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LOCK-IT-100

A Phase III, 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

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The LOCK-IT-100 study was sponsored by CorMedix Inc..

Disclosure Information

- Dr. Anil Agarwal, Professor Medicine, Ohio State University is a consultant to CorMedix Inc.
- Dr. Prabir Roy-Chaudhury, Professor Medicine, University of North Carolina, is a consultant to CorMedix Inc, WL Gore, Medtronic, Bard-BD, Humacyte, Akebia, Vifor-Relypsa, and Bayer. He is Founder and CSO for Inovasc, LLC.
- Dr. Michael Allon, Professor Medicine, University Alabama at Birmingham is a consultant to CorMedix Inc.
- Ms Elizabeth Masson, EVP, Head of Clinical Operations at CorMedix Inc.
- Dr. Eugene Poggio, President, Biostatistical Consulting, Inc, provided statistical services to CorMedix Inc.
- Dr. Paul Chew, Chief Medical Officer at CorMedix Inc.
- Dr. Antony Pfaffle, Chief Science Officer at CorMedix Inc.

Learning Objectives

Discuss the results of LOCK-IT-100, a landmark randomized, controlled trial of an investigational catheter lock solution (CLS) containing taurolidine, which demonstrated a statistically significant reduction in catheter-related bloodstream infections (CRBSIs) in patients on hemodialysis (HD)

Background

- Infections are the 2nd leading cause of death in HD patients
- HD patients are at risk for bloodstream and vascular access infections due to immuno-compromised status and frequent vascular access
- Although central venous catheters (CVC) comprise only 18.8% of HD vascular accesses they account for 69.8% of access-related BSIs (Nguyen et al, 2017)
- Average hospitalization cost of CRBSI is estimated from $17,000-32,000 per episode and is higher with metastatic infections, e.g., endocarditis (Kosa and Lok, 2013)

Neutrolin® Catheter Lock Solution in the EU (1.35% Taurolidine; 3.5% citrate;1000 U/mL Heparin)

Approved in EU via CE Mark as Class III Medical Device in multiple indications that require use of a tunneled, cuffed CVC for vascular access to prevent CRBSIs and to maintain catheter patency:

- Hemodialysis patients
- Oncology patients receiving chemotherapy, IV hydration, and medication
- Patients receiving total parenteral nutrition

Neutrolin® Mechanism of Action

- Taurolidine denatures surface proteins and chemically alters membrane lipids
- Taurolidine has broad spectrum antibacterial and antifungal activity and a mechanism of action that does not lend itself to microbial resistance
- Antimicrobial resistance has not been identified *in vitro* or in clinical use

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Neutrolin® CLS: Mode of Administration

- Neutrolin is instilled in the HD arterial and venous lumens following each dialysis session to the fill volume of each lumen
- It is aspirated, not flushed, before initiation of the next HD session
- There is no intended systemic administration

Taurolidine, Citrate, Heparin (TCH) CLS in HD
Previous Open Clinical Studies in EU Showed Benefit

- Reidenberg et al. (2017) showed Neutrolin reduced CRBSIs compared to recent CRBSI rates in HD
- Murray et al. (2014) showed TCH reduced staph bacteremia compared to historical heparin controls
- Solomon et al. (2012) showed TCH reduced all-cause bacteremias compared to historical heparin controls

Neutrolin®Catheter Lock Solution in the US

- Neutrolin is an investigational new drug being developed as a catheter lock solution (CLS) to prevent CRBSI in patients with ESRD receiving HD through a CVC
- FDA has awarded Fast Track status and Qualified Infectious Disease Product Designation
- The LOCK-IT-100 study was designed to provide evidence of safety and effectiveness of Neutrolin to support the marketing approval as a CLS in the US

LOCK-IT-100: Primary Objective

- To determine the efficacy and safety of Neutrolin as a catheter lock solution compared to heparin (1000 Units/mL) to reduce CRBSI in ESRD subjects
- Primary Endpoint: Time to CRBSI
- Sample Size: 80% power to determine 55% reduction with two-sided 5% alpha level requires 56 CRBSI events

LOCK-IT-100: Secondary Endpoints

- Catheter removal for any reason
  - not needed because of mature AV fistula
  - due to catheter malfunction
- Loss of catheter patency defined as:
  1. rt-PA administration or
  2. catheter removal due to malfunction

LOCK-IT-100:
CRBSI Definitions of Signs and Symptoms

One or more:

1. Fever at or above 37.8° C;
2. Rigors documented by a medical professional

- **AND**

Two or more:

1. Tachycardia >100 bpm;
2. Tachypnea > 24/min;
3. SBP < 90 mm Hg or decrease > 30 mmHg;
4. Obvious change in mental status from documented baseline

- **AND**

LOCK-IT-100: CRBSI Definitions of Signs and Symptoms

- One positive blood culture (other than for coagulase negative Staphylococcus which requires a confirmatory culture) from:

1. A peripheral venipuncture; or
2. The arterial or venous dialysis port (or the venous or arterial dialysis circuit blood lines if on dialysis)

- In a subject with no other apparent source of BSI other than the HD catheter, BSI was assessed by the Clinical Adjudication Committee (CAC) of independent, external experts

LOCK-IT-100:
Definition of Study Completion

- All assessments through study closure
- CRBSI meeting study definition
- Catheter removal for any reason
- Death
- Transfer to a non-study site
- Termination of dialysis

LOCK-IT-100: Key Inclusion Criteria

- ESRD with HD at least twice-per-week
- HD catheter flow at least 250 ml/min
- Int. jugular or subclavian site with tip in RA-SVC junction
- Life expectancy at least 180 days
- CVC use for at least 60 days going forward
- Single pool Kt/V > 1.2 over last 30 days
- Women of childbearing potential with negative pregnancy test and reliable contraception

LOCK-IT-100: Key Exclusion Criteria

- Antibiotics within last 14 days
- Compromised catheter exit site
- rt-PA use within previous 30 days with current catheter
- Fill volume of catheter lumen unknown
- Use of antimicrobial- or heparin-coated catheter
- Active or chronic bleeding diathesis in prior month
- Hypercoagulable status or atrial thrombus
- Open, non-healing ulcers
- Immunosuppression that increases infection risk
- Active malignancy

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LOCK-IT-100
Baseline Demographics (I)
Randomized Population

Demographic	Neutrolin (403) %	Heparin (403) %
Mean age (years) (SD)	60.8 (14.22)	60.9 (14.39)
<65 years (%)	59.3	58.6
≥ 65 to < 75 years (%)	24.6	23.6
≥ 75 years (%)	16.1	17.9
Female (%)	45.7	38.2
White (%)	61.5	65.0
Black or African-American (%)	31.3	27.8
Asian (%)	3.7	4.5

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Baseline Demographics (II)
Randomized Population

Demographic	Neutrolin (403) %	Heparin (403) %
Other Race (%)	3.4	2.7
Hispanic or Latino Ethnicity (%)	43.9	46.9
Diabetes (%)	69.0	68.7
BMI (mean) kg/m^2	29.7	29.2
Months Since 1st Dialysis (SD)	21.2 (37.5)	19.8 (37.0)
≤ 12 Months on Dialysis (%)	67.5	68.5
Internal Jugular CVC (%)	92.1	90.6
Subclavian CVC (%)	7.4	7.7
Other CVC (%)	0.5	1.5

LOCK-IT-100: Primary Endpoint Analysis

- The planned maximum number of events for the primary endpoint was 56 CAC-adjudicated CRBSIs
- A planned interim analysis was to be conducted on the first 28 cases
- At the interim analysis, the unblinded results of the primary endpoint analysis and Serious Adverse Events were provided to the Data and Safety Monitoring Board (DSMB)
- **DSMB recommended termination of LOCK-IT-100 based on an observed 72% reduction in the risk of CRBSI by Neutrolin® compared to heparin**

LOCK-IT-100 Primary Endpoint Interim Analysis at 28 CRBSIs

	Neutrolin (N=327)	Heparin (N=326)
No. (CRBSI/1000 CD)	6 (0.136)	22 (0.491)
Total Catheter-Days Follow-up	43,957	44,823
Hazard Ratio (95% CI)**	0.28 (0.11, 0.70)	
p-value*	.0034	

CD= Catheter-Days

* Log-Rank Test

** Cox Proportional Hazards Model

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LOCK-IT-100 Primary Endpoint
Full Analysis Population at 41 CRBSIs

	Neutrolin (N=397)	Heparin (N=398)
No. (CRBSI/1000 CD)	9(0.133)	32(0.465)
Total Catheter Days Follow-up	67,593	68,890
Hazard Ratio (95% CI)**	0.29 (0.14, 0.62)	
p-value*	.0006	

CD= Catheter-Days

* Log-Rank Test

** Cox Proportional Hazards Model

LOCK-IT-100 Secondary Endpoint
Catheter Removal for Any Reason
Full Population Analysis at 41 CRBSIs

	Neutrolin (N=397)	Heparin (N=398)
Subjects with CVC Removal (%)	236 (59.4)	225 (56.5)
Median Time (days) (95% CI)	197 (171,224)	225 (187,248)
Event Rate/1000 CD	3.48	3.23
p-value*	0.416	
Cox-Proportional Hazard (95% CI)	1.08 (0.90, 1.29)	

*Log-Rank Test
CD= Catheter Days

LOCK-IT-100 Secondary Endpoint
Catheter Removal for Positive Reasons
Full Population Analysis at 41 CRBSIs
Post-Hoc

