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RESEARCH**

APPLICATION NUMBER:

214520Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Summary Review

NDA #	214520
Applicant	CorMedix Inc.
Date of Resubmission	May 15, 2023
PDUFA Goal Date	November 15, 2023
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	See electronic signature
Proprietary Name / Established (USAN) names	Defencath (taurolidine and heparin) catheter lock solution
Dosage forms/Strength	• 3 mL containing taurolidine 40.5 mg/3 mL (13.5 mg/mL), and heparin 3,000 USP Units/3 mL (1,000 USP Units/mL) • 5 mL containing taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL)
Proposed Indication	Reduction in incidence of catheter-related bloodstream infections (CRBSI) in patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC)
Regulatory Action	Approval

1. Background

Defencath is a catheter lock solution (CLS) which contains taurolidine (13.5 mg/mL) and heparin (1,000 USP units/mL) as the active ingredients and citrate as a pH buffer. Taurolidine is a derivative of aminosulfonamide-taurinamide. A proposed mechanism of action for the antimicrobial activity is via transfer of methylol groups that interact with bacterial and fungal cell walls causing damage to the cell walls and inhibiting adherence of microorganisms to biological surfaces. Heparin is included in the solution for its anticoagulant properties. Defencath is instilled within the lumens of the hemodialysis (HD) catheter after HD treatment and withdrawn prior to the next HD session. It is not intended for systemic administration.

The Applicant, CorMedix, originally submitted NDA 214520 on June 30, 2020, and received a Complete Response (CR) letter on February 26, 2021, due to product quality deficiencies. As for clinical data, the Applicant provided adequate information to support the effectiveness of Defencath in reducing the incidence of CRBSIs in patients with kidney failure receiving chronic HD through a CVC. Substantial evidence of effectiveness is provided by data from a single, randomized, active-controlled phase 3 clinical trial. In this trial, Defencath met the primary endpoint of time to CRBSI in demonstrating a 71% risk reduction in CRBSIs (95% confidence interval, 38%, 86%, p value 0.0006) in the Defencath arm versus the heparin comparator arm. Please see the NDA Multidisciplinary Review and Evaluation

signed into DARRTS on February 26, 2021, for additional details related to the original submission.

The Applicant resubmitted the NDA on February 25, 2022, and provided a response to the product quality deficiencies, a request for approval under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), resubmission of request for proprietary name review, clinical safety update report, revised container and carton labeling, and draft labeling (prescribing information). The Applicant received another CR on August 4, 2022, due to unacceptable status of the drug substance (heparin sodium) and drug product manufacturing facilities. Please see the NDA review signed into DARRTS on August 3, 2022, for additional details.

2. Current Submission

The Applicant, CorMedix, resubmitted NDA 214520 on May 15, 2023, in response to the Agency's CR action. The proposed indication and dosing regimen are the same as in the original NDA.

In this submission, the Applicant provided the following: (1) response to product quality deficiencies; (2) description of manufacturing process and process controls for the drug product; (3) data results of batch analysis of the drug product; (4) request for approval under LPAD; (5) revised container and carton labeling; and (6) revised draft labeling (prescribing information).

Product Quality/Chemistry, Manufacturing and Controls (CMC):

During the first review cycle, this NDA was not recommended for approval by the Office of Pharmaceutical Quality (OPQ) due to two Product Quality related deficiencies (Facility and Process) which were included in the CR letter dated February 26, 2021. Specifically, (1) the drug product manufacturing facility (ROVI Pharma Industrial Services S.A.) was found inadequate following a 704(a)(4) based review; and (2) inadequate in-process controls were proposed for the (b) (4) in the drug product manufacturing process. In addition, a comment recommending the inclusion of the (b) (4) in the drug product manufacturing process was also included in the CR letter.

In the second review cycle the fill volume and the (b) (4) issues were addressed adequately; however, the status of the drug product manufacturing facility was again found unacceptable. In addition, the proposed commercial manufacturer of the heparin sodium drug substance ((b) (4)) was also found unacceptable. Therefore, the NDA was again recommended for CR from the Product Quality perspective (refer to the OPQ Review # 3 dated July 28, 2022).

The CMC related changes proposed in the current NDA resubmission include the addition of an alternate heparin drug substance supplier ((b) (4)) and inclusion of the 3 mL fill volume/strength as an additional drug product commercial packaging presentation. There are no changes to the drug product formulation/composition,

container closure or manufacturing process. Several testing sites associated with the proposed addition of (b) (4) as an additional heparin drug substance manufacturer have also been added via this NDA resubmission. The CMC information provided in this NDA resubmission related to the drug product, manufacturing, and microbiological controls has been found acceptable. In addition, all commercial manufacturing facilities currently listed in the NDA, which now include (b) (4) as a new heparin sodium drug substance, have been found acceptable. It should be noted that (b) (4), initially proposed as the commercial heparin sodium manufacturer, was withdrawn by the Applicant from the NDA on September 29, 2023. Therefore, this NDA is now recommended for approval by the OPQ Review Team (*for details refer to the OPQ Review dated November 7, 2023, in DARRTS*)

Clinical/Labeling:

In the resubmission, the Applicant provided a brief safety update, revised labeling, and a request for approval under LPAD.

I. Safety Update

The Applicant has submitted results from a literature review in April 2023 evaluating adverse events related to the use of the product. Two papers were found which included one case report in a patient receiving long-term parenteral treatment and a retrospective study in adults receiving home parenteral nutrition. In the retrospective study, the study drug was instilled and left in the catheters after administration of parenteral nutrition. Upon re-access of the catheters the study drug was flushed into the patients and not withdrawn. There were mild to severe adverse events (AEs) related to the study drug with no deaths. The events included severe AE's such as dyspnea, flushing, rash, and dizziness and more mild symptoms such as dysgeusia, nausea, and malaise. In many of the patients, re-challenge of the study drug did not result in repeat AEs. In the case report, the study drug was instilled into a chest tube catheter and aspirated prior to administering treatment. The Sponsor concludes that these adverse events will not alter the labeling of study drug and in these cases the study drug was not used as intended. All reported AEs were also consistent with the AEs seen in the clinical trial previously submitted by the Applicant.

In both the case report and retrospective study, the study drug was not used as intended by the Sponsor. The study drug is only indicated for renal failure patients who are receiving hemodialysis through a central venous catheter and is meant to be withdrawn and not flushed into the patient. The use, catheter type, and patient population in both studies are not consistent with intended indication of the study drug and there is agreement with the Applicant's evaluation.

II. Labeling

Prescribing Information

This Prescribing Information (PI) review includes a high-level summary of the significant labeling comments/changes (not necessarily direct quotations) and the rationale for major changes incorporated into the finalized PI (the PI that will be approved or is close to being approved). The finalized PI was compared to the Applicant's labeling submitted on May 15, 2023, which was revised per the labeling comments and discussions sent to the Applicant by the FDA on August 4, 2022.

