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

Document Date: October 6, 2017

NCT02651428

CLINICAL STUDY PROTOCOL

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

Protocol Number:	LOCK-IT-100
Date of Protocol:	October 06, 2017 (Version 8)
Investigational Product:	Neutrolin® (1.35% (13.5 mg/mL) taurolidine, 3.5% (26.1 mg/mL) citrate and heparin 4,000 USP Units/4mL (1,000 USP Units/mL))
Indication:	Prevention of Catheter-Related Bloodstream Infection in Subjects Receiving Hemodialysis Therapy as Treatment for End Stage Renal Disease
IND No.:	113,764
Development Phase:	Phase 3
Sponsor:	CorMedix Inc. 1430 U.S. 206, Suite 200 Bedminster, NJ 07921 Phone: +1 908 517 9500
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GCP Certification:	

SIGNATURE PAGE

STUDY TITLE: 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.

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature: Date:

_____ _____

Antony E. Pfaffle, MD
Chief Scientific Officer
CorMedix, Inc.

_____ _____

Eugene C. Poggio, PhD
Chief Biostatistician
Biostatical Consulting Inc.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated. I will comply with all relevant ICH and GCP requirements during the conduct of this study.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the investigational product (IP) and the conduct of the study.

Investigator's Signature	Date
Name of Investigator (Typed or Printed)	
Institution, Address*	
Phone Number*	
Coordinating Investigator's Signature (where required)	Date
Name of Coordinating Investigator (Typed or Printed)	
Institution	

*If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).

Protocol Synopsis	
Name of Sponsor/Company:	CorMedix Inc.
Name of Finished Product:	Neutrolin®
Name of Active Ingredients:	Taurolidine (1.35% (13.5 mg/mL), 3.5% (26.1 mg/mL) citrate and heparin 4,000 USP Units/4 mL (1,000 USP Units/mL))
Title of Study:	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.
Protocol No:	LOCK-IT-100
Investigators:	Multicenter
Study centers:	Up to 85 centers in the US
Study duration:	Subjects will be followed until a CRBSI has occurred, the catheter is removed, the subject withdraws, or the study is ended.

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.

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 KDOQI for the placement, care and use of central venous catheters (CVC) for HD therapy.

Number of subjects planned and assignment to treatment:

Approximately 900 randomized subjects are planned for this trial. In this study, one-half of the subjects (450 subjects) will receive Neutrolin® and the other half will receive heparin 4,000 USP Units/4mL (1,000 USP Units/mL) with benzyl alcohol preservative as a comparator. Subjects will be assigned in a 1:1 ratio using permuted blocks without

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additional stratification for both groups. For the purpose of this blinded study, the term investigational product will refer to either Neutrolin® or the comparator.

Diagnosis and main criteria for inclusion and exclusion:

Adult subjects (≥ 18 years) with ESRD undergoing chronic HD with a permanent, tunneled silicone or polyurethane catheter that has demonstrated the ability to achieve a minimum blood flow of at least 250 mL/min for at least two consecutive dialysis sessions to enable successful HD. Subjects may not be entered into this trial if they have been treated with antibiotics within 14 days of randomization for any systemic infection or have active exit site infection around the CVC, or received thrombolytic treatment within 30 days of randomization.

Test product, dose and mode of administration:

Neutrolin® and the active control will be packaged in identical vials, and will be used as a catheter locking solution for HD catheters in the following manner:

- Day 1 (day of first administration of blinded, randomized therapy): following randomization and entry into the trial, instill CLS following the index HD episode, as described in the protocol;
- Subsequent HD sessions: CLS will be removed prior to HD and instilled in the catheter following the HD session, as described in the protocol.

Duration of treatment:

Subjects are to be followed from randomization until either:

- The development of a CRBSI;
- Withdrawal from the study;
- 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.

Reference therapy, dose, and mode of administration:

Heparin 4,000 USP Units/4mL (1,000 USP Units/mL) as a CLS for the active control.

Criteria for evaluation:

Primary endpoint: Time to CRBSI:

The primary objective of this study is to demonstrate the effectiveness of Neutrolin® as a CLS in ESRD subjects undergoing HD treatment using a permanent, cuffed, tunneled

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silicone or polyurethane HD catheter. The study will evaluate whether Neutrolin® is superior to the active control heparin by documenting the time to CRBSI and consequently delaying the time until the occurrence of CRBSI.

The definition of CRBSI used in this study requires that the same organism is grown from at least one blood culture from:

- a peripheral site or bloodline sample

and

- either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis).

Blood cultures must be taken from two sites to enhance the validity of the culture testing results. One aerobic and 1 anaerobic blood culture bottle should be taken from each site.

If the subject has clinical symptoms, while on or off dialysis, blood cultures will be obtained using peripheral venipuncture from a source not intended for future vascular access, and the venous or arterial hub of the HD CVC (or the venous or arterial dialysis circuit blood line if on dialysis). If a peripheral site is not available, as soon as the patient is evaluated, blood cultures can be obtained from both the venous and arterial hubs of the HD CVC (or the dialysis circuit blood lines if on dialysis), preferably before the study subject receives antibiotics. Ten to twenty mL of blood should be collected, without discarding any of the CLS.

Necessary clinical indication for suspicion of infection includes the following:

One of the following symptoms:

- Fever (defined as ≥37.8° C)
  or
- Rigors, defined as shivering from a feeling of being cold, often with copious sweating, as documented by a medical professional

OR two or more of the following symptoms:

- Tachycardia defined as a heart rate greater than 100 beats per minute
- Tachypnea, as defined as a RR greater than 24 breaths per minute

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- Low blood pressure as 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.

All attempts will be made to document as many signs and/or symptoms as possible at the time of suspected CRBSI.

An investigator may choose to obtain blood cultures on other suspicions of CRBSI, but the CRBSI case definition requires the clinical indication for suspicion of infection criteria listed above in addition to the blood culture criteria listed above. An alternate source of infection should not be clinically suspected.

Clinical Adjudication Committee

While sites will seek to identify that a CRBSI is present and will be responsible for collecting the clinical data and blood cultures as outlined in the protocol, each case will be reviewed by a Clinical Adjudication Committee (CAC) for the final assessment of CRBSI status. The CAC is a multi-disciplinary committee of specialists who will review both the clinical documentation as well as the blood culture results to determine if the case is a CRBSI. However, because the CAC determination is based on data obtained from the clinical sites, and the review cannot be initiated without blood culture results, it is imperative that the sites follow the protocol definition of CRBSI, and collect blood cultures when a CRBSI is suspected.

Secondary Endpoints

1. Catheter Removal:

Catheter removal for any reason, for example as a result of CRBSI, catheter malfunction, or the catheter is no longer needed for hemodialysis, during the follow up period of the trial.

2. Catheter Patency:

Loss of catheter patency following enrollment in the study. Loss of catheter patency is defined as required use of a tissue plasminogen activating factor (tPA) or removal of catheter due to dysfunction.

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Statistical Methods:

Subject demographic, clinical and laboratory data will be summarized by treatment arm using descriptive statistics.

Primary effectiveness analysis:

CRBSI

The time to CRBSI will be compared between the treatment arms using a log-rank test at a 2-sided 5% alpha level. The null hypothesis is that there is no difference in the risk of CRBSI over time between the two treatment groups. Subjects 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 for CRBSI discontinues.

The primary analysis will be based upon the Full Analysis Population defined as randomized subjects receiving at least one dose of assigned treatment. While testing will be based upon the log-rank test, the estimated treatment effect will be the incidence of CRBSI calculated as the number of subjects with a CRBSI episode divided by the duration of follow-up over subjects (follow-up will be based upon the same time as used for the log-rank test). The rate will be presented as the event rate per 1,000 days with 95% confidence interval presented for the comparison of rates between the treatment arms. This confidence interval will be derived assuming that the number of days until CRBSI follows an exponential distribution.

Similar methods of analysis will be used to estimate the overall rate of catheter loss for any reason and the rate of loss of catheter patency. The fixed sequence testing procedure will be used for the comparison of the two treatments with respect to the effectiveness endpoints. Therefore, the analysis comparing the two treatments for catheter loss 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®.

Sample Size

This trial has been designed to achieve 80% power for the comparison between treatment

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arms subject to the following specifications: testing will be conducted at a 2-sided overall 5% alpha level, Neutrolin® is associated with a 55% reduction in the risk (i.e., incidence) of CRBSI relative to the control arm, 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, and the event rates will be monitored over the course of the trial to determine the times of the interim and final statistical analyses. It is expected that approximately 900 subjects will be randomized for this trial.

Safety analyses

The safety information will be presented based upon descriptive analysis characterizing the relative rates of deaths, adverse events, serious adverse events and loss of patency between the treatment arms. The treatment arms will also be evaluated with respect to changes in laboratory parameters.

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LIST OF IN-TEXT TABLES

1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine transaminase (or SGPT)
ANCOVA	analysis of covariance
AST	aspartate transaminase (or SGOT)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control
CAC	Clinical Adjudication Committee
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CK-MB	creatine kinase, muscle and brain (subunits)
CLS	Catheter lock solution
CMS	Center for Medicare and Medicaid Services
CRBSI	catheter related bloodstream infection
CRP	C-reactive protein
CVC	central venous catheter
dL	deciliter
DSMB	Data Safety and Monitoring Board
DRG	Diagnosis-related grouping
ECG	Electrocardiogram
CRF	case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agent
ESRD	end-stage renal disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HD	hemodialysis
ICH	International Conference on Harmonisation
ID	user identification
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ISN	International Society of Nephrology
ITT	intent-to-treat (population)
IV	Intravenous
IVRS	Interactive Voice Response System
KDOQI	Kidney Disease Outcomes Quality Initiative
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
MRSA/MRSE	Methicillin resistant S. aureus/S.epidermidis
NCR	carbonless (no carbon required)
PIN	Personal identification number
PP	per-protocol (population)
PVP	Polyvinylpyrrolidone
Qb	blood flow
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase (or AST)
SGPT	serum glutamic pyruvic transaminase (or ALT)
SmPC	summary of product characteristics

SOP	Standard Operating Procedure
Sp Kt/V	Single pool Kt/V
TEAE	treatment-emergent adverse event
tPA	Tissue plasminogen activator (Cathflo®)
WHO	World Health Organization

2.0 INTRODUCTION

2.1 CLINICAL NEED FOR PREVENTION OF CATHETER-RELATED BLOODSTREAM INFECTIONS

As of December 31, 2010, there were 593,086 End Stage Renal Disease (ESRD) patients in the United States (U.S.), of whom 383,992 were receiving hemodialysis (HD) therapy [1]. For patients on HD, the arteriovenous fistula is the best possible vascular access, due to its high blood flow, low complication rate and longevity [2]. Because of these characteristics the Center for Medicare & Medicaid Services (CMS) and ESRD networks implemented a national vascular access improvement process called "Fistula First" in 2003 [3]. Although this program has increased the numbers of fistulas in both prevalent (patients currently receiving chronic dialysis) and incident (patients starting chronic dialysis) HD patients, an unintended consequence has been to increase the number of patients using central venous catheters (CVC) as their primary source of vascular access. In 2006, 82% of patients in the US started chronic HD with a CVC, while more than 25% of prevalent HD patients used a CVC as their primary vascular access [4].

Infection is the second most common cause of death in HD patients, and the presence of a CVC is a significant risk factor for infection-associated mortality [5, 6]. The frequency of catheter-related bloodstream infection (CRBSI) generally ranges between 2 and 5.5 episodes/1,000 catheter days, which equates to approximately 1 or 2 infections/year in CVC-dependent patients [5, 7]. Given the current prevalent HD population, it is estimated that there are up to 160,000 episodes of CRBSI/year in catheter-dependent patients, and that up to 20% require hospitalization or have serious complications including endocarditis, septic arthritis, epidural abscess, osteomyelitis or severe sepsis [6, 7]. A single episode of CVC-related CRBSI in the U.S. has been estimated to cost up to $45,000, and the aggregate yearly cost for all episodes of CRBSI in this population is nearly $800 million [3, 7].

