis session. All subjects will receive standard of care consistent with clinical practice guidelines recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) for the placement, care and use of central venous catheters (CVC) for HD therapy.

The primary endpoint is the presence or absence of a CRBSI (analysis will be made using the time to CRBSI). Subjects are to be followed from randomization (HD catheter will be in place prior to randomization) until occurrence of CRBSI, catheter removal, or the end of the study, whichever occurs first. The study has been designed to continue until approximately 56 subjects have experienced a CRBSI. It is expected that some subjects may be treated for 2 years or more.

1.3 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized in a 1:1 ratio to receive either Neutrolin® or the active control heparin (1,000 USP units/mL) as a CLS. Permuted block randomization (centralized) will be utilized without additional stratification.

1.4 Blinding

This is a double-blind study. The sponsor, subjects and investigator staff will not have access to unblinded data (with the exception of sponsor staff required to be unblinded as needed to make safety reports to regulatory agencies) until the study is unblinded for the final study analysis. Prior to the final study analysis, the DSMB will have access to unblinded data as needed for their review. To maintain the double-blind nature of this study, the DSMB reports will be prepared by an independent statistical group that will not otherwise be involved with the study.

1.5 Sample Size

This trial has been designed to achieve 80% power for the comparison between treatment arms subject to the following specifications: testing will be conducted at a 2-sided overall 5% alpha level using the log-rank test, Neutrolin is associated with a 55% reduction in the risk of CRBSI relative to the control arm, a 1 to 1 ratio will be used for the allocation of subjects to treatment arms, and one interim analysis will be performed at the midpoint of the trial with adjustment of the alpha level using the method of Pocock. Fifty-six CRBSI events in total will be needed to achieve the desired power. The interim analysis will be conducted based on the first 28 CRBSIs. The total sample size is expected to be approximately 900 subjects.

2 Statistical Methods

2.1 Analysis Populations

Three analysis populations will be defined. These populations are

- Randomized Population – all subjects randomized. Subjects will be analyzed according to their allocated group determined by randomization.
- Full Analysis Population – all subjects randomized and receiving one or more doses of study medication. This population has been designed to be consistent with the intent-to-treat principle as the decision to begin treatment in this double-blind trial could not be influenced by knowledge of the assigned treatment (ICH-E9). Subjects will be analyzed according to their allocated group determined by randomization.
- Safety Population – all subjects taking at least one dose of study medication. Subjects will be analyzed according to the treatment they actually received. It is expected that the Safety Population will be identical to the Full Analysis Population.

2.2 Study Drug Dosing and Compliance

Study drug dosing will be assessed by calculating the duration of exposure, i.e., the length of time each subject received study drug, the total number of times drug was administered, the total number of vials administered, and the average dose. Study drug compliance will be assessed by calculating, at the subject level, the percentage of dialysis sessions at the study site at which the correct dosing was administered.

2.3 Study Endpoints

Primary Endpoint

CRBSI defined as one positive blood culture (other than for coagulase negative *Staphylococcus*, which requires a confirmatory culture) from:

1. a peripheral site or blood line sample or
2. either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis)

in a patient with no other apparent source of bloodstream infection other than the hemodialysis catheter, as assessed by the Clinical Adjudication Committee (CAC).

Secondary Endpoints

- Catheter Removal: Catheter removal for any reason during the follow-up period of the trial.
- Loss of Catheter Patency: Loss of catheter patency is defined as required use of a tissue plasminogen activating factor (tPA) or removal of the catheter because of dysfunction during the follow-up period of the trial.

2.4 Statistical Assessment of the Trial Objectives

2.4.1 Primary Endpoint Analysis

The primary analysis will be conducted using a log-rank test for the time to CRBSI at an overall 2-sided 5% alpha level. The null hypothesis is that there is no difference in the hazard rates of CRBSI over time between the two treatments. The time until CRBSI will be calculated as the number of days post randomization until the occurrence of a CAC-adjudicated CRBSI or the subject is censored. Subjects without a CRBSI will be treated as censored in this analysis if the catheter is removed for reasons other than CRBSI (e.g., catheter removed because no longer required) or follow-up is completed in the absence of CRBSI. Because an interim analysis for efficacy will be performed, the method of Pocock will be used to control the overall alpha level. Therefore, the nominal significance level at the interim and final statistical analyses for the primary efficacy endpoint will be 0.0294.