The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 1. Major Labeling Changes and the Rationale for the Changes

Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
HIGHLIGHTS (HL)	• Indications and Usage, Dosage and Administration, Dosage Forms and Strengths sections of the Highlights were updated to align with the changes made to the FPI described below. • In the Adverse Reactions section of the HL, (b) (4) was removed from the listing of the adverse reactions because it is not listed in the adverse reactions table in the Adverse Reactions section of the FPI (subsection 6.1).
FULL PRESCRIBING INFORMATION (FPI) Sections	
1 INDICATIONS AND USAGE	• Added the age group "Adult" to the indication statement and the Limitations of Use statement to provide clear and consistent communication to health care practitioners about the indicated population as per the FDA Guidance for Industry: Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products-Content and Format Guidance for Industry. • The Applicant's proposed Limited Population labeling in the Indications and Usage sections in the HL and FPI were accepted. For additional details, refer to the Limited Population Pathway for Antibacterial and

	Antifungal Drugs (LPAD) Request below and the FDA Guidance for Industry: Limited Population Pathway for Antibacterial and Antifungal Drugs
2 DOSAGE AND ADMINISTRATION	Revised the following proposed statement by the Applicant for clarity to read as, "Use 3 mL or 5 mL single-dose vial (depending on the volume of the catheter lumens) to instill DEFENCATH into the catheter lumens at the conclusion of each HD session for patients with kidney failure requiring chronic HD" instead of "(b) (4) 3 mL (b) (4) 5 mL (depending on the volume of the catheter lumens) (b) (4) DEFENCATH into the catheter lumens at the conclusion of each HD session for patients with kidney failure requiring chronic HD."
5 WARNINGS AND PRECAUTIONS	In subsection 5.1, (Heparin-Induced Thrombocytopenia) and subsection 5.2 (Drug Hypersensitivity), removed the statement (b) (4) from the text because this information is not necessary, and it may be used in promotion to minimize the risk.
6 ADVERSE REACTIONS	In the <i>Clinical Trials Experience</i> subsection 6.1, removed the statement (b) (4) " because (b) (4) is not discussed further in section 14.
14 CLINICAL STUDIES	Removed the statement (b) (4) " since it did not provide any additional details for the information included in section 6 where the results are adequately described.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	- In the product quality sections, the Applicant was requested to specify the two different volumes of the available catheter lock solution (3 mL and 5 mL) with revisions to the presentation format as follows: 3 mL of catheter lock solution in a single-dose vial containing taurolidine 40.5 mg/3mL (13.5 mg/mL), and heparin 3,000 USP units/3 mL (1,000 USP Units/mL) 5 mL of catheter lock solution in a single-dose vial containing taurolidine 67.5 mg/5mL

	(13.5 mg/mL), and heparin 5,000 USP units/5mL (1,000 USP Units/mL) • The following temperature excursion statement was added to the storage conditions in section 16 (How Supplied/Storage and Handling) as per USP: “excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].” • Refer to the Product Quality/Chemistry, Manufacturing and Controls (CMC) section above for additional details.
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Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Carton labeling
- Container labeling

III. Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) Request

The Applicant again requested approval of the NDA under LPAD. The product will be indicated to reduce the incidence of CRBSI in adult patients with kidney failure receiving chronic hemodialysis through a central venous catheter as it has only been evaluated in this specific population with unmet need. Seeking approval under the LPAD pathway is appropriate as the safety and effectiveness of Defencath CLS have not been established for use in populations other than adult patients with kidney failure receiving chronic hemodialysis through a central venous catheter, i.e., Defencath CLS has not been studied in other populations with other types of catheters.

3. Regulatory Action

NDA 214520 for Defencath (taurolidine and heparin) catheter lock solution will receive an approval action.

Reviewers:

Clinical Reviewer: Gregory Mak, MD

Clinical Team Leader: Mukil Natarajan, MD

Application Technical Lead and Cross-Discipline Team Leader: Dorota Matecka, PhD

Associate Director of Labeling: Abimbola Adebawale, MS, PhD

Deputy Division Director: Dmitri Iarikov, MD, PhD

Division Director: Peter Kim, MD, MS

Director, Office of Infectious Diseases: John Farley, MD, MPH

Signatures: *{See appended electronic signature page}*

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NDA Summary Review

NDA #	214520
Applicant	CorMedix Inc.
Date of Resubmission	February 25, 2022
PDUFA Goal Date	August 25, 2022
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	July 31, 2022
Proprietary Name / Established (USAN) names	Defencath (taurolidine and heparin) catheter lock solution
Dosage forms/Strength	Solution/67.5 mg/5 mL (13.5 mg/mL) and 5,000 USP Units/5 mL (1,000 Units/mL), respectively
Proposed Indication	Reduction in incidence of catheter-related bloodstream infections (CRBSI) in patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC)
Regulatory Action	Complete Response

1. Background

Defencath is a catheter lock solution (CLS) which contains taurolidine (13.5 mg/mL) and heparin (1,000 USP units/mL) as the active ingredients and citrate as a pH buffer. Taurolidine is a derivative of aminosulfonamide-taurinamide. A proposed mechanism of action for the antimicrobial activity is via transfer of methylol groups that interact with bacterial and fungal cell walls causing damage to the cell walls and inhibiting adherence of microorganisms to biological surfaces. Heparin is included in the solution for its anticoagulant properties. Defencath is instilled within the lumens of the hemodialysis (HD) catheter after HD treatment and withdrawn prior to the next HD session. It is not intended for systemic administration.

The Applicant, CorMedix, originally submitted NDA 214520 on June 30, 2020, and received a Complete Response (CR) letter on February 26, 2021. Please see the NDA Multidisciplinary Review and Evaluation signed into DARRTS on February 26, 2021, for additional details related to the original submission.

2. Current Submission

The Applicant, CorMedix, resubmitted this NDA on February 25, 2022, in response to the Agency's CR action. The proposed indication and dosing regimen are the same as in the original NDA.

In this submission, the Applicant provided the following: (1) response to product quality deficiencies; (2) request for approval under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD); (3) resubmission of request for

proprietary name review; (4) clinical safety update report; (5) revised container and carton labeling; and (6) revised draft labeling text.

Product Quality/Chemistry, Manufacturing and Controls (CMC):

During the first review cycle, this NDA was not recommended for approval by the Office of Pharmaceutical Quality (OPQ) due to two Product Quality related deficiencies (Facility and Process) which were included in the CR letter dated February 26, 2021. Specifically, (1) the drug product manufacturing facility (ROVI Pharma Industrial Services S.A.) was found inadequate following a 704(a)(4) based review; and (2) inadequate in-process controls were proposed for the (b) (4) in the drug product manufacturing process. In addition, a comment recommending the inclusion of the (b) (4) in the drug product manufacturing process was also included in the CR letter.

In the current NDA resubmission, OPQ notes that the Process deficiency and the comment regarding (b) (4) have been addressed adequately. However, the status of the drug product manufacturing facility (ROVI Pharma Industrial Services S.A.) is still unacceptable based on the most recent inspection conducted during the current review cycle in June 2022. Additionally, the drug substance (heparin sodium) manufacturing site (b) (4) is currently also unacceptable based on a cGMP inspection conducted in (b) (4) and followed by an OAI (Official Action Indicated) letter issued in (b) (4). Due to the unacceptable status of the drug product and drug substance facilities, the overall recommendation of "Withhold" was entered in Panorama for this NDA on July 25, 2022, and this NDA is recommended for Complete Response (CR) by OPQ.