The pathogenesis of CRBSI in CVC-dependent patients is believed to be due to bacterial colonization of the CVC due to biofilm formation [7-9]. Biofilm forms rapidly, usually within 24 hours in all CVCs, and represents a complex bacterial community embedded in a film made up of polysaccharides, minerals and bacteria [8, 10]. Biofilm protects bacteria and is essential for the virulence of most organisms [10]. In HD CVCs, it is recognized that colonization of the catheter occurs commonly, but does not cause overt symptoms or sepsis until reaching a critical colony count [11]. It also appears that bacterial colonization of biofilm can induce chronic inflammation as manifest by resistance to erythropoietin [9, 12].

Current catheter use is associated with a significant increase in morbidity and mortality [3, 13]. All-cause mortality is increased 2-3 fold in patients with CVCs, and is reduced by about 50% in patients that switch from a CVC to either a fistula or graft [4]. Additionally, the relative risk of infection-related hospitalization and death is increased 2-3 fold, and even cardiovascular mortality is increased in this population [3-5, 13]. Chronic inflammation is important in the pathogenesis of cardiovascular disease, and may be the reason that cardiovascular mortality is increased in HD patients with CVCs [4, 13, 14]. CVC use is also associated with catheter malfunction and thrombosis, central

venous stenosis, reduced quality of life, greater risk for inadequate dialysis, and both local and systemic infection [3, 4].

Given the significant morbidity, mortality and cost associated with CRBSI in CVC-dependent patients, it is obvious why prevention of CRBSI is considered one of the most important unmet medical needs in the dialysis population [7, 15].

2.2 BACKGROUND ON CATHETER LOCK SOLUTIONS

The current standard of catheter care is designed to minimize CRBSI and catheter dysfunction due to thrombosis. This generally involves:

- Locking the CVC interdialytically with a heparin-saline solution
- Infection control precautions are taken pre- and post-HD treatment to prevent contamination of the exit site and catheter hub
- Per HD organization-specific policy and procedure if a dressing is ordered by the physician, infection control precautions are taken when catheter dressings are changed around the catheter
- In extremely rare situations, an antibiotic lock might be used for patients with a history of intercurrent CVC infection, particularly if a CVC is the last vascular access possible for the patient.

In the US, heparin is the current standard of care as a CLS to prevent thrombosis. Although there are no large randomized controlled trials supporting a specific dose, heparin has historically been used at a concentration of 5,000 USP Units/mL, and more recently at 1,000 USP Units/mL, with the amount of heparin solution instilled matched to the catheter filling volume [16]. Recently, the American Society of Diagnostic and Interventional Nephrology issued a guidance document recommending the use of 1,000 u/mL heparin (or 4.0% citrate) as the standard CLS, and this standard has been widely adopted in U.S. dialysis units [17]. While heparin is generally considered effective to maintain catheter patency, bacteria such as staphylococcal species survive and commonly create a biofilm in heparin-locked catheters. It is thought that the preservatives in commercially available heparin solutions may provide some degree of antimicrobial activity, but current rates of CRBSI suggests that it has minimal antimicrobial activity [18].

Heparin, however, does not have any anti-infective properties. The search for a locking solution that would contain both anti-thrombotic and anti-infective properties has been ongoing for decades. Antibiotic solutions have been tried but the inevitable growth of resistant bacterial species associated with their prolonged use has limited enthusiasm for their use for prophylaxis against CRBSIs. Concentrated 30% citrate, functions as both an anti-coagulant and anti-infective agent, but when flushing the catheter lock, it may lead to cardiac arrhythmias by inducing severe hypocalcemia. While aspiration of the catheter locking solution prior to catheter use is the standard clinical preference and practice, flushing of catheter lock occurs when either 1) clots or fibrin make aspiration impossible, 2) lapses in medical protocol inevitably occur, or 3) IV access is urgent and medical personnel who are not familiar with hemodialysis do not aspirate and discard the locking solution. Furthermore, catheter overfills at the time of locking and/or subsequent leakage

at the tip or through catheter side-holes are additional concerns. These concepts also apply to higher concentrations of heparin, where a flush of both catheter lumens containing 6 cc of solution will bolus the patient with 30,000 unit of heparin. Thus a locking solution with the least pharmacologic effect and toxicity when injected is most desirable, even though under most circumstances this solution is withdrawn and discarded.

Although there are potentially a number of possible strategies to reduce the incidence of CRBSI in CVC-dependent patients, antimicrobial CLS appear to have the most potential [4]. During the last 8 years, there have been a number of small randomized controlled trials (RCTs) that have clearly demonstrated the effectiveness of antimicrobial CLS in reducing CRBSI [7, 12]. Five of these studies used antibiotics, one used 30% citrate and the other used taurolidine/citrate. Although they appeared to be effective in the short-term, traditional antibiotic CLS have the risk of bacterial resistance or systemic toxicity, and 30% citrate may represent a safety risk [7].

Antimicrobial resistance is a growing concern, and dialysis patients are among those at highest risk for resistant infections. In 2005, just over 15% of the methicillin-resistant *Staphylococcus aureus* (MRSA) infections were seen in dialysis patients [15]. The portion of the HD population at greatest risk appears to be those using CVCs. The same 2005 reports shows that approximately 85% of HD patients with MRSA infections had an invasive device or catheter in place at the time of the infection [15]. The long-term use of prophylactic or therapeutic antibiotics, such as vancomycin, is a risk factor for development of staphylococcal subpopulations with decreased susceptibility against glycopeptide antibiotics, particularly in the patient populations with devices such as CVCs [19]. This data reflects that it will be important to control CRBSIs in a manner that limits the likelihood of greater antimicrobial resistance in the HD patient population.

CLS are also used to reduce the rate of catheter dysfunction due to thrombosis. Catheter dysfunction due to thrombosis can be treated by the instillation of a thrombolytic agent (such as urokinase or tPA) into the catheter lumen [4]. Ultimately, if all interventions are unsuccessful, the occluded catheter is exchanged or replaced.

Based upon current clinical evidence, a product possessing the following characteristics would be an optimal CLS:

- Broad spectrum antibacterial/antifungal:
  - Prevent formation of biofilm
  - Prevent CRBSI
- Maintain catheter useable life:
  - Reduced need for thrombolytics and catheter replacement
  - Reduced need for catheter removal due to CRBSI
- Maintain adequate flow rate:
  - Maximal Qb $\geq$300 mL/min to ensure effective dialysis
- Safe:
  - No bleeding risk
  - Lack of significant exposure to the systemic circulation
- Does not promote emergence of resistant bacterial infections.

Thus, to solve this problem, CorMedix has proposed a catheter locking solution (Neutrolin®) consisting of a combination of:

- Taurolidine as an anti-infective
- Heparin in standard concentrations as an anticoagulant and
- Citrate in relatively low doses to adjust the pH and enhance the solubility of Taurolidine in solution.

Neutrolin® (composed of taurolidine 1.35%, citrate 3.5%, and heparin 4,000 USP Units/4mL (1,000 USP Units/mL)) is a novel antimicrobial and anticoagulant solution, which will potentially satisfy these characteristics. Taurolidine is a non-toxic, broad-spectrum antibacterial and anti-fungal compound that has also been demonstrated to prevent biofilm formation [18, 20]. Taurolidine does not have any known anticoagulant properties. Indeed, early studies of Taurolidine with the addition of citrate as a catheter lock, but without the addition of heparin, were associated with higher rates of catheter thrombosis than those obtained in patients using standard heparin locks. These preliminary observations prompted the addition of heparin to the Taurolidine-citrate lock as noted above. Two RCTs and considerable experiential data have demonstrated the safety and effectiveness of taurolidine and citrate when used as a CLS to prevent CRBSI [21-24].

The most extensive information to date on the risk reduction that might be expected in the current study is perhaps that provided by Murray *et al* [25]. In their study that included 158 *Staphylococcal* bacteremia events in 135,446 catheter-days among tunneled central venous catheter patients, they found a 56% reduction in risk with respect to *Staphylococcal* bacteremia rates when 5000 IU/ml of heparin was replaced with 1.35% taurolidine/4% citrate/500 IU/ml heparin (p=0.004). An observational study by Solomon *et al* [26]. similarly found a 59% reduction in risk of bacteremia when comparing 106 patients (12,036 catheter-days) treated with 1.35% taurolidine/4% citrate/500 IU/ml heparin to 34 patients (6,471 catheter-days) treated with 5000 IU/ml of heparin.

In the past decade, several CLS containing antimicrobial agents have been marketed in countries outside of the US. CorMedix is not aware of any of these products being discontinued or withdrawn for safety-related reasons from any country where they are marketed. These products contain one, two or all three active ingredients of Neutrolin®. These products are listed Table 1.

Table 1: Currently available catheter lock solutions

Product	Company	Mechanism and composition	Launched	Comments
Citra-Lok™	Dirinco Group – Dutch-Swiss Company	Anticoagulant and antimicrobial effect 30 and 46.7% citrate	Available in non US markets. Direct customer sales in EU and distributors elsewhere	Anticoagulant Unable to launch in US due to citrate concentration restriction
TauroSept®	Geistlich/ Gambro	Antimicrobial: 2% taurolidine + PVP	Available in non US markets. Launched in EU	Taurolidine + PVP
TauroLock™	TauroPharm	Antimicrobial & anticoagulant: 1.35% taurolidine + 4% citrate	Available in non US markets. Launched in EU & Middle East 2006	Antimicrobial + anticoagulant
TauroLock-Hep™ 100/500	TauroPharm	Antimicrobial & anticoagulant: 1.35% taurolidine + 4% citrate + heparin 100/500 u/mL	Available in non US markets. Launched in EU in Nov 2007	Antimicrobial + anticoagulant
DuraLock-C™	MedComp – US based company	Anticoagulant and antimicrobial effect 46.7% citrate	Available in non US markets	Has a unique luer lock vial – direct fit to catheter line
Loxxit™	Citra Anticoagulants, Inc. – US based company	Anticoagulant: 46.5% trisodium citrate	Available in non US markets	Was the original company to sell citrate to MedComp prior to removal from the market
Heparin	Generic	Anticoagulant 1,000-5,000 u/mL	Generic. Available in US	Anticoagulant only

2.3 OVERVIEW AND RATIONALE FOR USE OF NEUTROLIN® AS A CATHETER LOCK SOLUTION

Neutrolin®, as noted above, is comprised of 1.35% taurolidine, 3.5% citrate, and heparin 4,000 USP Units/4mL (1,000 USP Units/mL). Taurolidine is a derivative of aminosulfonamide-taurinamide, and is a unique, non-toxic compound with both anti-adherence and antimicrobial properties against a broad range of bacteria and fungi. Additionally, studies have also shown that taurolidine inhibits *Staphylococcus* coagulase (a clotting activator) and other clotting pathways, which may be of further benefit in the maintenance of catheter patency. The antimicrobial properties of taurolidine are hypothesized to be related to its methylol transfer groups that bind irreversibly to bacterial or fungal cell walls.[18] *In vitro* experiments have shown taurolidine to be efficacious in eradicating catheter biofilm caused by a variety of gram-positive and gram-negative bacteria, as well as *Candida albicans*.[18]

Citrate is an effective anticoagulant [27]. Citrate acts as a chelating agent, in particular binding calcium and magnesium. Citrate removes locally available calcium that is required to complete the coagulation cascade. Given this mechanism, the FDA warned against widespread use of citrate at higher concentrations due to the risk of hypocalcemia, when a patient died of cardiac arrest after an inadvertent systemic instillation of 46.7% citrate [28]. Neutrolin® contains 3.5% citrate which would be safe even under the worst-case assumptions for inadvertent instillation and subsequent effects on serum calcium. [29, 30]

The concentration of heparin in Neutrolin® is 4,000 USP Units/4mL (1,000 USP Units/mL), which is now widely used as standard of care in most U.S. dialysis centers. It is thought that this dose will provide a complementary anticoagulation effect to citrate, while reducing the risk that would be associated with inadvertent systemic administration of higher doses of heparin. The active control in this trial is heparin 4,000 USP Units/4mL (1,000 USP Units/mL).