The primary analysis will be based upon the Full Analysis Population. While testing will be based upon the log-rank test, the estimated treatment effect will be the difference between treatment groups in the incidence rate of CRBSI, calculated as the number of subjects with a CRBSI divided by the number of catheter-days of follow-up over subjects (follow-up will be based upon the same time as used for the log-rank test). The rates will be presented as the event rates per 1000 catheter-days with a 95% confidence interval for the purpose of comparison of rates between the treatments. This confidence interval will be derived assuming that the number of catheter-days until CRBSI follows an exponential distribution.

In the primary analysis of the primary endpoint, cases considered to be indeterminate by the CAC will be excluded. A sensitivity analysis will be performed in which cases considered to be indeterminate will be treated as CRBSI events.

2.4.2 Secondary Endpoint Analyses

Time until catheter removal for any reason and time to loss of catheter patency will be analyzed using similar methods as for the primary analysis in the Full Analysis Population. Loss of catheter patency is defined as required use of a tissue plasminogen activating factor (tPA) or removal of the catheter due to dysfunction. For these endpoints, subjects will be considered censored as of their final clinical assessment if the event of interest is not observed. Otherwise, the event time will be the number of catheter-days between randomization and the event. The fixed sequence testing procedure will be used for the comparison of the two treatments with respect to the efficacy endpoints. Therefore, the analysis comparing the two treatments for catheter removal for any reason will be formally conducted only if the analysis for the primary effectiveness endpoint yields a statistically significant result favoring Neutrolin®, and the analysis comparing the two treatments for loss of patency will be formally conducted only if the analysis for catheter loss for any reason also yields a statistically significant result favoring Neutrolin®.

In addition to basic descriptive statistics, the rates per 1000 catheter-days of follow-up will be presented for both endpoints. Also, the reason for catheter loss will be summarized by treatment group.

2.5 Study Day and Visit Windows

Study day is defined as

$$\text{Study Day} = \begin{cases} \text{event date-randomization date} + 1 & \text{(on or after the day of randomization)} \\ \text{event date-randomization date} & \text{(before the day of randomization)} \end{cases}$$

The following data will be collected at each dialysis session (2 or 3 times per week) until study completion:

- weight
- vital signs (temperature, blood pressure, pulse, respiratory rate)
- exit site assessment
- mean blood flow (Qb)
- adverse event assessment
- interventions such as thrombolytic therapy
- CRBSI assessment
- concomitant medications

The following data will be collected monthly:

- weight
- vital signs
- hematology
- chemistry
- dialysis treatment adequacy assessment - Single pool Kt/V (Sp Kt/V)
- concomitant medications

For descriptive analyses that may require the assignment of visits to months (e.g., hematology graphs), assessments will be assigned to analysis months (every 4 weeks) based upon the date the assessment took place regardless of the CRF page completed. Assessments will be mapped to visits as outlined in Table 1. Should more than one assessment exist within a given visit window the value closest to the scheduled visit should be used (choose the later visit if equally close). For data collected at each dialysis visit, analysis windows will not be assigned, and the nominal visits (week/day) will be used for data display.

Table 1 Monthly Visit Windows

Visit	Start of Window	End of Window
Baseline	Date of informed consent	0
Month 1	1	41
Month 2	42	69

Month m	m*28-14		m*28+13

For subjects where the reference date is missing, the study day will also be missing.

2.6 Handling of Missing Data

The primary and secondary analyses have been designed to characterize the risk of various events for the time period each subject has his or her first on study catheter. In this framework, missing data will exist if a subject discontinues follow-up for these events while the study is ongoing and the initial catheter is still in place. The statistical technique that will be used in the primary statistical analysis to deal with missing data is to treat the subject as censored at the time the catheter is removed for reasons other than CRBSI or follow-up is prematurely discontinued. This method will be appropriate if the reason for discontinuing follow-up is not related to a change in the subject that would be predictive of an increased risk of a CRBSI.