Clinical/Labeling:

In the resubmission, the Applicant provided a brief safety update, revised labeling, and a request for approval under the LPAD pathway.

I. Safety Update

The safety update noted that CorMedix found no new safety information that would reasonably affect the draft labeling. In addition, they report conducting a literature review in February 2022 that revealed no reportable safety events in their global safety database related to taurolidine-containing products.

II. Labeling

The Applicant revised the labeling per the Agency's comments in the February 26, 2021, CR letter.

The following is a high-level summary of the significant labeling

comments/changes (not necessarily direct quotations) added to the prescribing information (PI) submitted on February 25, 2022.

- The Applicant was requested to replace the proprietary name (PN), DEFENCATH with “TRADENAME” throughout the prescribing information (PI) because the PN was denied (please refer to the Proprietary Name Request Unacceptable letter, dated July 20, 2022).
- The Applicant was requested to revise the National Drug Code (NDC) numbers to provide differentiation between the individual vials and the carton containing 25-single-dose vials and add these to the “How Supplied/Storage and Handling” section of the PI.
- The changes listed above will also be updated on the carton and container labeling

III. Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) Request

The Applicant again requested approval of the NDA under the LPAD pathway. Seeking approval under the LPAD pathway would be reasonable, given the limited population studied, i.e., patients with kidney failure receiving chronic HD through a CVC, in whom the risk-benefit considerations may be acceptable. As the NDA is receiving a CR action, a final determination regarding approval under the LPAD pathway will be made during the next review cycle. Of note, LPAD language was included in the draft PI sent to the Applicant based on the understanding that this will likely be acceptable when a resubmission is provided that addresses the facility issues.

3. Regulatory Action

Due to the unacceptable status of the drug substance (heparin sodium) and drug product manufacturing facilities, this Class 2 resubmission of NDA 214520 will receive a complete response action for this review cycle.

Reviewers:

Clinical Reviewer: Mukil Natarajan, MD

Clinical Team Leader: Hiwot Hiruy, MD, PhD

Application Technical Lead and Cross-Discipline Team Leader: Dorota Matecka, PhD

Associate Director of Labeling: Abimbola Adebawale, PhD

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Signatures: *{See appended electronic signature page}*

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NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

NDA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	214520
Priority or Standard	Priority
Submit Date(s)	June 30, 2020
Received Date(s)	June 30, 2020
PDUFA Goal Date	February 28, 2021
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	February 10, 2021
Established/Proper Name	Taurolidine 1.35% (13.5 mg/mL) and heparin 5,000 units/5 mL (1,000 Units/mL) catheter lock solution
(Proposed) Trade Name	Defencath
Pharmacologic Class	Thiadiazinane antimicrobial (taurolidine) and anti-coagulant (heparin)
Code name	N/A
Applicant	CorMedix Inc.
Dosage form	Catheter lock solution
Applicant proposed Dosing Regimen	Instill catheter lock solution from the vial using a 3 mL or smaller syringe into the central venous catheter lumen in a quantity sufficient to fill the catheter lumen
Applicant Proposed Indication(s)/Population(s)	Prevention of catheter related bloodstream infections (CRBSIs) in patients with end-stage renal disease receiving hemodialysis through a central venous catheter
Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Reduction in incidence of CRBSIs in patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter
Recommended Dosing Regimen	Instill 2 mL to 3 mL (depending on the volume of the catheter lumen) of Defencath catheter lock solution into the catheter lumen at the conclusion of each HD session

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NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

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OPQ = Office of Pharmaceutical Quality

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OPDP = Office of Prescription Drug Promotion

OSI = Office of Scientific Investigations

OCHEN = Office of Cardiology, Hematology, Endocrinology and Nephrology

DCN = Division of Cardiology and Nephrology

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NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

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NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

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NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AV	arteriovenous
BLA	biologics license application
CAC	clinical adjudication committee
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CLS	catheter lock solution
CoNS	coagulase-negative <i>Staphylococcus</i> infection
CRBSI	catheter-related bloodstream infection
CRF	case report form
CVC	central venous catheter
DAI	Division of Anti-Infectives
DHOT	Division of Hematology Oncology Toxicology
ESRD	end-stage renal disease
FAP	full analysis population
FDA	Food and Drug Administration
FICI	fractional inhibitory concentration index
GLP	good laboratory practice
HD	hemodialysis
HIT	heparin-induced thrombocytopenia
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
IR	information request
IRB	institutional review board
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
NDA	new drug application
OID	Office of Infectious Diseases
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PT	preferred term
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

TK	thymidine kinase
tPA	tissue plasminogen activating factor
ULN	upper limit of normal
WBC	white blood cell

1. Executive Summary

1.1. Product Introduction

Defencath® is a catheter lock solution (CLS) which contains taurolidine (13.5 mg/mL) and heparin (1,000 USP units/mL) as the active ingredients and citrate as a pH buffer. Taurolidine is a derivative from aminosulfonamide-taurinamide. A proposed mechanism of action for the antimicrobial activity is via transfer of methylol groups that interact with bacterial and fungal cell walls (Torres-Viera et al. 2000; Shah et al. 2002) causing damage to the cell walls and inhibiting adherence of microorganisms to biological surfaces. Heparin is included in the solution for its anticoagulant properties. Defencath is instilled within the lumens of the hemodialysis (HD) catheter after HD treatment and withdrawn prior to the next HD session. It is not intended for systemic administration. The product has Class III Drug-Device CE Mark approval in Europe as a catheter lock solution since 2013 (https://www.cormedix-europe.com/files/cto_layout/PDFs/E-NEU01-01-2015_IFU_English.pdf).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the effectiveness of Defencath in reducing the incidence of catheter-related bloodstream infections (CRBSIs) in patients with kidney failure receiving chronic HD through a central venous catheter (CVC). Substantial evidence of effectiveness is provided by data from a single, randomized, active-controlled Phase 3 clinical trial, LOCK-IT-100. In this trial, Defencath met the primary endpoint of time to CRBSI in demonstrating a 71% risk reduction in CRBSIs (95% confidence interval, 38%, 86%, p value 0.0006) based on the clinical adjudication committee (CAC)-assessed incidence of CRBSIs in the Defencath arm versus the heparin comparator arm.

A single adequate and well-controlled trial was considered adequate to support the safety and effectiveness of Defencath in reducing the incidence of CRBSIs in patients with kidney failure receiving chronic HD through a CVC based on the following:

1. The persuasive and highly statistically significant findings on the primary endpoint of time to CRBSI. CRBSI as defined in the trial is a clinically meaningful endpoint and development of CRBSIs may result in significant morbidity and mortality, particularly in this patient population who rely on their CVCs for life-saving HD.

At the interim analysis which was conducted when 28 CAC-adjudicated CRBSIs had occurred, there were 6 CRBSI cases in the Defencath arm and 22 CRBSI cases in the heparin arm with a statistically significant difference in favor of Defencath ($p=0.0034$). In the final analysis conducted once all ongoing subjects completed the study, there were 9 CAC-adjudicated CRBSIs in the Defencath arm and 32 CAC-adjudicated CRBSIs in the heparin arm (71% risk reduction, 95 % confidence interval, 38%, 86%, $p=0.0006$).