The effectiveness and safety of Neutrolin® as a CLS in subjects with a tunneled silicone or polyurethane HD catheter is being studied for the following reasons:

1. There is a critical unmet medical need to reduce the incidence of CRBSI
2. There is substantial clinical experience with taurolidine/citrate ± heparin CLS – they are currently used extensively in many European countries for this indication, and for which there is considerable safety and effectiveness data
3. Ease of use – instillation methodology is identical to current heparin lock solutions used in clinical practice
4. Good safety profile in the case of inadvertent systemic administration – large doses of taurolidine given as a systemic infusion have shown no measurable effect in large randomized trials, and there is no known systemic activity on the coagulation system or on routine laboratory measurements. [31] The other active ingredients (citrate and heparin) are at low concentrations that would not be expected to cause significant systemic risk

5. Unlikely to cause bacterial resistance – taurolidine is a broad-spectrum antimicrobial agent, which has not demonstrated the emergence of bacterial resistance to date
6. The potential to prevent or reduce colonization of bacteria and fungi within the catheter lumen, thereby reducing the risk from the formation of a microbial biofilm on the luminal surface and
7. The potential to reduce inflammation associated with biofilm formation on HD catheters. [32]

Taurolidine has been used since the 1970's in Europe as an antimicrobial lavage and gel. A solution similar to Neutrolin® (without heparin) was used in combination with the Dialock Hemodialysis Access Device, an implantable hemodialysis access port, in a clinical trial of HD subjects in Germany, performed by Dr. Klaus Sodemann. This pilot study enrolled and examined 70 subjects over a two year period, with very favorable results [20]. In a separate study, Dr. Sodemann described his anecdotal experience treating 53 HD catheter subjects with a taurolidine, citrate CLS combination, which also showed an extremely low rate of CRBSI [22]. A CLS with the active ingredients 1.35% taurolidine, 4% citrate, and heparin (100 or 500 USP Units/mL) is currently marketed in Europe and the Middle East (TauroLock®).

A solution of Taurolidine citrate was granted the CE mark in 2004 and is sold by Tauro-Implant GmbH; the manufacturer of a Taurolidine locking solution for the former Biolink. Subsequently, Tauro-Implant launched a solution containing Taurolidine-citrate and heparin in 2007. CorMedix obtained a CE mark approval for its Taurolidine-Citrate-heparin product (Neutrolin) on July 5, 2013. Neutrolin was granted a CE mark as a Class III Drug-Device with separate reviews by both the Medicinal Evaluation Board of Netherlands and TUV-SUD Germany. It has been in commercial distribution in Germany since December 2013. Neutrolin was initially approved for use in the prevention of CRBSI and maintenance of catheter patency in hemodialysis patients using a tunneled, cuffed central venous catheter for vascular access.

On September 10, 2014, CorMedix was granted label expansion to include approval for additional indications for use in oncology patients receiving chemotherapy, IV hydration and IV medications via central venous catheters. The expansion also included patients receiving medication and IV fluids via central venous catheters in intensive or critical care units (cardiac care unit, surgical care unit, neonatal critical care unit, and urgent care centers). An indication for use in total parenteral nutrition was also approved.

A feasibility trial using taurolidine 1.35% and citrate 3.5% (without heparin) as a CLS in ESRD subjects undergoing HD via a CVC was conducted in the United States by Allon [33]. This trial was performed to evaluate the incidence of CRBSI when taurolidine/citrate solution was used as a CLS in HD catheters over a 90-day period. The study was a prospective, non-randomized, open-label, single arm feasibility study conducted at two centers, and was designed to evaluate the preliminary safety and potential effectiveness of taurolidine/citrate solution to reduce the incidence of CRBSI in subjects using CVCs.

The results of the study suggested that taurolidine/citrate solution had significant antimicrobial effects. In 1,679 catheter days of follow-up, there was only a single

episode of catheter-related bacteremia. These results were compared to three other bodies of data: 1) infection rates reported from the literature; 2) each subject's own experience in their previous 90 days (when only heparin was used as the CLS); and 3) a concurrent cohort of 30 subjects at the Principal Investigator's dialysis center in whom only heparin was used to lock their CVCs. In comparison to each of these groups, the taurolidine/citrate treated subjects had a much lower rate of CRBSI.

The study also evaluated access patency and the incidence of serious adverse events. All adverse events reported in the study were reviewed by an independent medical monitor and adjudicated as to the severity of the event and relation to the investigational product, if any. No serious adverse events, apart from the single episode of CRBSI, were observed in the taurolidine/citrate-treated subjects.

Access patency rates were evaluated by looking at both catheter removal due to presumed thrombotic catheter dysfunction, and the requirement for use of thrombolytic therapy. Freedom from catheter removal represents the overall effectiveness of maintaining the subject's catheter for use as an effective HD access. Catheter removal in the taurolidine/citrate group was similar to literature reports and to concurrent HD subjects at the Principal Investigator's institution who were receiving standard heparin locks. Thrombolytic intervention, however, was higher than expected in the taurolidine/citrate group.

For the current trial, the taurolidine/citrate solution has been optimized by adjusting the pH to be closer to that of blood (adjusted the pH from 5.1-5.6 to the current pH of 5.8-6.3). *In vitro* studies have demonstrated that the optimized pH reduces taurolidine-citrate interactions with red blood cells that may have led to clot formation in the earlier trial. Additionally, in vitro studies as well as experiential clinical data have suggested that at least some subjects benefit from the inclusion of heparin to the locking solution, [23, 24] to complement the antithrombotic properties of citrate. Therefore, heparin is included in the Neutrolin® formulation.

As in the previous study, Neutrolin® is intended to be used in a manner identical to a conventional heparin CLS, and will be instilled into the HD catheter at the discontinuation of each dialysis session and removed prior to the initiation of the next dialysis session. The control arms for this trial will be heparin at a concentration of heparin 4,000 USP Units/4mL (1,000 USP Units/mL). Subjects in both study arms will have the CLS instilled into their catheters in a volume equal to the catheter fill volume. Both the investigational lock solution and the control lock solution are to be withdrawn prior to initiating the next dialysis session.

2.4 SAFETY OF NEUTROLIN®

The three active ingredients in Neutrolin® (1.35% taurolidine, 3.5% citrate, and heparin 4,000 USP Units/4mL (1,000 USP Units/mL)) have been evaluated in pre-clinical studies conducted to assess their stability in solution (data on file). These studies evaluated the active ingredients at various concentrations and conditions with regards to physical and chemical compatibility, biocompatibility, impact on effectiveness for microbial growth inhibition, and impact on anticoagulant properties. These pre-clinical *in vitro* studies demonstrated that the solutions are physically and chemically stable when mixed at

various concentrations and conditions, the component ingredients are biocompatible, the antimicrobial effectiveness of taurolidine is maintained when mixed with citrate and heparin, and combining the active ingredients does not affect the ability of the solution components to prevent coagulation.

In clinical trials using a taurolidine/citrate CLS solution without heparin, an increased need for thrombolytic treatment has been reported in some, but not all studies; however, the rate of catheter replacement due to thrombotic catheter dysfunction has not been different in any of the studies [20, 21, 23, 24, 34]. Based upon discussions with numerous users of the taurolidine/citrate CLS available in the EU, we believe that at least certain populations of HD patients do have an increased requirement for thrombolytic treatment when heparin is not included in the formulation. No other adverse events were associated with the use of the taurolidine/citrate CLS in these previous clinical trials or reports.

Taurolidine is a broad spectrum antimicrobial agent and is commercially available in Germany, Austria, Switzerland, Poland, and the Netherlands as a 2% solution (Taurolin® Geistlich Pharma AG, CH-6110 Wolhusen, Switzerland). Taurolin® is intended for local use, particularly for intraperitoneal use and within the urinary bladder. Intraperitoneal administration of taurolidine has been shown to significantly reduce morbidity associated with peritonitis [36].

Taurolidine has been given systemically to humans in doses up to 30 grams per day with no significant adverse outcomes [31]. The concentration of taurolidine in Neutrolin® is approximately 400 times less than what has been used previously without safety issues, and considered negligible from a safety perspective. It should not be anticipated that taurolidine at 1.35% poses any risk in case of unintended bolus administration.

As noted previously, citrate is known to chelate calcium, and hypocalcemia is a known risk associated with the use of high concentrations of citrate (30% or greater). 4% citrate (alone) has been demonstrated to be equivalent to heparin as a CLS [29, 30] and is more than 10-fold lower than the concentration issued a warning by the FDA [28]. This low citrate concentration is regarded as safe in case of unintended bolus administration, as the citrate would be expected to rapidly distribute in the extracellular space and be metabolized by the liver within minutes [20]. However, it is possible that mild hypocalcemia symptoms might be seen with rapid flushing of Neutrolin®, although such use is not anticipated or recommended [38].

When used as a CLS, heparin has the potential to cause a prolongation of clotting times due to inadvertent escape from the catheter at instillation and between dialysis treatments. Depending on the half-life of the heparin used, there could be an increased bleeding risk for 12-24 hours [16]. The heparin concentration in Neutrolin® is identical to the concentration currently used in clinical practice (1,000 USP Units/mL). Therefore, the bleeding risk associated with inadvertent systemic administration of Neutrolin® should be no greater than current standard of care.

When taurolidine/citrate is used as a CLS for CVCs in other indications where catheter flushing is routine, some subjects have reported an “unusual taste” following infusion, as well as pain with inadvertent injection into a peripheral vein [38].

In studies evaluating the pharmacokinetics of taurolidine given by rapid and high dose peripheral infusion, burning, pain and erythema at the infusion site as well as facial flushing, numbness and pain in the shoulder of the infusion arm have been reported [38]. This is obviously a very different situation from the dosing, site of infusion and intended use compared with Neutrolin®.

The HD catheters utilized in this study are commercially available, tunneled catheters made from silicone or polyurethane. Testing has been performed to demonstrate the compatibility of Neutrolin® ingredients with silicone or polyurethane materials to enable the product to be used with any HD catheter that is made of one of these two materials (data on file). The catheters are not considered part of the drug under investigation and consequently will not be supplied by CorMedix.

Since the initial CE mark approval in Germany in 2013, there has been no serious or unexpected adverse events reported. As part of CorMedix's post approval surveillance program or what the company refers to as the Neutrolin Use Monitoring Program (NUMP), 163 patients on Hemodialysis with chronic cuffed central venous catheter (CVCs), who are being treated with Neutrolin as their catheter lock solution, are being followed. So far, with 163 patients enrolled and 36 reported on representing 1,625 dialysis patient days, no infections have been reported. Occasionally, patients report a mild transient change in taste, which resolves in a few minutes. Based on the prevalence data found in the literature, 2.5-5.5 infections per 1000 dialysis patient days would be expected [5]. No thrombosis or clots were observed in the patient population where, based on information in the literature, we would have expected to see 6.7-26.6/1000 dialysis patient days in a similar number of dialysis patients receiving HD with CVCs over that same time period [40].

2.5 RATIONALE FOR THE FORMULATION OF NEUTROLIN®

Neutrolin® is a CLS that has been developed for use with vascular access devices. Neutrolin® is a proprietary solution containing 1.35% taurolidine, 3.5% citrate and heparin 4,000 USP Units/4mL (1,000 USP Units/mL), as active ingredients. The Neutrolin® solution, as well as the heparin control solution, depending on treatment group, is to be instilled into CVCs for subjects undergoing HD, in a volume equal to the manufacturer’s stated catheter lumen volume. Thus, the instilled solutions are not intended to be infused systemically (although the complete contents of each catheter lumen containing Neutrolin® could be injected without safety concerns). This inadvertent intravenous dose would be 100 fold less than the no observed adverse effect level in the most sensitive animals in toxicology studies.