To explore the reasons for missing data and to assess any bias associated with premature discontinuation, all reasons for subjects terminating study follow-up will be summarized by treatment arm.

A sensitivity analysis will be performed in which cases considered to be indeterminate by the Clinical Adjudication Committee are treated as CRBSI events.

2.7 Safety Analyses

Statistical analyses will be descriptive in nature and testing for statistical significance will not be routinely applied. Safety analyses will be based upon the clinical database only. Events recorded in the safety database will be reconciled with the clinical database prior to database lock.

2.8 Interim Analysis

A DSMB will meet periodically to review the accumulating study data. The primary purpose of these reviews is to monitor safety and data quality.

Additionally, the DSMB will oversee interim analyses for efficacy and for futility that will be performed when 28 CAC-adjudicated CRBSI events (1/2 of the required total number of 56 events) have occurred. If statistical significance is obtained for the primary efficacy endpoint at this time, the recommendation will be to stop the study early for efficacy. If the futility analysis indicates that continuing the study would be futile, the recommendation will be to stop the study early for futility. In either case, the DSMB will report its recommendation only to the CorMedix Executive Committee, which will make the final decision as to whether or not to stop the study in consultation with the FDA.

3 Summary Tables Listings and Figures

3.1 General Conventions

Unless otherwise stated, summary statistics including the number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median

values to one more, and the standard deviation, to two more decimal places than the raw values. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

For efficacy and safety analyses, age will be calculated relative to the date of randomization.

For adverse events reported on a per-subject basis, medical history and concomitant medications, the denominator for the percentage calculation will be the number of subjects in the analysis population and in the subgroup of interest at risk in each treatment arm.

All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001".

All non-efficacy summary tables will use either the Randomized Population or the Safety Population. All efficacy summary tables will use the Full Analysis Population unless specified otherwise. Summaries will be provided by treatment group.

Not all data collected (e.g., vital signs at each dialysis visit) will be summarized or listed. All such data will be included in the appropriate analysis file for display and summarization as needed during the preparation of the clinical study report (i.e., ad hoc displays).

3.2 Subject Disposition and Treatment

The total number of subjects screened, randomized, completed, discontinued from the study, and in each analysis population will be summarized by treatment group and overall. The reason for termination for all subjects who discontinued will be summarized by treatment group and overall. A listing of subjects who discontinued from the study by reason for termination will also be presented.

Subjects randomized but not included in a given analysis population will be summarized by analysis population and the reason for exclusion will be presented.

3.3 Violations of Inclusion/Exclusion Criteria

Subjects enrolled in the trial without meeting the inclusion/exclusion criteria will be summarized for the Randomized Population with the following information: treatment assigned and inclusion/exclusion criteria violated.

3.4 Study Treatment

The following information will be presented by treatment arm and overall:

- duration of exposure
- total number of times drug administered
- total number of vials administered
- average dose
- compliance (100*No. of dialysis sessions at study site at which the correct dosing was administered/total number of dialysis sessions at study site)

- dose interruptions: percentage of months with dose interruptions and percentage of months with more than 3 consecutive missed doses.

3.5 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Randomized Population. No statistical testing will be performed. Baseline characteristics will include summaries of the following:

- Subject demographics including age, sex, and race
- Baseline disease characteristics
- Pre-existing medical conditions
- Prior therapies

3.5.1 Medical History

Medical history will be descriptively summarized based upon the MedDRA system organ class (SOC) and preferred term by treatment and overall for the Safety Population. Data summaries will be sorted by the overall frequency of reporting within SOC.

3.6 Clinical Data

3.6.1 Concomitant Medications

Concomitant medications will be descriptively summarized based upon the coded values (WHO) by treatment for the Safety Population. Data summaries will be sorted by the overall frequency of recorded use. Medications with end dates prior to dosing will not be included in these summaries. A table of medications used prior to dosing (including routine medications given with HD) will also be provided.