2. Results based on FDA re-adjudication of the CRBSI cases were consistent with the results based on CAC-adjudication of the CRBSI cases.
3. Multiple sensitivity analyses, including using CRBSI plus death as an event also demonstrated statistically significant findings in favor of the Defencath treatment arm.
4. Results using the protocol defined definition of CRBSI were consistent with those of the results based on adjudication by the CAC.
5. The trial was conducted at 70 sites across the United States and no particular sites were considered to be the major drivers of the efficacy findings.
6. The Data and Safety Monitoring Board recommended early termination of the study based on the statistically significant reduction in the risk of CAC-adjudicated CRBSIs observed at the interim analysis. The review team agrees that based on the results of the Phase 3 trial, conducting another randomized placebo-controlled trial in this population would likely not be considered ethical.

From a safety standpoint, loss of catheter patency occurred more frequently in the Defencath arm (63 subjects, 16%) than in the heparin arm (48 subjects, 12%) (see section 8.2.5.1). Thrombolytic therapy such as tissue plasminogen activating factor (tPA) usage was also higher among subjects in the Defencath arm, occurring in 46 subjects (12%) in the Defencath arm and 33 subjects (8%) in the heparin arm. The overall number of catheter removals was also greater in the Defencath arm compared to the heparin arm, with 236 subjects (59%) in the Defencath arm and 225 subjects (57%) in the heparin arm reporting catheter removal during the study follow-up period. The main driver of the observed difference in catheter removal rates between the two arms was the higher number of patients with AV graft/fistula maturation (a positive reason for catheter removal) in the Defencath arm with 156 subjects (39%) compared to 129 subjects (32%) in the heparin arm reporting catheter removal for AV graft/fistula maturation.

The overall benefit-risk assessment was considered acceptable for the limited population of patients with kidney failure receiving chronic HD through a CVC. However, as the status of the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., was found unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA) (see section 4.2 of this review for additional details), the NDA will receive a complete response (CR) action during this review cycle.

Of note, the Applicant requested approval of the NDA under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway. Seeking approval under the LPAD pathway seems reasonable, given the limited population studied, i.e., patients with kidney failure receiving chronic HD through a CVC, in whom the risk-benefit considerations may be acceptable. As the NDA is receiving a CR action, a final determination regarding approval under the LPAD pathway will be made during the next review cycle.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 214520, the Applicant is seeking approval of Defencath for prevention of CRBSI in patients with kidney failure receiving hemodialysis (HD) through a central venous catheter (CVC). The labeled indication will be reduction in the incidence of CRBSI in patients with kidney failure receiving chronic HD through a CVC. Defencath contains taurolidine (13.5 mg/mL), a thiadiazine antimicrobial, and heparin (1,000 USP Units/mL), an anticoagulant, as the active ingredients, and citrate as a pH buffer. Defencath has not been previously approved or marketed in the United States.

The efficacy and safety of Defencath were evaluated in a single, multicenter, double-blind, randomized, active-controlled Phase 3 trial, LOCK-IT-100, in patients with kidney failure receiving HD through a CVC. LOCK-IT-100 evaluated the efficacy and safety of Defencath as a catheter lock solution (CLS) compared to the active control, heparin (1,000 USP units/mL), in reducing the incidence of CRBSIs. The primary efficacy endpoint was time to CRBSI. Due to low capture of CRBSI events during the trial, there were changes implemented in the protocol while the blind was maintained; these changes included introduction of a clinical adjudication committee (CAC) for ascertaining CRBSIs, revision of the definition of the primary endpoint to incidence of CAC-adjudicated CRBSIs, and introduction of an interim analysis. The CAC reviewed subjects' medical records to ensure that they met the clinical and microbiological criteria for a protocol-defined CRBSI event. To confirm the validity of the CAC adjudication, the FDA conducted a readjudication of the cases reviewed by the CAC and performed a sensitivity analysis based on the results.

The interim analysis, which was conducted when 28 CAC-adjudicated CRBSIs had occurred, showed 6 CRBSI cases in the Defencath arm and 22 CRBSI cases in the heparin arm with a statistically significant difference in favor of Defencath ($p=0.0034$). The Data and Safety Monitoring Board recommended early termination of the study based on the results of the interim analysis. The final analysis at the completion of the study showed 9 CRBSI cases in the Defencath arm and 32 CRBSI cases in the heparin arm. This result was statistically significant in favor of Defencath (71% risk reduction, 95 % confidence interval, 38%, 86%, $p=0.0006$). The event rate per 1,000 catheter-days for the final analysis population was 0.13 and 0.46 in the Defencath and the heparin arms, respectively. A number of sensitivity analyses were conducted including a sensitivity analysis with the FDA readjudication of CRBSI events. Three cases were adjudicated differently by the CAC and the FDA; however, the overall number of CRBSI cases remained the same in the CAC and FDA assessments. A sensitivity analysis using the original, more stringent protocol definition of CRBSI prior to CAC adjudication also demonstrated a significant result in favor of Defencath with no CRBSI cases in the Defencath arm and six CRBSI cases in the heparin arm ($p=0.0251$). A sensitivity analysis evaluating CRBSIs due to gram-positive organisms showed

8 CRBSI cases in the Defencath arm and 18 CRBSI cases in the heparin arm; however, this difference was not statistically significant ($p=0.0551$).

Loss of catheter patency occurred more frequently in the Defencath arm (63 subjects, 16%) than in the heparin arm (48 subjects, 12%) and is a serious concern as patients with kidney failure may have limited options for vascular access in the absence of a mature arteriovenous (AV) graft or fistula. Thrombolytic therapy such as tPA usage was also higher among subjects in the Defencath arm, occurring in 46 subjects (12%) in the Defencath arm and 33 subjects (8%) in the heparin arm. The mechanism by which taurolidine may affect loss of catheter patency is not clear; however, increased catheter malfunction/loss of patency and need for thrombolytic treatment have been previously reported in publications with use of CLSs containing taurolidine. There was a numerically increased number of catheter removals observed in the Defencath arm, with 236 subjects (59%) in the Defencath arm and 225 subjects (57%) in the heparin arm reporting catheter removal during the study follow-up period. Of note, differences in the number of catheter removals between the two arms did not appear to be secondary to loss of catheter patency. Although there were differences in rates of CRBSI between the two treatment arms, the main driver of the observed difference in catheter removal rates between the two arms was the greater number of patients with AV graft/fistula maturation (a positive reason for catheter removal) in the Defencath arm with 156 subjects (39%) in the Defencath arm compared to 129 subjects (32%) in the heparin arm reporting catheter removal for AV graft/fistula maturation.

The remainder of the adverse reactions observed in the LOCK-IT-100 trial were consistent with prior knowledge of the safety of taurolidine, heparin, and the citrate excipient and included heparin-induced thrombocytopenia, hypersensitivity reactions, hemorrhage/bleeding, hemodialysis catheter malfunction, thrombocytopenia, nausea, vomiting, dizziness, musculoskeletal chest and neck pain, hypocalcemia, and dysgeusia.