Taurolidine is primarily used for its broad spectrum, bactericidal, anti-biofilm and anti-adherence properties. Additional benefits include a lack of cross-resistance to commonly used antibiotics. As previously noted, both citrate and heparin are effective anticoagulants. The concentrations of the active ingredients in the Neutrolin® solution are expected to effectively prevent (or increase the time to) catheter-related bloodstream infection, while maintaining catheter patency in a manner that is not inferior to heparin. Further, it is expected that the active ingredients at the planned concentrations will be safe within the planned subject population.

3.0 STUDY OBJECTIVES

3.1 PRIMARY 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.

3.2 SAFETY OBJECTIVES

The safety objectives of this study are to characterize any increased risks associated with the use of Neutrolin® used as a CLS with respect to adverse events and laboratory assessments as well as catheter removal for reasons other than CRBSI.

3.3 PRIMARY ENDPOINT

CRBSI is defined as follows:

CRBSI requires that the same organism is grown from at least one blood culture from:

- a peripheral site or bloodline sample

and

- either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis)

Blood culture procedures are outlined in Section 7.1.4.

Necessary clinical indication for suspicion of infection includes the following:

One of the following symptoms:

- Fever (defined as ≥37.8° C)
  or
- Rigors, defined as shivering from a feeling of being cold, often with copious sweating, as documented by a medical professional

OR two or more of the following symptoms:

- Tachycardia defined as a heart rate greater than 100 beats per minute
- Tachypnea, as defined as a RR greater than 24 breaths per minute
- Low blood pressure as 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.

All attempts will be made to document as many signs and/or symptoms as possible at the time of suspected CRBSI.

An investigator may choose to obtain blood cultures on other suspicions of CRBSI, but the CRBSI case definition requires the clinical indication for suspicion of infection criteria listed above in addition to the blood culture criteria listed above.

If the subject has clinical symptoms, while on or off dialysis, blood cultures will be obtained using peripheral venipuncture from a source not intended for future vascular access, and the venous or arterial hub of the HD CVC (or the venous or arterial dialysis circuit blood line if on dialysis). If a peripheral site is not available, as soon as the patient is evaluated, blood cultures can be obtained from both the venous and arterial hubs of the HD CVC (or the dialysis circuit blood lines if on dialysis), preferably before the study subject receives antibiotics. Ten to twenty mL of blood should be collected, without discarding any of the CLS.

3.3.1 Clinical Adjudication Committee

While sites will seek to identify that a CRBSI is present and will be responsible for collecting the clinical data and blood cultures as outlined in the protocol, each case will be reviewed by a Clinical Adjudication Committee (CAC) for the final assessment of CRBSI status. The CAC is a multi-disciplinary committee of specialists who will review both the clinical documentation as well as the blood culture results to determine if the case is a CRBSI. However, because the CAC determination is based on data obtained from the clinical sites, and the review cannot be initiated without blood culture results, it is imperative that the sites follow the protocol definition of CRBSI, and collect blood cultures when a CRBSI is suspected.

4.0 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN AND PLAN

This is a randomized, double-blind, active-control, parallel-arm, multicenter study. Subject will be followed until a CRBSI has occurred, the catheter is removed, the subject withdraws, or the study is ended.. Approximately 900 subjects with end stage renal disease undergoing HD using a tunneled silicone or polyurethane HD catheter are anticipated be randomized from up to 85 centers in the United States.

Subjects will attend a screening visit up to fourteen days prior to dosing. At this visit entry criteria will be checked and baseline characteristics will be collected. If the subject meets eligibility criteria, at the Baseline Visit, subjects will be randomized and begin the first day of dosing. Study visits will occur on dialysis treatment days. Every four weeks at one of these dialysis visits a more extensive visit will occur including the collection of vital signs and labs, as outlined in section 7.1.5. Subjects are to remain in the study until they have met the primary endpoint, withdrawn from the study, their catheter is removed, or until the study completes.

All subjects will receive standard of care therapy consistent with current practice guidelines, and will be randomized to either Neutrolin® (1.35% taurolidine, 3.5% citrate, heparin 4,000 USP Units/4mL (1,000 USP Units/mL)) or the active control heparin 4,000 USP Units/4mL (1,000 USP Units/mL) in a 1:1 ratio.

4.1.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be formed to periodically review the accumulating study data. The primary responsibilities of the DSMB will be to monitor subject safety and study conduct and to oversee the interim analysis. The DSMB will have access to both unblinded safety and efficacy data. The DSMB will be independent of the sponsor and will consist of 4 individuals, three physicians and one statistician, with relevant clinical and statistical expertise.

The DSMB will oversee the interim analyses for efficacy and for futility that will be performed when 28 CAC-adjudicated CRBSI events have occurred. If statistical significance is obtained for the primary efficacy endpoint, the recommendation will be to stop the study early for efficacy. If the futility analysis indicates that it is futile to continue the study, 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 FDA.

An independent statistical team will prepare the data summaries for DSMB review. No additional study (or sponsor) staff will have access to the unblinded DSMB summaries. A DSMB charter with standard operating procedures to control potential biases will be developed and implemented prior to any data analysis.

4.1.3 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will be formed to review each case of suspected CRBSI and make a final determination of the case status, after a thorough review of the clinical and laboratory data obtained for each suspected case. The CAC will consist of experts in the fields of nephrology and infectious disease. The CAC will independently and critically assess the circumstances surrounding the suspected CRBSI event while remaining blinded to patient treatment assignment.

All study subjects, including those who completed the study prior to implementation of the CAC process, with one or more positive blood cultures (other than for coagulase negative Staphylococcus, which requires a confirmatory culture) will be adjudicated for the presence of a CRBSI event by the CAC, which will remain blinded to treatment assignment. However, because the CAC determination is based data obtained from the investigative sites for suspected CRBSI, and the review cannot be initiated without blood culture results, it is imperative that the sites collected blood cultures when a CRBSI is suspected.

The results of the CAC adjudication will not be provided back to the investigator/site.

4.2 DISCUSSION OF STUDY DESIGN

This randomized, double-blind, active-control, parallel-arm, multicenter study is designed to demonstrate whether the CLS Neutrolin® will reduce the occurrence of CRBSI. Safety and efficacy information, including maintenance of catheter patency and catheter loss, as well as adverse event occurrence will be evaluated against the active control heparin, which is the current standard CLS in United States clinical practice. All subjects will receive standard of care therapy consistent with current clinical practice guidelines and best practices.

The population chosen for this study will be representative of the general HD patient population using CVCs as their vascular access.

Further discussion of the study design is located within Section 5.

5.0 SELECTION OF STUDY POPULATION

This study will enroll subjects with End Stage Renal Disease who are receiving HD treatment using a permanent cuffed tunneled silicone or polyurethane HD catheter as their vascular access. The specific inclusion and exclusion criteria for enrolling subjects into this study are described in the following sections.

5.1 INCLUSION CRITERIA

Potential study subjects must satisfy the following criteria to be enrolled into the study:

All subjects 18 years or older (meeting the following inclusion criteria):

1. Subject has ESRD and undergoes chronic HD at least two times per week

2. Subject has a HD catheter that has demonstrated the ability to achieve a minimum blood flow of at least 250 mL/min for at least two consecutive dialysis sessions to enable successful HD

3. The HD central venous catheter is placed in a jugular or subclavian vein, with the tip of the catheter typically sitting at a junction of superior vena cava and right atrium

4. The subject is not expected to expire within 180 days

5. The subject is likely to require the use of a CVC for at least 60 days

6. The subject (or the legal guardian) understands the nature of the study and provides written informed consent prior to the study enrollment

7. The subject is willing to comply with specified follow-up evaluations and prescribed dialysis therapy and

8. The subject is receiving adequate hemodialysis as assessed by the investigators and based on a single pool Kt/V measurement > 1.2 (within the last 30 days).

9. All females of childbearing potential must have a negative pregnancy test at the screening visit (i.e., subject is not pregnant). Females of childbearing potential must agree to use an acceptable method of contraception for the duration of the study. Reliable forms of birth control are defined as:,
    - Abstinence as documented in the medical records and CRF.
    - Depo-Provera, or other hormonal contraceptive (oral, implant, ring, patch) for the duration of the study. (NOTE: The subject must have used the chosen method of birth control for at least 1 month/cycle prior to enrollment into the study).
    - Double barrier method (spermicidal jelly or foam with condoms or diaphragm.

Subjects that would not be required to use the required birth control methods are those who are:

- Post-menopausal, defined as:
  - 12 months of spontaneous amenorrhea or
  - 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL or
- Surgically sterilized (i.e., previous tubal ligation or hysterectomy).

5.2 EXCLUSION CRITERIA

Subjects who meet any of the following criteria may not be enrolled into the study:

1. Subjects who received antibiotics within the last 14 days

2. Visible evidence of compromised skin integrity is present at the catheter exit site or evidence of a catheter exit site infection

3. Subject has received any thrombolytic treatment (i.e., tPA – Cathflo®) in their current catheter within 30 days of randomization

4. Fill volume of HD catheter is unknown or cannot be determined

5. Subjects using any type of antimicrobial-coated or heparin-coated catheter

6. Documented chronic bleeding diathesis, active or recurrent bleeding within 1 month prior to randomization

7. Documented history of an atrial thrombus or known hypercoagulable state

8. Subjects with open, non-healing skin ulcers

9. Current requirement for systemic immunosuppression that would increase risk of infection; such as:
   a) Steroid dose higher than 10 times the physiologic dose (>50 mg Prednisone/day)
   b) Methotrexate dose sufficiently high to suppress WBC below 5,000
   c) Biologic immunomodulators (anti-TNF, anti-CD4, etc) within 1 month
   d) Azathioprine dose greater than 2.5 mg/kg/day (175 mg for average adult)
   e) Calcineurin inhibitors:
      - cyclosporine dose greater than 8 mg/kg (560 mg for average adult)
      - tacrolimus dose greater than 0.4 mg/kg (30 mg for average adult)
   f) Sirolimus dose greater than 10 mg daily for average adult

10. Active malignancy requiring or anticipated to require chemotherapy likely to cause leukopenia and/or immunosuppression

11. Known allergy or absolute contraindication to citrate, taurolidine or heparin or a history of heparin-induced thrombocytopenia

12. Unstable malignancy

13. Cirrhosis with encephalopathy

14. Subject is currently taking another medication with known systemic drug interaction with citrate, taurolidine, or heparin

15. Subject is currently enrolled in another investigational device and/or drug trial or has participated in another investigational device and/or drug trial within 30 days prior to enrollment

16. Subject is anticipated to receive a renal transplant within 90 days (subjects can be on the transplant list, but a subject with a known or anticipated transplant date within the next 90 days should be excluded)

17. Any other medical condition which renders the subject unable to or unlikely to complete the study, or which would interfere with optimal participation in the study or produce significant risk to the subject.

Subjects who are screened, but are deemed to not meet eligibility criteria may be re-screened one time if subject circumstances have changed or a new catheter has been placed, and the subject is now expected to be eligible (e.g., course of antibiotic therapy is completed more than 14 days from re-screening date). Re-screened subjects must first be approved by the medical monitor. Subject must be off of systemic antibiotics for at least 14 days to be eligible for re-screening, and must meet all other entry criteria on the re-screening date to be eligible. If the medical monitor approves a re-screening, the subject will be assigned a new subject number. Subjects who have been randomized and received at least 1 dose of investigational product cannot be re-entered into the study at a later point.

5.3 STUDY COMPLETION, EARLY WITHDRAWAL, NEW CATHETER PLACEMENT

5.3.1 Study Completion

A subject is considered as completing the study if at least one of the following conditions is met:

- All assessments through study closure;
- CRBSI meeting primary endpoint definition;
- Catheter removal;

- Death;
- Transfer to a non-study site; or
- Termination of dialysis.