3.7 Analysis of Efficacy Endpoints

3.7.1 CRBSI

The clinical criteria associated with CRBSI will be summarized by treatment group. This summary will consist of the number and percent of subjects with each of the following

- Fever (defined as ≥37.8° C)
- Rigors, defined as shivering from a feeling of being cold, often with copious sweating, as documented by a medical professional
- Tachycardia, defined as a heart rate greater than 100 beats per minute
- Tachypnea, defined as a RR greater than 24 breaths per minute
- Low blood pressure, defined as a systolic blood pressure less than 90, as measured by a clinician (RN or MD) with a BP cuff, or a decrease in blood pressure greater than 30 mmHg
- An obvious change in mental status from previously documented baseline

A listing of this information will also be provided.

3.7.2 Primary Efficacy Analysis

The number of subjects in each treatment arm will be summarized in the Full Analysis Population using the following categories:

- Occurrence of CAC-adjudicated CRBSI,
- Subject followed without occurrence of CAC-adjudicated CRBSI at the time the study was closed to further follow-up, or
- Subject was censored (provide count for each reason censored) for other reasons.

The p-value for the log-rank comparison, hazard ratio (HR) with 95% confidence interval (active/control), and the incidence of CRBSI with 95% CI for each treatment group will be presented. The log-rank test will be performed using PROC LIFETEST in SAS. The HR and confidence interval will be calculated using PROC PHREG in SAS with only treatment in the MODEL statement and study day as the response variable.

Kaplan-Meier curves will be displayed by treatment group for the time until CRBSI (implemented using PROC LIFETEST).

3.7.3 Secondary Efficacy Analyses

The analyses of the time until catheter removal for any reason and of time until loss of catheter patency will be based on the Full Analysis Population using the log-rank comparison, hazard ratio with 95% confidence interval (active/control), and incidence of the event of interest with 95% CI. For these endpoints, subjects will be considered censored as of their final clinical assessment if the event of interest is not observed. Otherwise, the event time will be the number of days between randomization and the event.

3.7.4 Additional Analyses

The HR for the primary analysis and relative risk for the incidence rates (along with 95% CIs for both) will be presented (tabular summary and graphically using a forest plot) for subgroups formed by the following variables (at baseline):

- age (< 65, ≥ 65 and ≥ 75 years of age)
- race
- sex
- diabetes
- months receiving dialysis ($\leq$12 months vs. $>$ 12 months)
- port location, and
- catheter type

3.8 Analysis of Safety Endpoints

All of the tables described in the following are to be conducted using the Safety Population.

3.8.1 Brief Summary of Treatment Emergent Adverse Events (TEAEs)

Adverse events are defined as treatment emergent if they start or worsen after a subject's first administration of study CLS. A brief summary of TEAEs, serious TEAEs, TEAEs leading to death,

TEAEs leading to drug discontinuation, TEAEs leading to study discontinuation, study drug-related TEAEs, and serious study drug-related TEAEs will be presented by treatment arm and overall. The total number of TEAEs and the number and percentage of subjects with at least one TEAE will be presented summarized by severity and by relationship to study drug for each treatment arm and overall. This information will also be listed.

3.8.2 TEAEs by System Organ Class and Preferred Term

The number and percentage of subjects reporting TEAEs will be tabulated by preferred term and system organ class (SOC) for each treatment group. TEAEs will be classified by SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Similar summaries will be produced for SAEs, TEAEs leading to termination, severe TEAEs, and TEAEs with a relationship to the investigational product.

TEAEs will also be summarized by SOC, preferred term, and severity and by SOC, preferred term and relationship to study medication. In the event of multiple occurrences of AEs with the same SOC/preferred term in one subject, the AE will be counted once as the occurrence with the highest severity or closest relationship for the summaries by severity and relationship, respectively.

3.8.3 Clinical Laboratory Tests

Descriptive statistics will be calculated for clinical laboratory tests (hematology, serum chemistry) at applicable visits. Where applicable, changes from baseline will be summarized by treatment group.