The Applicant has provided substantial evidence of the effectiveness of Defencath and adequate safety for the indication of reduction in the incidence of CRBSI in patients with kidney failure receiving chronic HD through a CVC. However, as the status of the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., was found unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA) (see section 4.2 of this review for additional details) the NDA will receive a complete response action in this review cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- CRBSIs are an important cause of morbidity and mortality, with particular relevance to patients with kidney failure who require vascular access for HD, sometimes for prolonged periods spanning months or years. - A significant number of patients with kidney failure use temporary or permanent CVCs as their primary vascular access for HD. In these patients, CRBSIs can occur an average of 1-2 times per year, making prevention of CRBSIs an important challenge. In addition to the morbidity and mortality directly tied to the resultant infections, CRBSIs also result in difficulties with maintaining vascular access needed for HD.	CRBSIs are serious and potentially life-threatening infections causing significant morbidity and mortality and are particularly relevant to patients with kidney failure who require temporary or permanent CVCs as vascular access for HD.
Current Treatment Options	- There are currently no FDA-approved antimicrobial or antiseptic CLSs for preventing or reducing the incidence of CRBSI. - Several antimicrobial and antiseptic solutions are used off-label as CLSs to reduce the risk of CRBSIs in susceptible populations. Examples of antimicrobial products that have been used as CLSs alone or in combination for CRBSI prophylaxis include vancomycin, gentamicin, ciprofloxacin, minocycline, amikacin, cefazolin, cefotaxime, and ceftazidime. Other products used as CLSs include alcohol, taurolidine, and trisodium citrate. - CDC guidelines for the prevention of CRBSIs recommend the use of prophylactic antimicrobial lock solutions in patients with long term catheters who have a history of multiple CRBSIs.	As there are no FDA-approved antimicrobial or antiseptic CLSs for preventing or reducing the incidence of CRBSIs, there is an unmet medical need for safe and effective therapies. s.

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The efficacy of Defencath was demonstrated in a single, randomized, controlled Phase 3 trial, LOCK-IT-100, in a population of patients with kidney failure receiving chronic HD through a CVC. An interim analysis showed that Defencath met the primary endpoint of time to CRBSI with 6 cases of CAC-adjudicated CRBSIs in the Defencath arm and 22 in the heparin arm ($p=0.0034$), resulting in a 71% reduction in incidence of CAC-adjudicated CRBSI. Analysis at the completion of the trial also showed reduction in CAC-adjudicated CRBSIs in the Defencath arm with statistical significance in favor of Defencath. Consistent results were seen in multiple sensitivity analyses.	In the Phase 3 trial, Defencath was found to be superior to the heparin control with a 71% reduction in the incidence of CRBSI in patients with kidney failure receiving chronic HD through a CVC.
Risk and Risk Management	The safety finding of concern in LOCK-IT-100 was loss of catheter patency with a higher incidence in the Defencath arm (16%) compared to the heparin arm (12%). Thrombolytic therapy such as tPA usage was also higher among subjects in the Defencath arm (12%) than the heparin arm (8%). The overall number of catheter removals was greater in the Defencath arm (59%) compared to the heparin arm (57%). The main driver of the observed difference in catheter removal rates between the two arms was the higher number of patients with AV graft/fistula maturation (a positive reason for catheter removal) in the Defencath arm (39%) compared to in the heparin arm (32%). The remainder of the ARs occurring in LOCK-IT-100 were consistent with prior knowledge of the safety of taurolidine, heparin, and the citrate excipient. No serious risks that would necessitate specific risk management strategies were identified.	The risk of loss of catheter patency will be discussed in the labeling for Defencath. No serious risks that warrant specific risk management strategies were identified. The ARs will be communicated via labeling and monitored via routine pharmacovigilance.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient-reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Catheter-related bloodstream infections (CRBSIs) are a significant public health problem, resulting in mortality and significant morbidity, including increased hospital length of stay and healthcare costs (Mermel 2000; Warren et al. 2006; Allon 2008; O'Grady et al. 2011). CRBSIs are of particular concern in kidney failure patients who require vascular access for hemodialysis (HD). Approximately 25% of U.S. HD patients use temporary or permanent central catheters as their primary vascular access for dialysis (Tokars et al. 2000; Allon 2004). More recent data suggest that up to 80% of patients still initiate HD with a tunneled HD catheter despite efforts to promote the use of functional arteriovenous fistulas at the start of dialysis (Lok 2007; System 2017). Among HD patients, bloodstream infections occur 2.5 to 5.5 times per 1,000 catheter-days, translating to approximately 0.9 to 2.0 episodes per year (Allon 2004); thus making prevention of CRBSI in the HD population an important challenge.

Strategies to reduce the risk of CRBSIs include routine infection control practices, such as use of proper hand hygiene, aseptic technique, and appropriate skin preparation regimens (O'Grady et al. 2011). While there are no FDA-approved prophylactic antimicrobial lock solutions, the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of intravascular catheter-related infections recommend the use of prophylactic antimicrobial lock solutions in patients with long-term catheters with a history of multiple CRBSIs despite adherence to best practices (O'Grady et al. 2011).

2.2. Analysis of Current Treatment Options

There are currently no FDA-approved antimicrobial or antiseptic catheter lock solutions (CLSs) for prophylactic use in the prevention of CRBSI. However, a number of antimicrobial and antiseptic solutions are used off-label as CLSs to reduce the risk of CRBSI in susceptible patients (Labriola and Pochet 2017; Golestaneh and Mokrzycki 2018). Antibacterial drugs which have been used as CLSs for CRBSI prophylaxis alone or in combination include vancomycin, gentamicin, ciprofloxacin, minocycline, amikacin, cefazolin, cefotaxime, and ceftazidime. Other products, such as alcohol, taurolidine, and trisodium citrate, have also been used as CLSs (O'Grady et al. 2011).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Defencath has not previously been approved or marketed in the United States. Of note, the product has had Class III Drug-Device CE Mark approval in Europe for the stated indication since 2013.

3.2. Summary of Presubmission/Submission Regulatory Activity

Defencath (at the time known as Neutrolin) underwent a product jurisdiction review following a request for designation (RFD) submitted on July 15, 2011 and was assigned to CDER on September 15, 2011. This decision was due to the proposed indication of prevention of CRBSI, in addition to (b) (4). For additional information, please refer to the designation letter for RFD110071, dated September 15, 2011.

The IND for Defencath was submitted to DAI on October 9, 2014. Fast Track and Qualified Infectious Disease Product designations were granted on January 8, 2015, and January 16, 2015, respectively. The Applicant requested approval of the NDA under the LPAD pathway at the time of NDA submission. The NDA was a rolling review submission. Part 1 of 3 was received on March 11, 2020, part 2 of 3 was received on June 1, 2020, and part 3 of 3 was received on June 30, 2020.

The safety and efficacy assessment of Defencath was evaluated in the Phase 3 trial, LOCK-IT-100. The trial aimed to evaluate the efficacy of Defencath in the prevention of CRBSI in HD patients. Enrollment started in 2015; however, the Applicant encountered procedural issues in the ability to capture CRBSI. Blood cultures were not being obtained at the dialysis study sites, urgent care centers, or emergency departments prior to administration of systemic antimicrobial drugs or the removal of the catheter, resulting in a potentially artificially low background CRBSI rate. Due to these issues, the Applicant implemented changes in the protocol while maintaining the study blind. These changes included: (1) introduction of a CAC for ascertaining CRBSIs, (2) revision of the definition of the primary endpoint to incidence of CAC-adjudicated CRBSIs, (3) increase in sample size from 632 to 900, and (4) introduction of an interim analysis to be performed after 28 events of CRBSI. These important changes were included in the final protocol amendment (Version 8) which was submitted in October 2017. Of note, 482 subjects or 59.2% of the total study population had been enrolled prior to the revisions that occurred in Version 8.