5.3.2 Early Withdrawal from Treatment

A subject should discontinue study treatment for any of the following reasons:

1. The investigator believes that for the subject's best interest; or
2. For safety reasons (e.g., an adverse event) the subject should stop treatment; or
3. Subject's request/withdrawal of consent

The subject, if agreeable, will continue to be monitored for safety parameters for 28 days following the last removal of the investigational product. At the end of the 28 day period after withdrawal (+7 days as needed for scheduling), subject should return to the site for a final safety visit, as outlined in 7.1.6.

CorMedix reserves the right to close the investigational site, withdraw a subject (discontinue provision of blinded investigational product treatment), or terminate the study at any time (see Section 11.8).

5.3.3 Interruption of investigational product dosing

Randomized Investigational Product should be administered at all visits starting from day 1 (date of randomization) through study completion unless contraindicated per investigator judgment. Additionally, there may be cases where the subject cannot attend the study center for a regularly scheduled dialysis visit (e.g. hospitalization, travel out of town), requiring an investigational product interruption. If more than 3 consecutive doses are missed, the study site must contact the medical monitor to review the circumstances of the interruption and assess if any additional actions are required.

If an investigational product interruption occurs, the subject should resume randomized investigational product dosing as soon as possible. The Investigational Product administration interruption of more than 3 consecutive doses should be clearly noted within the source documents and in two study records – (1) on the investigational product drug dosing CRF, and (2) on the interruption of investigational product CRF at the next monthly visit.

6.0 STUDY TREATMENTS

6.1 IDENTITY OF INVESTIGATIONAL PRODUCTS

Neutrolin® is a unique formulation of taurolidine 1.35%, citrate 3.5%, and heparin 4,000 USP Units/4mL (1,000 USP Units/mL). Neutrolin® CLS and heparin CLS will be packaged in identical vials. The catheter lock solution is to be instilled in catheters using a volume matching the fill volume of the hemodialysis catheter, which typically varies from 3.6-5.0 mL.

Vials should be stored at controlled room temperature between 15 and 25° C, and should not be frozen. All vials are single use only, and any leftover solution should be discarded according to the institution's procedures for disposal of biohazardous waste.

6.2 BLINDING

The Neutrolin® lock solution will match the control lock solution with respect to volume, color, viscosity, and smell and will be packaged in identical containers (at an off-site, central facility).

The label will remain affixed to the investigational product container and will contain all identifying information except for the identity of the drug contained therein (e.g., active investigational product or active control).

The blind should not be broken until all subjects have completed the study and the database is finalized. The blind should only be broken if specific emergency treatment would be dictated by knowing the treatment status of an individual subject. In such cases, a system will be in place for revealing assigned treatment. **The blind should not be broken without consultation with the Medical Monitor**. The date and reason for the unblinding must be documented.

6.3 TREATMENTS TO BE ADMINISTERED

Neutrolin® or active control (heparin, 1,000 USP Units/mL) will be used as a CLS as follows:

1. Flush each lumen with 10 mL of saline.
2. Withdraw CLS from the vial using a 3 mL or smaller syringe (to ensure accurate volume). Use one syringe for each lumen.
3. Instill CLS into the access device in a quantity sufficient to fill the catheter lumen. Consult the manufacturer's instructions for specific fill volume. CLS is intended to remain inside the access device until the next hemodialysis treatment.
4. Prior to initiation of the next hemodialysis treatment, CLS should be withdrawn from the catheter and discarded according to the institution's biohazardous waste policy.

Day 1 (day of randomization): Following HD treatment, Neutrolin® or heparin control solution will be instilled.

Subsequent dialysis sessions: the lock solution will be removed from the HD catheter (if possible) prior to the initiation of dialysis. At the end of dialysis, Neutrolin® lock solution or heparin control will be instilled as described above.

6.4 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUP

Central randomization will be used for this study. Subjects will be assigned in a 1:1 ratio using permuted blocks without additional stratification.

6.5 SELECTION OF NEUTROLIN® COMPOSITION AND CONTROL

Neutrolin® is available in Europe and the Middle East with a choice of two concentrations of heparin. For this study, the Neutrolin® formulation was selected to match the heparin content of standard care in the United States.

The active control in this trial is heparin 4,000 USP Units/4mL (1,000 USP Units/mL). Although there is no uniform standard, 1,000 USP Units/mL heparin is used in most HD CVCs. [17, 41].

6.6 SELECTION AND TIMING OF THE CATHETER LOCK SOLUTION

As noted above, subjects will be randomly assigned in a double-blind fashion either to Neutrolin® or control group. Given that Neutrolin® and heparin are used as CLS, they will be instilled in both limbs of the subject's HD catheter at the completion of each dialysis session.

The Neutrolin® or control lock solution will be removed prior to each dialysis treatment, and instilled as a fresh lock solution following each dialysis treatment.

6.7 PRIOR AND CONCOMITANT THERAPY/PROCEDURES

Prior and concomitant medications and procedures are recorded throughout the study, including 30 days prior to randomization, in the corresponding CRF. As part of routine medical care, the study nurse should inquire about any new medications and procedures at every routine dialysis visit.

Systemic antibiotic treatment (oral or parenteral) during the study is permitted if required for the treatment of infections documented not to be CRBSI (e.g., pneumonia, urinary tract infection, etc.). Blood cultures should be taken prior to the administration of any systemic antibiotic or antifungal treatments, unless there is a documented microbiological cause other than CRBSI. Systemic antibiotic treatment is permitted as part of standard of care for suspicion of CRBSI once blood cultures are collected.

Randomized investigational product instillation in the HD catheter may continue while receiving systemic antibiotics and after completion of the antibiotic regimen. Investigational product does not need to be interrupted. Use of antibiotic therapy will be collected in the CRF.

All medications different from the investigational product (prescriptions or over-the-counter medications) and procedures administered 30 days prior to randomization, and

during the course of the study until the final safety visit must be documented in the concomitant therapy section of the CRF.

6.7.1 Prohibited Concomitant Medications

The use of systemic antibiotics within 14 days prior to enrollment, as well as any thrombolytic treatment (i.e., tPA – Cathflo®) instilled in their current catheter within 30 days of randomization is prohibited, as outlined in the exclusion criteria (Section 5.2). Current requirement for systemic immunosuppression that would increase risk of infection; such as those described in section 5.2 are also prohibited. If a subject requires treatment with a systemic immunosuppressant at doses higher than described in the exclusion criteria (Section 5.2; Exclusion Criteria 9) then the subject should be withdrawn from the study. There are no other prohibited medications.

6.8 STANDARD OF CARE FOR PREVENTION OF CRBSI

In determining an appropriate standard of care, careful consideration was given to current practice guidelines, clinical practice standards of care, and scientific evidence in support of particular treatments. Guidelines established by KDOQI and the CDC will be used in this trial as implemented by the site [2, 42].

The definition of standard of care for this study is as follows:

1. All catheter and exit site care to be performed only by dialysis staff and subjects trained to do so;
2. Conduct all catheter procedures following CDC best practices and/or facility standard operating procedures;
3. Asepsis will be maintained through preexisting protocol at the study site. For example, use 2% Chlorhexidine in 70% ethanol or acceptable alternative for cutaneous antisepsis unless the subject has a history of sensitivity, in which case Chlorhexidine aqueous or 70% ethanol should be used;
4. Use only sterile gauze or sterile semi-permeable transparent dressings to cover the catheter site.

6.9 STANDARD OF CARE FOR HEMODIALYSIS

All subjects will be provided with standard of care HD treatment according to the prescribing physician's prescription and current standards of care for each dialysis facility. However, this prescription must be intended to provide the subject with a spKt/V of at least 1.2.

The protocol will allow for only the use of a permanent, cuffed, tunneled silicone or polyurethane HD catheter.

6.10 TREATMENT COMPLIANCE

Every effort will be made by the site personnel to ensure that subjects receive catheter lock instillations per protocol and return for scheduled visits. Each dose of blinded investigational product will be administered on the day dictated by the subject's dialysis schedule (refer to Schedule of Assessments table).

6.11 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

It is the responsibility of the clinical investigator to ensure that all investigational product received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained in the Regulatory Binder. The study staff must be instructed to return all original containers to the investigator site secure drug storage area, whether empty or containing investigational product. Investigational product returned by study staff will be stored and disposed of according to the sponsor's instructions. Contents of the investigational product containers must not be combined. The investigational product accountability will be verified by the sponsor or sponsor designee during on-site monitoring visits. Investigational product will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. Investigational product will be stored at room temperature.

The investigator agrees not to supply the investigational product to any person other than sub-investigators, designated staff, and the subjects participating in the study. Investigational product may not be relabeled or reassigned for use by other subjects except under special circumstances approved by the sponsor.

The investigator will retain and store all containers, which are full, empty, or contain unused investigational product, until these containers are inventoried by the sponsor or sponsor's designee. The sponsor or the sponsor's designee will provide instructions, which the investigator agrees to follow to return or dispose of all containers, whether empty or containing investigational product. The investigator agrees neither to dispense the investigational product from, nor store it at, any site other than the study sites agreed upon with the sponsor.

7.0 EFFECTIVENESS AND SAFETY VARIABLES

7.1 SCHEDULE OF ASSESSMENTS

The schedule of study visits and assessments is displayed in the following Schedule of Assessments Table:

Table 2. Study Flow Chart	Screening	Baseline Visit	Routine Dialysis Visits	Monthly Assessments[c]	Per protocol (when CRBSI suspected)[b]	Final Safety Visit
Study Assessments	Day -14 to 0[a]	Day 1	Dialysis visits after day 1, though study completion	Every 4 weeks (+/- 5 days)		28 (+7) days following the removal of last IP dose
Informed consent	X					
Assess inclusion/exclusion criteria	X	X				
Randomization		X				
Investigational product Administration		X	X	X		
Demographics	X					
Medical and surgical history (including vascular access status)	X				Focused	
Medication history	X					
Physical exam	X				Focused	X
Vital signs (Temp, Pulse, Respiratory Rate)	X	X	X	X	X	X
Blood pressure (pre-and post-dialysis)[l]	X	X	X	X	X	X
Height	X					
Weight (pre-and post-dialysis) [j]	X		X	X		X
Blood Cultures[d]					X	
Serum pregnancy test[e]	X			X		X
Blood glucose, leukocyte count, CRP, and procalcitonin					X	
Hematology [f]	X			X		X
Blood chemistry[g] (including adjusted serum calcium and albumin)	X			X		X
spKt/V	X			X		
Dialysis prescription parameters [j]	X	X	X	X		
Dialyzer Blood Flow [j]	X	X	X	X		
Treatment Time [j]	X	X	X	X		
Interventions[h]	X	X	X	X	X	X
Assessment of Skin around catheter[i]	X	X	X	X	X	X
Adverse & clinical endpoint events		X	X	X	X	X
Concomitant medication[k]	X	X	X	X		X
Verify compliance with study product administration				X		

[a] Some historical data earlier than Day -14 may be needed
[b] Document primary endpoint
[c] Visit to occur every 4 weeks concurrently with one of the dialysis treatment visits for the duration of subject participation in the

study.

[d] Blood cultures must be drawn if CRBSI is suspected

[e] Applies only to female subjects of child-bearing potential

[f] Hematology panel: complete blood count (CBC) with differential, platelets, and reticulocyte count (%)

[g] Blood chemistry panel: sodium, potassium, chloride, blood urea nitrogen (BUN), serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin, adjusted serum calcium, serum albumin, carbon dioxide, and glucose

[h] Use of tPA or other thrombolytic treatments

[i] Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising

[j] Parameters determined at each dialysis session

[k] Concomitant medications taken during the 30 days prior to randomization and used any time through the final study visit should be recorded in the concomitant medications CRF. As part of routine medical care, the study nurse should inquire about any new medications at every routine dialysis visit.

[l] Blood pressure for Screening and Final Safety Visits should be taken only pre-dialysis (not post-dialysis), if visit occurs during dialysis session. For the CRBSI assessment, it should be taken at the time of blood culture collection. For all other Assessments, blood pressure should be taken pre- and post-dialysis.