3.8.4 Vital Signs

Vital signs, actual values and changes from baseline, will be summarized by treatment group for the monthly visit (note, data summaries for each dialysis visit will not be produced) using descriptive statistics.

3.8.5 Other Safety Analyses

Dialyzer blood flow, time between end of last medication and start of treatment, and spKt/V will be summarized by treatment arm using descriptive statistics for a summary of previous dialysis treatment. Dialyzer blood flow, ESA Dose, IV Iron Dose, and Heparin will be summarized by treatment arm and visit using descriptive statistics for dialysis sessions.

3.8.5.1 Pregnancy

Pregnancies will be summarized by treatment arm. Outcomes will be listed for each pregnancy.

4 Changes to the Protocol-Specified Analyses

The definition of the primary endpoint was revised from the protocol, as per agreement with the FDA. It reflects use of a Clinical Adjudication Committee.

The protocol stated that the number and percentage of subjects who received drug or control at all visits will be presented to summarize compliance and duration of exposure, but this will not be done.

The protocol stated that the primary analysis of the primary endpoint would be repeated using all randomized subjects with available data, but this will not be done.

The protocol stated that physical examination data will be summarized descriptively by treatment group, but this will not be done.

The protocol stated that changes in vital signs parameters from baseline will be summarized across treatment groups at each applicable post-randomization visit, but this will be done only for the monthly visits.

The protocol stated that the number and percentage of subjects with abnormal laboratory results will be provided, but this will not be done.

5 References

Pocock, S.J., Group sequential methods in the design and analysis of clinical trials. *Biometrika*, 1977. 64: 191-199.

Approval Sheet

Product:	Neutrolin®
Protocol Number:	LOCK-IT-100
Date:	January 29, 2018

The individuals signing below have reviewed and approve this statistical analysis plan.

Roger B Johnson

Roger B. Johnson, Ph.D.
Director, Biostatistics
Biostatistical Consulting Inc.

29 JAN 2018
Date

Eugene C. Poggio

Eugene C. Poggio, Ph.D.
Chief Biostatistician
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29 JAN 2018
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Liz Masson

Liz Masson
Vice President, Clinical Operations
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29 Jan 2018
Date

Note: Paul Flyer drafted the original SAP and Roger Johnson revised it.

Addendum to Statistical Analysis Plan

A Phase 3, prospective, multicenter, double-blind, randomized, active control study to demonstrate the safety and effectiveness of Neutrolin® in preventing catheter-related bloodstream infections in subjects receiving hemodialysis therapy as treatment for end stage renal disease

LOCK-IT-100

Sponsored by:

CorMedix Inc.

November 10, 2018

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1.0 Introduction

The planned interim analysis of the study was conducted, and the study was stopped at the recommendation of the Data Safety Monitoring Board because of the demonstration of efficacy based on the primary endpoint. The interim analysis was conducted, as planned, based on data through the date of occurrence of the 28th Clinical Adjudication Committee (CAC)-adjudicated catheter-related blood stream infection (CRBSI) (03 December 2017). While the data for the interim analysis were being source verified and cleaned, the study continued and more data were accrued. The purpose of this addendum to the Statistical Analysis Plan (SAP) is to describe (1) planned efficacy analyses of the three efficacy endpoints based on all of the efficacy data through the last patient's last visit (LPLV), (2) planned safety analyses of all of the safety data through the LPLV, and (3) other analyses.

1.1 Efficacy Analyses

Primary Endpoint

The primary endpoint is catheter-related blood stream infection (CRBSI), defined as one positive blood culture (other than for coagulase negative *Staphylococcus*, which requires a confirmatory culture) from:

1. a peripheral site or blood line sample or
2. either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis)

in a patient with no other apparent source of bloodstream infection other than the hemodialysis catheter, as assessed by the Clinical Adjudication Committee (CAC).