[Table 1](#) summarizes the protocol revisions for the LOCK-IT-100 trial.

Table 1. History of Protocol Revisions for the LOCK-IT-100 Trial

Version	Date	Subjects (%) Enrolled	Cumulative Enrollment (%)
1	September 22, 2014	0 (0.0%)	0 (0.0%)
2	March 26, 2015	0 (0.0%)	0 (0.0%)
3	August 21, 2015	0 (0.0%)	0 (0.0%)
4	October 16, 2015	14 (1.7%)	14 (1.7%)
5	December 21, 2015		
6	February 5, 2016	468 (57.5%)	482 (59.2%)
7	December 20, 2016	0 (0.0%)	482 (59.2%)
8	October 6, 2017	332 (40.8%)	814 (100.0%)
Total Number (%) of Subjects Enrolled			814 (100.0%)

Source: Applicant's CSR Table 1, Page 41

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The Office of Scientific Investigations (OSI) performed an audit of 3 clinical sites (Drs. Murillo, Jamal, and Bien) that enrolled patients in the Phase 3 trial. The results of the inspections indicated that the trial was conducted adequately, and the study data submitted, including the primary and key secondary efficacy endpoint data, appear acceptable.

For additional information, please refer to OSI's clinical inspection summary, signed into DARRTS on 12/8/20.

4.2. Product Quality

The NDA, as amended, has not provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product, Defencath (taurolidine and heparin) catheter lock solution. Defencath catheter lock solution is provided as a sterile, preservative-free, clear, aqueous-based solution of taurolidine 67.5 mg/5 mL (13.5 mg/mL), and heparin 5,000 USP Units/5 mL (1,000 USP Units/mL), in a single-dose vial. The formulation also contains citric acid (as a pH adjuster and to increase the solubility of taurolidine), sodium hydroxide and/or hydrochloric acid (for pH adjustment), and water for injection. The manufacturing process includes (b) (4)

(b) (4). The drug product solution is filled into a clear, glass USP Type (b) (4) vial with a latex-free, (b) (4) stopper, and aluminum/plastic flip-top cap. The stability information submitted in the NDA supports the 24-month expiration dating for the drug product to be

stored in commercial vials and carton at room temperature. Quality information provided for both drug substances (taurolidine and heparin sodium), the drug product, and information related to the microbiological quality aspects of the drug product was found acceptable. However, the status of the drug product manufacturing facility, ROVI Pharma Industrial Services S.A., was found unacceptable by the Office of Pharmaceutical Manufacturing Assessment (OPMA), and the overall recommendation of “Withhold” was entered into Panorama for this NDA on January 29, 2021. In addition, there are several issues regarding the drug product manufacturing process that will need to be addressed in the next review cycle. Therefore, this NDA is currently recommended for Complete Response (CR) by the Office of Pharmaceutical Quality (OPQ). The following deficiency will be included in the CR letter (for details, refer to the OPQ review # 2 dated February 19, 2021, in DARRTS):

“During a review of records requested under Federal Food, Drug, and Cosmetic Act section 704(a)(4) provided by Rovi Pharma Industrial Services S.A. (FEI 3016688535) manufacturing facility the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved. If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID-19 (FDA 2021).

4.3. Clinical Microbiology

Defencath contains taurolidine (1.35%), heparin (1,000 Units/mL), and citrate (3.5%) (as an excipient) and is intended to be instilled in the CVC lumen and remain in place between HD treatment sessions. It is not intended to be systemically administered. Regarding the ingredients of Defencath:

- The taurolidine concentration (1.35%) is equivalent to 13,500 µg/mL and has been shown to have antimicrobial activity, making the environment inside the CVC hostile to bacterial and fungal growth.
- Heparin at a concentration of 1,000 Units/mL does not contribute to the antimicrobial activity (Capdevila et al. 2001) of Defencath. It is an anti-thrombolytic agent and is added as an anticoagulant to prevent clot formation.
- Citrate is not an active ingredient but has been added to the drug product to adjust the pH and enhance the solubility of taurolidine in solution. The 3.5% concentration is below the level that would be required for antimicrobial activity. Citrate concentrations of 2.2% are able to completely kill *Staphylococcus aureus* and *Staphylococcus epidermidis*. However, complete killing of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans* was only achieved at 30% (Weijmer et al. 2002), which is 10 times

the amount found in Defencath. In a meta-analysis of 13 randomized-controlled studies, citrate (4% to 46.7%) failed to show an advantage to heparin as a CLS in the prevention of CRBSI (Zhao et al. 2014).

For the purposes of the review, this section will focus on taurolidine, the active ingredient associated with the antimicrobial activity of Defencath. Taurolidine, a derivative of the amino acid taurine, is unstable in biological fluids and is rapidly hydrolyzed to formaldehyde, methylene glycol, taurultam, and taurinamide in aqueous solution, ultimately breaking down to taurine (Myers et al. 1980; Gong et al. 2007). Formaldehyde causes denaturation of surface proteins and alteration of membrane lipids. Methylene glycol causes methoxylation of proteins and lipids (Myers et al. 1980; ATSDR 1999). This nonspecific toxic mechanism of action has been studied in vitro and in vivo. Based on these studies, taurolidine:

- Reacts with the cell wall constituents of gram-negative bacteria and decreases microbial adhesion (Gorman et al. 1987a; Gorman et al. 1987b). This results in decreasing bacterial adherence to human cells. Chemical changes in bacterial cells are more destructive to bacterial function than changes to human host cells (Gorman et al. 1987c; Jurewitsch et al. 1998).
- Neutralizes endotoxin activity in vitro (Blenkharn 1987) and in vivo (Pfaffmann and Leslie 1979).
- Inhibits microbial (bacteria, yeast) adherence to buccal epithelial and uroepithelial cells, and suppresses the formation of bacterial fimbriae (Gorman et al. 1987a). Taurolidine has a higher affinity than mannose (the natural substrate) for bacterial fimbriae protein that is responsible for bacterial adhesion to human cells (Caruso et al. 2010).

The necessary inhibitory and bactericidal concentrations of taurolidine are in the range of 125 to 2048 mg/L, and it appears that taurolidine requires contact times with bacteria greater than 4 to 24 hours at least 4x MIC to show bactericidal activity. There is a low frequency of resistant mutants ($<10^{-9}$) at 2x and 4x MIC against *E. coli*, *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, and *P. aeruginosa*. For further information on antibacterial activity and resistance (see Section [16.3](#))

The study design and results of the single Phase 3 trial are described elsewhere in the review (see Section [8.1](#)). In this study, although there was a higher number of gram-positive infections in the both groups, the infection frequency for gram-negative organisms was significantly lower in the Defencath group compared to the heparin group. The most predominant gram-positive organisms were *S. aureus* followed by *S. epidermidis*, which were identified in both groups ([Table 2](#)). In this trial, the one gram-negative organism in the Defencath group was *Klebsiella pneumoniae*, whereas, the 14 gram-negative isolates in the heparin arm were a wide variety of organisms, including members of *Enterobacterales*, *P. aeruginosa*, and *Stenotrophomonas maltophilia*. There were no anaerobes or yeasts associated with CRBSI events in this study.