7.1.1 Screening Visit (Day-14 to Day 0)

The screening period starts when the subject signs the informed consent document. Subjects who are screened for eligibility but are not enrolled in the trial must be entered on the Screening Log, indicating the reason(s) for exclusion. The following procedures will be performed within the 14 day period preceding randomization:

- Informed consent
- Review of inclusion and exclusion criteria
- Demographics (including age, sex, race)
- Physical examination and vital signs (NOTE: a physical examination conducted by the investigator within the past 30 days can be an applicable physical examination for study purposes)
- Blood pressure (pre- dialysis if performed at a dialysis session)
- Weight (pre-and post-dialysis, in kg)
- Medical and surgical history
- Height
- Concomitant medications and medication history
- Blood sample for clinical laboratory assessments:
    - Hematology
    - Blood chemistry and liver function
    - Serum pregnancy test (women of childbearing potential)
- Record blood flow (Qb) data for last 2 dialysis treatments for current catheters. If catheter has been in place for < 14 days, document at least 1 Qb from an available dialysis treatment
- Document HD prescription
- Document spKt/V (within the last 30 days)
- Obtain dialysis duration time for last 2 dialysis treatments. If catheter has been in place for < 14 days, document dialysis duration time from all available dialysis treatments

- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g., erythema, edema, induration, or discharge), and bruising
- Document catheter interventions (e.g., use of tPA) used within 30 days prior to screening (current HD catheter).

7.1.2 Baseline Visit (Day 1, Day of Randomization)

The following assessments are to be conducted:

- Confirm inclusion and exclusion criteria (see Section 5)
- Vital signs (before dialysis treatment)
- Blood pressure (pre and post dialysis)
- Randomization
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising
- Administer and document dialysis treatment per dialysis prescription parameters
- Record mean Qb
- Following dialysis, record actual dialysis treatment time
- Adverse and clinical endpoint event assessment
- Concomitant medications (taken in the 30 days prior to randomization)
- Interventions – record use of thrombolytic therapy if required (NOTE: tPA use within 30 days prior to randomization is an exclusion)
- Investigational product administration – instill CLS upon discontinuation of the dialysis procedure using the procedure described in Section 6.3.

All subjects will receive standard of care HD treatment and catheter care as noted in Section 6.8.

7.1.3 Routine Dialysis Visits Until Study Completion

Visits conducted two to three times weekly on regularly scheduled dialysis visit days from study day 1 to study completion:

- Vital signs (before dialysis treatment)
- Blood pressure (pre and post dialysis)
- Weight (pre and post dialysis)
- Review of concomitant medications
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising
- Remove study product from the catheter
- Administer and document dialysis treatment per dialysis prescription parameters
- Record mean Qb
- Following dialysis, record actual dialysis treatment time
- Adverse and clinical endpoint event assessment
- Interventions – record use of thrombolytic therapy if required
- Investigational product administration – instill CLS after dialysis procedure using standard protocol.

7.1.4 Subject Assessment and Management if CRBSI Suspected

Infection monitoring will be done prior to and during all dialysis sessions. Sites are expected to collect data relating to a possible CRBSI occurring at their own facility, but also if the subject is assessed by another facility. If the subject demonstrates clinical signs or symptoms compatible with bacteremia, including any one of the following: change in body temperature, fever, observed rigors; or any two of the following: hypotension, tachycardia, increased respiratory rate, or an obvious change in mental status; or on any other clinical sign or symptom consistent with an infection. Assessment of a CRBSI should also occur under the following circumstances: the prescription of systemic antibiotic or antifungal therapy unless there is a documented microbiological source other than CRBSI, and at the time of catheter removal unless the subject is receiving systemic antibiotic or antifungal therapy or has received such therapy in the previous week.

Blood cultures for the assessment of a CRBSI should be obtained following the procedure documented below. Additionally, vital signs, blood glucose, CRP, procalcitonin, and leukocyte count should be obtained as part of the CRBSI assessment.

Blood cultures must be taken from two sites to enhance the validity of the culture testing results. One aerobic and 1 anaerobic blood culture bottle should be taken from each site.

If the subject has clinical symptoms, while on or off dialysis, blood cultures will be obtained using peripheral venipuncture from a source not intended for future vascular access, and the venous or arterial hub of the HD CVC (or the venous or arterial dialysis circuit blood line if on dialysis). If a peripheral site is not available, as soon as the patient is evaluated, blood cultures can be obtained from both the venous and arterial hubs of the HD CVC (or the dialysis circuit blood lines if on dialysis), before the study subject receives antibiotics. Ten to twenty mL of blood should be collected, without discarding any of the CLS. Site of blood withdrawal (peripheral veinipuncture or catheter hub or dialysis circuit blood line) should be recorded in the CFR.

Blood cultures should be obtained using the following procedure:

- Wash hands and use appropriate personal protective equipment, including gloves
- Clean the arterial port with an alcohol prep pad, allow to dry, and avoid touching the arterial port after cleaning
- Two Bact/Alert system blood culture bottles should be used – 1 for the aerobic culture, and 1 for the anaerobic culture for each site of blood sample collection (CVC/dialysis circuit or peripheral site)
    - Verify that the flip-off caps on the bottles are intact and aseptically remove the cap
    - Clean each bottle with an alcohol prep pad
- Collect specimen in the aerobic bottle first
    - Hold bottle upright and ensure that the bottle remains upright at all times to prevent back flow of culture media into the dialysis arterial line
    - Peel open the BD Vacutainer Safety-Lok Blood collection Set and thread the luer end of the tubing into the vacutainer holder

  - Insert safety-lok blood collection set, with vacutainer attached into the arterial port
  - Push and hold vacutainer holder over the top of the vial to puncture the septum
- Remove holder from the vial and immediately push and hold vacutainer over the second Bact/Alert system blood culture bottle for the anaerobic culture
- When the second bottle is filled, withdraw the vacutainer from the bottle.
- The safety-lok needle should be discarded in a biohazardous sharps container
- Attach the printed labels with patient identifier to the blood culture bottles on the designated area, but do not cover the barcode on the bottle
- Prepare blood culture bottles for shipment to the laboratory.
- Do not refrigerate or freeze the bottles.

The following assessments are to be conducted when a CRBSI is suspected:

- Assessment of CRBSI signs and symptoms
- Vital signs
- Blood pressure
- Assessment for alternate sources of infection
- Focused physical examination (can be performed by appropriately delegated study personnel)
- Blood cultures – Aerobic and anaerobic cultures to be collected as noted above
- Blood glucose, CRP, procalcitonin, and leukocyte count
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g., erythema, edema, induration, or discharge), and bruising, and obtain microbiological cultures if any catheter site exudate
- Document catheter interventions (e.g., use of tPA) used within 30 days.

If a study subject presents to an Emergency Department (ED), urgent care center, or other treatment facility, the PI will coordinate the evaluation of the subject with the treating physician at the facility whenever possible. A review of the hospital records (complete history, physical examination, and progress and discharge notes) will be performed and recorded by the site on the corresponding CRF (e.g., Adverse Event and Concomitant Medication). A CVC and/or peripheral blood cultures will be obtained and the results should be entered on the local lab CRF in Medidata/Rave Any other clinically-indicated testing will be done to rule out other potential causes of bacteremia.

If a study subject receives Emergency Department or inpatient care, the subject or family members should inform the ED or inpatient attending physician that he/she is participating in a study and request that the Study Physician (or designee) be informed and ALL records (including microbiology reports) from the ED or inpatient visit be sent to the Study Physician. The Study Physician (or designee) will provide any Study related information requested by the ED or inpatient physician and will review all records, when received.

7.1.5 Monthly Assessments (+/- 5 days)

The following assessments are to be conducted every 4 weeks (i.e. monthly), and will be conducted as a part of one of the regularly scheduled dialysis treatment visits that occur 3 times weekly:

- Weight (pre-and post-dialysis, in kg)
- Vital signs (before dialysis treatment; monthly assessment is concurrently collected at dialysis treatment visit)
- Blood pressure (pre and post dialysis)
- Blood sample for clinical laboratory assessments:
    - Hematology
    - Blood chemistry and liver function
    - Serum pregnancy test for women of childbearing potential
- Verify compliance with study product administration
- Verify and document dialysis prescription parameters
- Dialyzer blood flow
- Actual treatment duration
- Interventions
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising
- spKt/V
- Concomitant medications
- Adverse and clinical endpoint event assessment (concurrently collected at dialysis treatment visit).

7.1.6 Final Safety Visit (28 days, + 7 days after removal of last dose of investigational product)

This visit would be completed 28 days after the removal of the investigational product from the HD catheter at the scheduled final safety visit for each subject. Subjects will return to a standard of care CLS to be instilled into the HD catheter after the completion of dialysis at this visit. If there is any reason why the subject cannot attend this visit, then the subject assessment should be done in the dialysis unit. There is a +7-day window to allow convenient scheduling.

The following assessments are to be conducted:

- Physical Exam (NOTE: a physical examination may be conducted by an appropriately delegated sub-investigator or medically qualified personnel)
- Vital signs
- Blood pressure (pre and post dialysis)
- Weight (pre- and post-dialysis, in kg)
- Blood sample for clinical laboratory assessments
    - Hematology

  - Blood chemistry
- Serum Pregnancy test
- Concomitant medications taken through the final study visit
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising
- Adverse and clinical endpoint event assessments
- Interventions – record use of thrombolytic therapy if required.

7.1.7 Early Withdrawal Visit for Last Observation

If the subject withdraws early, a visit should be completed at the PI institution whenever possible. If there is any reason why the subject cannot attend this visit, then the subject assessment should be done in the dialysis unit. If the subject has transferred to another unit, the subject should be contacted by telephone in order to obtain the informational components of the visit assessments and every effort should be made to collect the appropriate blood samples. There is a 7-day window allowed in order to allow convenient scheduling.

The following assessments are to be conducted:

- Physical Exam (NOTE: a physical examination conducted by the an appropriately delegated sub-investigator or medically qualified personnel)
- Vital signs
- Blood pressure (pre and post dialysis)
- Weight (pre- and post-dialysis, in kg)
- Blood sample for clinical laboratory assessments
  - Hematology
  - Blood chemistry
- Concomitant medications
- Assess skin around catheter for signs and symptoms of breakdown, infection (e.g. erythema, edema, induration, or discharge), and bruising
- Adverse and clinical endpoint event assessments.

In the event of early withdrawal, the HD catheter should be locked using another non-investigational therapy. The subject, if agreeable, will continue to be monitored for safety parameters for 28 days following the last removal of the investigation product. At the end of the 28-day period after withdrawal (+7 days as needed for scheduling), subject should return to the site for a final safety visit, as outlined in 7.1.6.

7.2 SCREENING/BASELINE ASSESSMENTS

7.2.1 Subject Demographics

The following demographic information will be collected at the screening visit and recorded in the CRF:

- Month, date, and year of birth
- Sex

- Race
- Height (cm)
- Weight (kg).

Weight will be recorded in regular clothing without jacket, coat, or shoes. Weight will also be collected at monthly visits and recorded in the CRF.

7.2.2 Medical and Surgical History

A relevant medical and surgical history will be obtained at the screening visit. The history will be reviewed to assess study eligibility and to provide an overview of the subject's medical history and current status. The history will be obtained, and subsequently coded using MeDRA terms.

In addition, details of the type of HD catheter will be recorded in the CRF. This will include the following:

- Name of tunneled silicone or polyurethane HD catheter, if available
- Manufacturer
- Fill volume per lumen.

7.3 EFFECTIVENESS MEASUREMENTS

Effectiveness assessments are based on the hypotheses that Neutrolin® is superior to heparin and will decrease the risk of CRBSI. CRBSI is the primary endpoint for this trial.

For the purposes of this study, once the subject has been randomized and has received at least one instillation of the assigned lock solution, all episodes that satisfy the definitions in section 7.3.1.1 will be considered definite episodes of CRBSI. Once the infection is confirmed as a CRBSI, the subject will be considered to have satisfied the infection endpoint and will be considered to have completed the study. The subject will receive standard of care therapy for CRBSI and the decision as to removal of the catheter will be left to the PI, although KDOQI guidelines should be followed. The use of an antibiotic CLS to treat the catheter following a documented episode of CRBSI will be discouraged.