The primary analysis of the primary endpoint was performed at the interim analysis, and it resulted in a positive outcome and the stopping of the study. This analysis of this endpoint represents the final formal analysis for this endpoint. Nevertheless, in order to summarize all of the available information on this endpoint, the analysis of the primary endpoint will be repeated using all of the data through the LPLV. The p-value from this analysis will be reported to provide a measure of the strength of evidence of efficacy from the study but it will not represent a second test of the null hypothesis for this endpoint. As for the interim analysis, the analysis of the primary endpoint based on all of the data through the LPLV will be conducted based on the Full Analysis Population using the Kaplan-Meier method. The time until CRBSI will be calculated as the number of days post randomization until the occurrence of a CAC-adjudicated CRBSI. A patient will be considered to have a CRBSI event if there is a CAC-determined CRBSI. If there is no such CRBSI, the patient will be censored at the earliest of the following dates:

1. Date of catheter removal, if any
2. Date of study completion, if any
3. Date of last study drug dose plus 3 days

Three days was added to the date of last study drug dose because the study drug would be withdrawn at the next dialysis session, which would typically be about three days later.

In this analysis of the primary endpoint, cases adjudicated as indeterminate by the CAC will not be considered to be CRBSI cases. A sensitivity analysis will be performed in which cases adjudicated as

indeterminate will be considered to be CRBSI cases. Subgroup analyses of the primary analysis of the primary endpoint will be conducted as described in the Statistical Analysis Plan. These analyses will be performed based (1) on all of the efficacy data through the data cutoff date for the interim analysis and also (2) on all of the efficacy data through the LPLV.

Secondary Endpoints

The secondary endpoints are as follows:

- Catheter Removal: Defined as catheter removal for any reason during the follow-up period of the trial.
- Loss of Catheter Patency: Defined as required use of a tissue plasminogen activating factor (tPA) or removal of the catheter because of dysfunction during the follow-up period of the trial.

Analyses of these endpoints were conducted and provided to the Data Safety Monitoring Board at the time of the interim analysis. Unlike the primary endpoint, however, the primary analyses of these endpoints will be based on data through the LPLV.

Time until catheter removal for any reason and time to loss of catheter patency will be analyzed based on the Full Analysis Population using the Kaplan-Meier method as for the primary endpoint.

A patient will be considered to have had loss of catheter patency if either of the following conditions are met:

1. If the reason for study completion is specified as "Catheter Removal (not due to CRBSI)" and the reason (for catheter removal) is indicated as being "Catheter Malfunction/Dysfunction – Loss of patency" or
2. If the Reported Name of Drug Med or Therapy (Preferred) is "Alteplase" and the item "For tPA usage, if the usage was directly related to a loss of patency" is indicated as "Yes".

The time of the event will be the number of days between randomization and the event. (If both of the above conditions are met, the date of occurrence of the earlier condition will be used.) If there is no such loss of catheter patency, the patient will be censored at the earliest of the following dates:

1. Date of catheter removal, if any
2. Date of study completion, if any
3. Date of last study drug dose plus 3 days

A patient will be considered to have had a catheter removal if there is a date of catheter removal. If a patient does not have a date of catheter removal, the patient will be considered censored at the earliest of the following dates:

1. Date of study completion, if any
2. Date of last study drug dose plus 3 days

The time to the event will be the number of days between randomization and the event.

1.2 Safety Analyses

Analyses of safety were conducted and provided to the Data Safety Monitoring Board at the time of the interim analysis. The primary analyses of safety, however, will be based on data through the LPLV. These analyses will be conducted as described in the Statistical Analysis Plan.

1.3 Other Analyses

Data for subject disposition, demographics and baseline characteristics, and study treatment will be analyzed as described in the Statistical Analysis Plan. Analyses will be performed based (1) on all of the data through the data cutoff date for the interim analysis and also (2) on all of the data through the LPLV.

Approval Sheet

Product:	Neutrolin®
Protocol Number:	LOCK-IT-100
Date:	November 10, 2018

The individuals signing below have reviewed and approve this addendum to the statistical analysis plan.

Roger B. Johnson, Ph.D. Director, Biostatistics Biostatistical Consulting Inc.	Date
Eugene C. Poggio, Ph.D. Chief Biostatistician Biostatistical Consulting Inc.	Date
Liz Masson Executive Vice President/Head, Clinical Operations CorMedix	11 Nov 2018 Date