Pathogenic organisms were cultured from exit sites and/or catheters in 16 subjects. Of the 16 subjects with positive catheter and/or exit site cultures, 3 subjects in the heparin arm had positive blood cultures for the same organism; there were none identified in the Defencath group. The taurolidine MIC values ranged from 64 to 1024 µg/mL against gram-positive bacteria and 512 to 1024 µg/mL against the gram-negative bacteria. None of the isolates tested for taurolidine susceptibility were from subjects in the Defencath group that had a CRBSI.

Table 2. CAC-adjudicated CRBSI Events by Pathogen Type in the LOCK-IT-100 Clinical Trial

	Defencath N=9	Heparin N=32	Total N=41
Gram-positive, n (%)	8 (88.9)	18 (56.3)	26 (63.4)
<i>Enterococcus faecalis</i>	0	3	3
<i>Staphylococcus aureus</i> ^a	4	8	12
CoNS ^b	1	4	5
<i>Streptococcus anginosus</i>	0	1	1
<i>Streptococcus bovis</i>	0	1	1
<i>Streptococcus saguinis</i>	0	2	2
Mixed infection ^c	0	1	1
Gram-negative, n (%)	1 (11.1)	14 (43.7)	15 (57.7)
<i>Enterobacteriales</i> ^d	1	12	13
<i>Pseudomonas aeruginosa</i>	0	1	1
<i>Stenotrophomonas maltophilia</i>	0	1	1

Source: 16265micro; 5354-cac-summaries-mins

^a Due to methicillin-resistant *Staphylococcus aureus*: Defencath=4; heparin=5

^b Due to *Staphylococcus epidermidis*: Defencath=1, heparin=3; *Staphylococcus lugdunensis* (heparin=1)

^c Mixed infection in one subject with *S. anginosus* and *S. epidermidis*.

^d Due to *Citrobacter koseri* (heparin=2); *Enterobacter aerogenes* (heparin=1); *Enterobacter cloacae species complex* (heparin=4), *Klebsiella pneumoniae* (heparin=2, Defencath=1); *Serratia marcescens* (heparin=3).

Abbreviations: CoNS = coagulase-negative *Staphylococcus* infection, CRBSI = catheter-related bloodstream infection

The Applicant has demonstrated in vitro activity of taurolidine against the following microorganisms. This list will be included in the Microbiology section of labeling.

- Gram-positive
 - *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus*)
 - *Staphylococcus epidermidis*
 - *Enterococcus faecalis*
- Gram-negative
 - *Escherichia coli*
 - *Klebsiella pneumoniae*
 - *Pseudomonas aeruginosa*
 - *Serratia marcescens*
- Fungi
 - *Candida albicans*
 - *Candida glabrata*

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

There are CLSs containing 1,000 units/mL of heparin approved for marketing in the United States. A CLS containing taurolidine and heparin, similar to Defencath, is approved in the European Union. Thus, there is significant human clinical experience with the components of Defencath in CLSs.

In addition to its use in CLS, heparin has been approved for systemic use in the United States, contributing to the clinical experience with this drug substance. Although taurolidine is not present in any drug products or devices marketed in the United States, there are published studies demonstrating that up to 5 g have been given intravenously over 0.5 to 2 hours to human subjects without significant toxicity. The amount of taurolidine in 5 mL of Defencath is 0.0675 g, about 74 times less than the 5 g tolerated by acute intravenous administration. Thus, if the maximum catheter fill volume of Defencath was accidentally pushed intravenously into the circulation rather than pulled out of the catheter and discarded according to the labeling instructions, it is unlikely to harm a patient. A rat study conducted with a diluted solution of Defencath did not use high enough levels of the active ingredients to adequately explore the toxicity of taurolidine and identify possible target organs of toxicity (if any). However, the medical reviewers found that previous clinical experience with taurolidine (particularly as a component of CLS) was adequate to support the clinical development of Defencath and the toxicology reviewer deferred to their judgement. Thus, additional acute or repeat-dose general toxicology testing in animals was not required for the components of Defencath.

Defencath is not intended for systemic administration, so the Division agreed to waive reproduction toxicity studies for taurolidine and deemed that these data were not needed for labeling.

Genotoxicity studies were required for taurolidine to label Defencath as a drug product because it is considered a new molecular entity. Although taurolidine is positive for genotoxicity in vitro regardless of metabolic activation (mouse lymphoma and Ames tests), it is negative in vivo. Data from a study in rats demonstrated that micronuclei were not induced in bone marrow polychromatic erythrocytes, and DNA damage was not detected in liver cells in a comet assay when taurolidine was administered intravenously up to a maximum tolerated dose of 600 mg/kg/day for three days. This suggests that in vivo, taurolidine is quickly metabolized and deactivated so that genotoxic substances related to this molecule are not able to reach DNA and cause damage.

At the levels where taurolidine exposure could be achieved in the clinic during use of the Defencath CLS, the risk of genotoxicity appears low.

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

In vitro studies using human blood showed that taurolidine did not interfere with the anti-coagulant properties of heparin. In addition, Defencath was not associated with hemolysis and it did not activate complement in vitro in human plasma.

Defencath appears reasonably safe to use as a CLS in patients with kidney failure receiving hemodialysis through a CVC. There is no objection to its approval from the pharmacology/toxicology review team.