Should a subject receive treatment with an antibiotic CLS following confirmation of one positive blood culture, this subject would be discontinued from the study. Documentation of the reason(s) for removal or retention of the catheter following an episode of CRBSI will be recorded in the case report forms.

Blood flow will be monitored during each dialysis session to ensure adequate blood flow is present for successful dialysis.

7.3.1 Primary Effectiveness Endpoint (CRBSI)

The primary endpoint is the occurrence of CRBSI. The primary hypothesis is that Neutrolin® is superior to the active comparator heparin, and will significantly decrease the risk of CRBSI.

7.3.1.1 Definition of CRBSI

CRBSI is defined for this trial as follows: CRBSI requires that the same organism is grown from at least one blood culture from:

- a peripheral site or bloodline sample

and

- either the arterial or venous catheter hub (or the venous or arterial dialysis circuit blood lines if on dialysis).

In the event that a peripheral sample is obtained, the cephalic vein will be avoided for preservation of future vascular access.

Blood cultures must be taken from two sites to enhance the validity of the culture testing results. One aerobic and 1 anaerobic blood culture bottle should be taken from each site.

If the subject has clinical symptoms, while on or off dialysis, blood cultures will be obtained using peripheral venipuncture from a source not intended for future vascular access, and the venous or arterial hub of the HD CVC (or the venous or arterial dialysis circuit blood line if on dialysis). If a peripheral site is not available, as soon as the patient is evaluated, blood cultures can be obtained from both the venous and arterial hubs of the HD CVC (or the dialysis circuit blood lines if on dialysis), preferably before the study subject receives antibiotics. Ten to twenty mL of blood should be collected, without discarding any of the CLS**.**

Necessary clinical indication for suspicion of infection includes the following:

One of the following symptoms:

- Fever (defined as ≥37.8° C)
  or
- Rigors, defined as shivering from a feeling of being cold, often with copious sweating, as documented by a medical professional

OR two or more of the following symptoms:

- Tachycardia defined as a heart rate greater than 100 beats per minute
- Tachypnea, as defined as a RR greater than 24 breaths per minute
- Low blood pressure as 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

All attempts will be made to document as many signs and/or symptoms as possible at the time of suspected CRBSI.

An investigator may choose to obtain blood cultures on other suspicions of CRBSI, but the CRBSI case definition requires the clinical indication for suspicion of infection criteria listed above in addition to the blood culture criteria listed above. No other alternate source of infection should be identified by clinically indicated testing as noted in Section 7.1.4.

7.3.1.2 Clinical Adjudication Committee

While sites will seek to identify that a CRBSI is present and will be responsible for collecting the clinical data and blood cultures as outlined in the protocol, each case will be reviewed by a Clinical Adjudication Committee (CAC) for the final assessment of CRBSI status. The CAC is a multi-disciplinary committee of specialists who will review both the clinical documentation as well as the blood culture results to determine if the case is a CRBSI. However, because the CAC determination is based on data obtained from the clinical sites, and the review cannot be initiated without blood culture results, it is imperative that the sites follow the protocol definition of CRBSI, and collect blood cultures when a CRBSI is suspected.

7.4 SAFETY MEASUREMENTS

Safety parameters will include AEs, clinical laboratory evaluations, vital signs, and physical exam findings.

7.4.1 Adverse Events

An AE is any unfavorable or unintended sign, symptom, or disease temporally associated with the use of the investigational drug whether or not considered related to the investigational drug. Collection of AE data will begin after the subject has signed the informed consent document and end 28 days after removal of the last dose of IP. Adverse events may include:

- Objective signs observed by the PI or study personnel
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study
- Pre-existing conditions that worsen in severity or frequency or have new signs/symptoms associated with them.

Other findings related to out-of-range laboratory values, ECGs, vital signs, etc., considered not clinically significant are not to be recorded in the AE CRF page.

Treatment-emergent AEs (TEAE) will be summarized in tables in the final study report. A treatment-emergent adverse event is an AE that starts or worsens after the subject's first administration of investigational product.

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal

relationship with this treatment. An AE can therefore be any unfavorable and unintended change in structure, function, signs, or symptoms temporally associated with the use of a medicinal product, whether or not related to the product. Worsening of a pre-existing condition is also considered an AE, as is the discovery of an abnormal finding during a physical examination that was not included in the medical history.

Where there is deterioration in the condition for which the investigational drug is being used, there may be uncertainty as to whether this is normal disease progression or an AE related to the investigational drug administration. If it is felt the investigational drug may have contributed to the deterioration, then this must be treated as an AE related to the investigational drug administration.

Causality Assessment of AEs
For all AEs, the PI will provide an assessment of causal relationship to the investigational drug. The causality assessment must be recorded in the AE CRF.

Adverse events will be considered investigational drug related if classified by the PI as possible, probable, or definite. For clarification, those AEs that occur after enrollment, but prior to the first administration of investigational product will be deemed not to be related to the investigational product. Association of AEs to the investigational drug will be made using the following definitions:

- **Probably Not:** The temporal association, subject history, or clinical condition is such that the investigational drug is not likely to have had an association with the observed event
- **Possible:** The event: a) follows a reasonable temporal association with the investigational drug, but b) could have been produced by the subject's clinical condition or other therapy
- **Probable:** The event: a) follows a reasonable temporal association with the investigational drug, b) abates upon discontinuation of investigational drug, and c) cannot be reasonably explained by the subject's clinical condition or other therapy
- **Definite:** The event: a) follows a reasonable temporal association with the investigational drug, b) abates upon discontinuation of investigational drug, c) cannot be reasonably explained by the subject's clinical condition or other therapy, and d) reappears on re-exposure to the investigational drug.

AE SEVERITY ASSESSMENTS

The PI will provide an assessment of the severity of each adverse reaction by recording a severity rating in the AE CRF. Signs and symptoms will be graded by the PI as mild, moderate, severe, or life threatening according to the following definitions:

- **Mild:** Causing no limitation of usual activity; Events are usually transient and easily tolerated, requiring no special treatment and causing no disruption of the subject's normal daily activities

- **Moderate:** Causing some limitations of usual activities; Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures. Moderate experiences may cause some interference with functioning
- **Severe:** Causing inability to carry out usual activities; Events interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment. They are usually incapacitating
- **Life-threatening:** Subject was at immediate risk of death from the event.

ASSESSMENT OF AE OUTCOME

The following definitions of AE outcomes will be used:

- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Not Recovered/Not Resolved
- Fatal
- Unknown.

CLINICAL FINDINGS

Any significant clinical findings in the final examination, including clinically significant laboratory abnormalities at the end of the subject's participation in the study, will be followed until the condition returns to pre-study status or can be explained as not being related to investigational drug. This also applies to all AEs that continue at the Final Safety Visit. Any treatment-emergent adverse event (TEAE) or SAE that occurs prior to the Final Safety Visit or within 28 days after removal of investigational product will be followed until event resolution, or until, in the opinion of the PI, becomes stable.

SERIOUS ADVERSE EVENTS (SAES)

The PI or other study personnel must immediately (within 24 hours of notification) inform the Sponsor/CRO of all SAEs that occur in study subjects.

A SAE is any AE that meets at least one of following criteria:

- Is fatal
- Is life-threatening, meaning the subject was, in the view of the PI, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death
- Is a persistent or significant disability, incapacity, or substantial disruption of the ability to conduct normal life functions
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization that is longer than 24 hours, or a hospitalization that requires an intervention to treat emergent symptomatology (non-diagnostic)
- Is a congenital anomaly or birth defect.

A SAE may also include events that are medically significant in the PI's judgment including medically significant laboratory abnormalities. Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subjects and may require medical or surgical interventions to prevent one of the outcomes as listed as above in this definition. For example, an important medical event may not be immediately life-threatening or result in death or hospitalization but may require intervention to avoid death or life-threatening conditions. In general, medically significant events are those which require medical/surgical intervention to prevent one of the outcomes listed above.

REPORTING OF SAES

All SAEs will be collected starting the day of Informed Consent signature until 28 days following removal of investigational product. All SAEs and deaths due to any cause that occur, are to be reported. SAEs are to be reported whether or not expected and regardless of relationship to investigational product, and must be reported to the Sponsor immediately upon discovery, by entering the SAE into the electronic clinical trial data system (Medidata/Rave), and by using an SAE reporting form provided by the Sponsor, and, if necessary, by telephone to the study Medical Monitor. Any additional SAE information and supporting documentation will be faxed to the safety hotline.

The Medical Monitor will advise the PI regarding the nature of any further information or documentation that is required. The PI should provide the following documentation at the time of notification or as they become available:

- SAE reporting form
- Admission notes
- Progress Notes, including consults (e.g. infectious disease)
- Concomitant and support medication pages
- Relevant diagnostic reports (including Microbiology reports)
- Relevant laboratory reports
- Hospital discharge summary

Notification must include the PI's assessment as to whether the event was or was not related to the use of the investigational product. The contact information for the Medical Monitor is provided in the Regulatory Binder at each study site, in the Contacts section and in the SAE section. In addition, the Sponsor's medical representative's contact information is also provided in the Binder.

All SAEs must be followed until the event resolves or, in the opinion of the PI, becomes stable. The Sponsor will report any serious, unexpected and drug-related AEs to applicable regulatory agencies and make these reports available to the clinical sites.

The PI must also promptly inform the governing IRB of the SAE and/or unanticipated problems involving risk to human subjects or others per the governing IRB's requirements and retain a copy of the submission and responses in the clinical site's regulatory binder.

7.4.2 Pregnancies

Pregnancy is not considered an AE. However, subject pregnancy must be reported by the investigational staff within 24 hours of their knowledge of the event using the pregnancy notification form. Any subject found to be pregnant during Screening will not be randomized into the study. The PI must promptly discontinue investigational product administration for any subject who is found to be pregnant during the study (randomization through Final Safety Visit) and notify the Medical Monitor immediately. Any subject found to be pregnant during the study will be withdrawn from the study. Any subject who is found to be pregnant during the study will be asked to confirm their consent to allow their treating physician to provide CorMedix with follow-up information on the pregnancy itself and the pregnancy outcome (e.g. miscarriage, elective termination, live birth).

7.4.3 Clinical Laboratory Evaluations

Blood samples for central clinical laboratory evaluations will be assessed at specified intervals as outlined in the Schedule of Assessments table. The investigator will also review standard of care monthly local laboratory evaluations, and report any Adverse Events per Good Clinical Practice. The investigator must review the per protocol central laboratory report in a timely manner, document this review by initialing/signing and dating the lab report, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

Clinical laboratory evaluations will include the following tests (at various times, detailed above):

- Hematology: CBC with differential, platelets, and reticulocyte count (%)
- Blood chemistry: calcium, albumin, sodium, potassium, chloride, carbon dioxide, BUN, serum creatinine, and glucose
- Liver function: serum albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and bilirubin
- Serum pregnancy test (women of childbearing potential).

7.4.4 Vital Signs

Sitting systolic and diastolic blood pressure, temperature, pulse rate, and respiratory rate will be assessed at each visit designated within the protocol schedule with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. Temperature will also be recorded.

7.4.5 Physical Examination

A complete physical examination will be performed at baseline and at the study completion visit to identify any changes that occur during the trial. Any abnormal findings will be recorded in the CRF. An assessment of skin around the catheter should be noted on the Physical Examination CRF. Any clinically significant abnormalities present at baseline will be reported as medical history and any clinically significant abnormalities that are develop during the study will be reported as AEs.

7.5 APPROPRIATENESS OF MEASUREMENTS

All measurements will be performed using standard methods that are generally recognized as being reliable, accurate, and relevant. Blood cultures are an established method to assess infections in the medical community. All laboratory measures and dialysis procedures outlined in this protocol are well established and consistent with the current standard of care.