	Neutrolin (N=397)	Heparin (N=398)
No Longer Needed for HD	162	131
Improved Renal Function	0	1
Total Removals-Positive Reasons	162 (41)	132 (33)
Total Catheter-Days Follow-up	67,780	69,465
Positive Events/1000 CD (95% CI)	2.39 (2.05, 2.79)	1.90 (1.60, 2.25)

CD= Catheter-Days

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LOCK-IT-100 Secondary Endpoint
Catheter Removal for Negative Reasons
Full Population Analysis at 41 CRBSIs
Post-Hoc

	Neutrolin (N=397)	Heparin (N=398)
CRBSI (%)	8 (2.0)	29 (7.3)
All Cath. Malfunction-Dysfunction (%)	62 (16)	57 (14)
Other (%)	4 (1.0)	7 (1.8)
Total	74 (19)	93 (23)
Total Catheter-Days Follow-up	67,708	69,318
Negative Events/1000 CD (95% CI)	1.09 (0.87, 1.37)	1.34 (1.09, 1.64)

CD= Catheter-Days

LOCK-IT-100 Secondary Endpoint
Loss of Catheter Patency
Full Population Analysis at 41 CRBSIs

	Neutrolin (N=397) (%)	Heparin (N=398) (%)
Loss of Catheter Patency (%)	63 (16)	48 (12)
rt-PA for Loss of Patency (%)	46 (12)	33 (8.3)
Catheter removal for Loss of Patency (%)	17 (4.3)	15 (3.8)
Total Catheter Days Follow-up	63,582	65,260
Rate/1000 Catheter Days (95%CI)	0.99 (0.77,1.27)	0.74 (0.55, 0.98)
p-value**	.12	

* CR = Catheter Removal Loss of Patency Malfunction/Dysfunction

** Log-Rank Test

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LOCK-IT-100 Safety
Treatment Emergent Serious Adverse Events
Incidence ≥2% in Either Treatment Arm (Safety Population)

Deaths & AE Preferred Terms	Neutrolin (N=398) %	Heparin (N=399) %
Deaths	4.5	5.3
Device-related Infection	1.5	2.0
Pneumonia	3.0	5.3
Sepsis	2.3	3.5
Acute Myocardial Infarction	1.3	3.3
Cardiac Failure, Congestive	3.0	1.8
Fluid Overload	3.5	3.0
Hypertension	1.0	2.5
Hyperkalemia	2.5	2.0
Respiratory Failure	1.8	2.3

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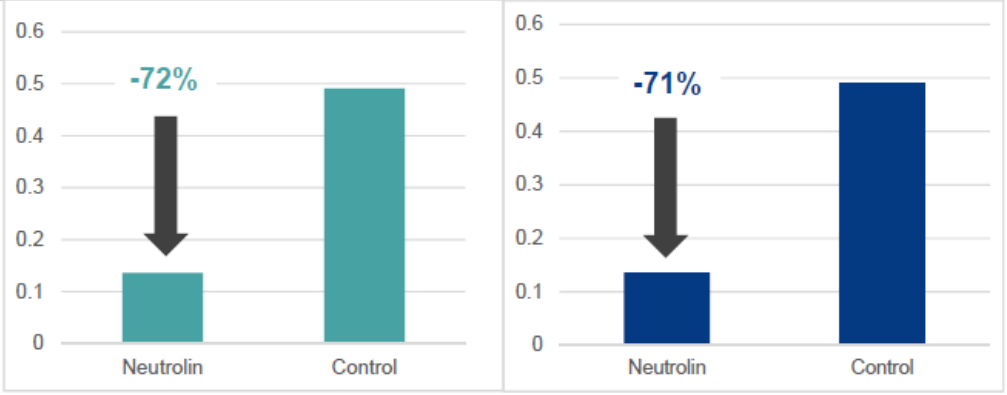
LOCK-IT-100 Primary Outcome Significant Reduction in CRBSIs

	Interim Analysis	Full Study
Total CRBSIs	28	41
Total Subjects	653	795
Neutrolin Reduced CRBSIs by:	72%	71%
Neutrolin (control) Event Rates*	0.136 (0.491)	0.133 (0.465)
p-value	0.0034	0.0006



Conclusion

- LOCK-IT-100, a landmark study, showed that in ESRD subjects with hemodialysis via a central venous catheter, **Neutrolin® catheter lock solution significantly reduced catheter-related bloodstream infections**, a leading cause of mortality in HD
- Compared to heparin, there was no significant difference in either catheter removals for any reason or loss of catheter patency
- Treatment-emergent serious adverse events were infrequent and similar between Neutrolin and heparin arms

Supplementary Resources

- Reidenberg BE, Wanner C, Polsky B, Castanheira M, Shelip A, Stalleicken D, Pfaffle AE. Postmarketing experience with Neutrolin (taurolidine, heparin, calcium citrate) catheter lock solution in hemodialysis patients. Eur J Clin. Microbiol & Infect. Diseases. https://doi.org/10.007/s10096-017-3157-7.
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