8.0 DATA QUALITY ASSURANCE

According to the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), CorMedix delegates to the CRO the responsibility for implementing and maintaining quality assurance and quality control systems with written SOPs.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Selection of qualified investigators and appropriate study centers
- Investigator meeting(s) and review of protocol procedures and CRF completion with the investigator and associated personnel before enrolling any subjects and during the study as needed
- Written instructions will be provided for collection, preparation, and shipment of laboratory samples, if appropriate
- Central laboratories for clinical laboratory parameters
- Site Initiation visit
- Early site visits post-enrollment
- Routine on-site monitoring visits
- Review of CRFs for accuracy and completeness, resolution of discrepancies with the investigator or designee, as appropriate
- Ongoing site communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report.

In addition, CorMedix and the CRO Clinical Quality Assurance Department may conduct periodic audits of the study processes at the study site, central laboratories, or other vendors. Audits may also be conducted on the clinical database and final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized representatives of CorMedix or the CRO and regulatory authorities.

8.1 MONITORING

The site monitor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will usually be made as soon as possible after enrollment has begun. Subsequent visits are made as needed per the monitoring plan. At these visits, the monitor will compare the data entered into the CRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the CRO site monitor and investigational staff and are accessible for verification by the site monitor. If electronic records are maintained at the investigational

site, the method of verification must be discussed with the investigational staff. At a minimum, source documentation must be available to substantiate: subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and effectiveness parameters; adequate reporting and follow-up of AEs; administration of concomitant medication; drug receipt/dispensing/return records; investigational product administration information; and date of subject completion, discontinuation from treatment, or withdrawal from the study, and the reason if appropriate. Specific items required as source documents will be reviewed with the investigator before the study.

If data are recorded directly into the CRF, at a minimum there should be an entry in the medical record that each of the assessments was done, and by whom and the date it was done.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRF and source documents will be discussed with the investigational staff. CorMedix expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

8.2 DATA MANAGEMENT AND CODING

Data generated within this clinical trial will be handled according to the relevant SOPs of the data management and biostatistics departments of the CRO. Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

8.3 QUALITY ASSURANCE AUDIT

Representatives of the sponsor or sponsor’s delegate may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRF. Subject privacy must, however, be respected.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a regulatory submission. The investigator should immediately notify CorMedix if they have been contacted by a regulatory agency concerning an upcoming inspection.

9.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 DETERMINATION OF 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, Neutrolin® is associated with a 55% reduction in the risk (i.e., incidence) of CRBSI relative to the control arm, 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, and the event rates will be monitored over the course of the trial to determine the times of the interim and final statistical analyses. It is expected that approximately 900 subjects will be randomized for this trial.

9.2 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 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.

9.3 ANALYSIS POPULATIONS

9.3.1 Randomized Population

The Randomized Population will include all subjects randomized. Subjects will be analyzed according to their allocated group determined by randomization.

9.3.2 Full Analysis Population

Subjects will be included in the Full Analysis Population according to the ITT principle for the primary and secondary analyses. The Full Analysis Population will include all subjects randomized and receiving one or more doses of study treatment. Subjects will be analyzed according to their allocated group determined by randomization.

9.3.3 Safety Population

The safety population will include 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.

9.4 SUBJECT DISPOSITION

The total number of subjects screened, randomized, completed, and discontinued from the study 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.

A table summarizing the analysis populations will be presented, with the number of randomized subjects as well as frequencies of exclusion from the respective analysis populations.

9.5 SUBJECT CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group for all subjects randomized.

Baseline characteristics will include a summary of the following:

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

9.6 COMPLIANCE AND DURATION OF EXPOSURE

The compliance and duration of drug or control exposure will be presented by treatment group. The number and percent of subjects who received drug or control at all visits will be presented to summarize compliance and duration of exposure.

9.7 ANALYSIS OF PRIMARY ENDPOINT

The time to CRBSI will be compared between the treatment arms using a log-rank test at an overall 2-sided 5% alpha level. The null hypothesis is that there is no difference in the risk of CRBSI over time between the two treatment groups. Subjects 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 incidence of CRBSI calculated as the number of subjects with a CRBSI episode divided by the number of years of follow-up over subjects (follow-up will be based upon the same time as used for the log-rank test). The rate will be presented as the event rate per 1,000 days with 95% confidence interval for the comparison of rates between the treatment arms. This confidence interval will be derived assuming that the number of days until CRBSI

follows an exponential distribution. The primary analysis will be repeated using all randomized subjects with available data.

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

9.7.1 Analysis of the Secondary Endpoints

Similar methods of analysis will be used to estimate the overall rate of catheter loss for any reason and the rate of loss of catheter patency. Loss of catheter patency is defined as required use of a tissue plasminogen activating factor (tPA) or removal of catheter due to dysfunction. The fixed sequence testing procedure will be used for the comparison of the two treatments with respect to the effectiveness endpoints. Therefore, the analysis comparing the two treatments for catheter loss 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®.

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

9.8 SAFETY

All safety analyses will be performed on the safety population, unless otherwise stated. Routine statistical testing will not be performed.

9.8.1 Adverse Events

AEs will be coded using the MedDRA. Adverse events are defined as treatment emergent if they start or worsen after a subject's first administration of study CLS. All AEs, including treatment emergent AEs (TEAEs), will be summarized by body system, preferred term, and treatment group, with the number of subjects and percentage reporting the event. A similar summary will be produced for SAEs, TEAEs leading to termination, severe TEAEs, and TEAEs with a relationship to the investigational product. Frequency (%) of TEAEs will be calculated for each body system, by preferred term, by treatment group. The severity of the TEAEs and the relationship to study medication will be summarized for each body system and preferred term by treatment group.

Withdrawals due to TEAEs will be summarized for each body system and preferred term by treatment group.

9.8.2 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 across treatment groups. The number and percentage of subjects with abnormal laboratory results will be provided.

9.8.3 Vital Signs, Physical Findings and Other Safety Evaluations

Vital signs and physical examination data will be summarized descriptively by treatment group. Changes in vital signs parameters from baseline will be summarized across treatment groups at each applicable post-randomization visit.

10.0 ETHICS

10.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

The investigator will provide the CRO with documentation of IRB approval of the protocol and informed consent before the study may begin at the study site(s). The investigator will supply documentation to the CRO of required IRB's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of subjects or the conduct of the trial. Similarly, the investigator will submit written summaries of the trial status to the IRB annually, or more frequently if requested by the IRB. Upon completion of the trial, the investigator will provide the IRB with a brief report of the outcome of the trial, if required.

10.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted and the informed consent will be obtained according to the ethical principles that have their origin in the Declaration of Helsinki (2004), the ICH Harmonized Tripartite Guideline for GCP (1997), the US Code of Federal Regulations (CFR) Title 21 parts 50, 56, and 312, and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

10.3 SUBJECT INFORMATION AND CONSENT

The informed consent form will be used to explain the risks and benefits of study participation to the subject in simple terms before the subject will be entered into the study. The informed consent form contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject and/or legal representative, after the receipt of detailed information on the study.

The investigator is responsible for ensuring that informed consent is obtained from each subject or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study medication. The investigator will provide each subject with a copy of the signed and dated consent form and will document in the subject's source notes that informed consent was given.

11 STUDY ADMINISTRATION

11.1 PROTOCOL MODIFICATIONS

Neither the investigator nor CorMedix will modify this protocol without a formal amendment. All protocol amendments must be issued by CorMedix and signed and dated by the investigator. Protocol amendments must not be implemented without prior IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IRB and relevant competent authority. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

In situations requiring a departure from the protocol, the investigator or other physician in attendance will contact the CRO medical monitor (see contact information on the protocol cover page). If possible, this contact will be made before implementing any departure from the protocol. In all cases, contact with the CRO must be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source document will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

11.2 REGULATORY APPROVAL AND NOTIFICATION

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

All investigators must certify that they will comply with all relevant IND and GCP regulatory requirements.

11.3 REQUIRED PRESTUDY DOCUMENTATION

The following documents must be provided to the CRO before shipment of investigational product or control solutions to the investigational site:

- protocol and amendment(s), if any, signed and dated by the investigator
- a copy of the dated and signed written IRB approval of the protocol, amendments, informed consent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee
- name and address of the IRB including a current list of the IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation from the IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion on the study
- regulatory authority approval signed and dated or notification, if applicable

- statement of investigator, if applicable
- documentation of investigator qualifications (e.g., curriculum vitae)
- completed investigator financial disclosure form from the investigator
- signed and dated clinical trial agreement, which includes the financial agreement
- any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- completed investigator financial disclosure forms from all sub-investigators
- documentation of sub-investigator qualifications (e.g., curriculum vitae)
- photocopy of the site signature log, describing delegation of roles and responsibilities at the start of the study
- name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- local laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

11.4 SUBJECT IDENTIFICATION REGISTER AND SUBJECT SCREENING LOG

The investigator agrees to complete a subject identification register to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification register will be treated as confidential and will be filed by the investigator in the trial center file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by initials and assigned number only.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

11.5 CASE REPORT FORM COMPLETION

Case report forms are provided for each subject in an electronic format.

Electronic Data Capture (EDC) will be used for this study. The majority of the study data will be transcribed by study personnel from the source documents onto a CRF and transmitted in a secure manner to the sponsor. Worksheets may be provided for the capture of some data for easier transfer to the CRF. The electronic file will be considered as the case report form.

All data relating to the study must be recorded in the CRF prepared by the sponsor. Data must be entered into CRFs in English. The CRFs are to be completed at the time or near the time of the subject's visit, with the exception of results of tests performed outside the investigator's office or clinic, so that they always reflect the latest observations on the subjects participating in the study. For tests performed outside the investigator's office or clinic, CRFs are to be completed upon receipt of test results.

Every effort should be made to ensure that all subjective measurements (e.g., pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel.

11.6 RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. CorMedix must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from

For case report forms completed on carbonless (NCR) paper, one copy is to be retained in the archives of CorMedix from the country in which the study is performed. A second copy must be archived by the investigator.

If it becomes necessary for CorMedix or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

11.7 STUDY COMPLETION

The final data from the center will be sent to CorMedix or designee no more than two weeks following completion of the final subject visit at that center. Continuation of this study beyond this time must be agreed upon by both the investigator and sponsor and may be implemented without amendment to the protocol.

11.8 STUDY TERMINATION

CorMedix reserves the right to close the investigational site or terminate the study at any time. Investigational sites will be closed upon study completion. An investigational site is

considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by CorMedix or investigator, or termination of a study by CorMedix may include but are not limited to:

- failure of the investigator to comply with the protocol, CorMedix procedures, or GCP guidelines
- safety concerns
- sufficient data suggesting lack of efficacy after conduct of interim analysis
- sufficient data suggesting efficacy after conduct of interim analysis
- inadequate recruitment of subjects by the investigator.

11.9 USE OF INFORMATION AND PUBLICATION

All information, including but not limited to information regarding the CRO or CorMedix operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, and formulation information) supplied by CorMedix to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remains the sole property of CorMedix. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without CorMedix prior written consent.

The investigator understands that the information developed in the clinical study will be used by CorMedix in connection with the continued development of Neutrolin®, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide CorMedix with all data obtained in the study.

The results of the study will be reported in a clinical study report and will contain all data from all investigational sites. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of CorMedix as author and owner of copyright in such work.

Sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to CorMedix for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by CorMedix in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, CorMedix will review these issues with the investigator. CorMedix will not mandate modifications to scientific content and does not have the right to suppress information. The investigator will recognize the integrity of a multicenter study by not publishing data derived from the individual site until the

combined results from the completed study have been published in full, within 12 months after conclusion, abandonment, or termination of the study at all sites, or CorMedix confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

11.10 PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the effectiveness, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

CorMedix ensures that the personal data will be:

- Processed fairly and lawfully
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- Adequate, relevant, and not excessive in relation to said purposes
- Accurate and, where necessary, kept current.

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) before collection of data. Such consent should also address the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

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