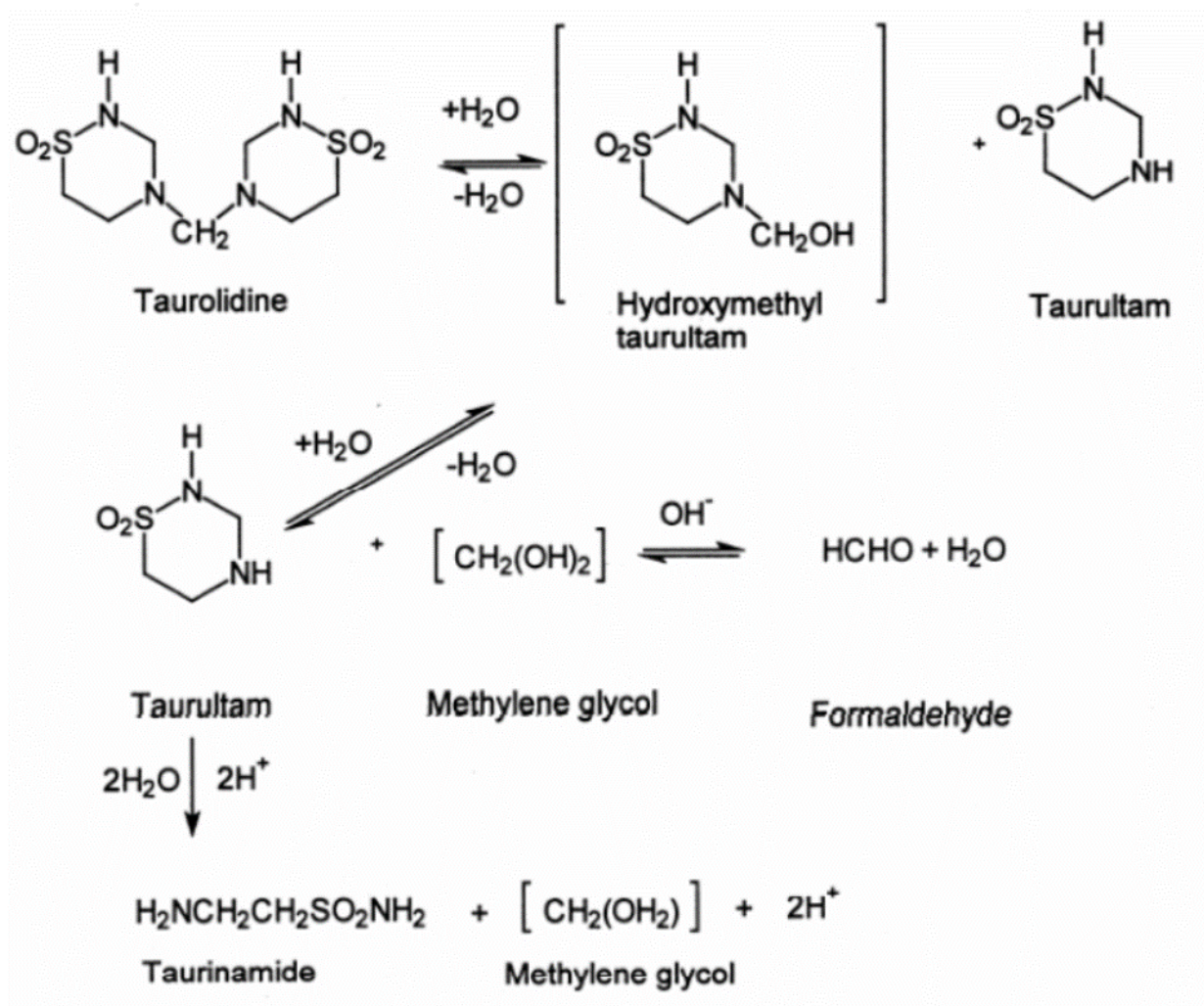
5.2. Referenced NDAs, BLAs, DMFs

- IND 113764 for taurolidine and heparin CLS.
- NDA 17064 for heparin (appears to be the oldest active approved application covering this drug substance).

5.3. Pharmacology

Taurolidine is unstable in biological fluids and is in equilibrium with both formaldehyde and methylene glycol, which are toxic to microorganisms. These substances are nonspecific toxicants, denature surface proteins, and cause chemical alteration to membrane lipids, including methoxylation. They can also be toxic to mammalian cells, although microorganisms appear to be more sensitive.

Figure 1. Equilibrium Between Taurolidine and its Reaction Products (From the Submission)



Heparin exerts anti-coagulant activity by binding to the plasma protein Antithrombin III, enhancing its serum protease activity and thus causing inhibition of activated coagulation factors involved in the clotting cascade.

5.4. ADME/PK

ADME/PK studies were not conducted with Defencath because the product is not intended for systemic administration and clinical exposure to its components is negligible when used as directed.

5.5. Toxicology

5.5.1. General Toxicology

A single dose intraperitoneal study conducted with Defencath in mice and a 14-day repeat-dose intravenous study conducted in rats (discussed in additional detail below) did not reveal signs of toxicity. Although neither of these studies were considered adequate for a pivotal nonclinical toxicology study to support human drug development (exposure to taurolidine was not sufficient to explore possible toxicity and identify potential target organs), a product similar to Defencath was approved for human use as a CLS in the European Union. There is considerable clinical experience with heparin, both in CLS and with systemic administration at doses of heparin exceeding the amount that would be present in a catheter lock filled with Defencath. Systemic administration of taurolidine has been studied in humans and single intravenous doses of up to 5 g have been given over 0.5 to 2 hours without significant acute toxicity (Gong et al. 2007). Thus, the review team did not require additional nonclinical toxicity testing of Defencath or its individual components in animals to support product development or approval, despite the shortcomings of the rodent studies.

Study Title/Number: 14-Day Repeat Dose Intravenous Toxicity Study- ISO/Report No. 10-6116-G13

Key Study Findings:

- A diluted solution of Defencath did not cause toxicity in rats when administered intravenously daily for 14 days. Animals received 9.6 mg/kg of taurolidine, 710 units/mg of heparin, and 18.5 mg/kg of citric acid each day in 40 mL of saline for injection. This was the only dose of test article used in the study.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Table 3. Methods (Report No. 10-6116-G13)

Category	Description
Dose and frequency of dosing	0.71 mL of Defencath (this amount contains 9.585 mg of taurolidine, 710 units of heparin, and 18.531 mg of citric acid) was diluted to 40 mL. Saline for injection was the control group. Rats received 40 mL/kg daily for 14 days.
Route of administration	Intravenous
Formulation/Vehicle	Saline for injection
Species/Strain	Albino rats (unspecified strain)
Number/Sex/Group	5
Age	At least 5 weeks of age
Satellite groups/Unique design	Dosing began on Day 0 and animals were sacrificed on Day 14 (one day after the final dose was given). The report did not state the length of the daily infusion time.
Deviation from study protocol affecting interpretation of results	No

Table 4. Observations and Results: Changes From Control (Report No. 10-6116-G13)

Parameters	Major Findings
Mortality	None
Clinical signs	Observed twice daily; none
Body weights	No changes related to test article.
Hematology	No treatment-related effects on hematology parameters.
Clinical chemistry	No treatment-related effects on serum chemistry parameters.
Gross pathology	No treatment-related gross changes were reported.
Organ weights	No test article-related effects on organ weights.
Histopathology	No drug-related changes were reported, but there was no comprehensive tabulation of the data for all of the tissues that were examined. If there were no findings in a tissue, the report did not include it in the table.
Adequate battery: No, only tissues examined were adrenals, brain, epididymis, gross lesions, heart, kidney, liver, lung, ovary, spleen, testes, uterus.	

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title/Number: Bacterial Reverse Mutation Assay/Study No. AE72DM.5021CH (b) (4)

Key Study Findings:

- Taurolidine was mutagenic in TA98 and TA100 in the absence and presence of metabolic activation.

GLP compliance: Yes

Test system: *S. typhimurium* TA98, TA100, TA1535 and TA1537; *E. coli* WP2uvrA

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study Title/Number: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay)/Study No. AE72DM.704RICH (b) (4)

Key Study Findings:

- Taurolidine-induced forward mutations at the thymidine kinase (TK) locus of L5178Y mouse lymphoma cells in the absence and presence of metabolic activation.
- Frequencies of both small and large colonies were increased.

GLP compliance: Yes

Test system: L5178Y/TK^{+/-} mouse lymphoma cells

Study is valid: Yes

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/Number: In Vivo Mammalian Erythrocyte Micronucleus Assay and Mammalian Alkaline Comet Assay in Rats/Study No. AE72DM.433MICH (b) (4)

Key Study Findings:

- Taurolidine did not induce micronuclei in immature erythrocytes from rat bone marrow following three daily intravenous doses up to 600 mg/kg/day (rats dosed up to the maximum tolerated dose).
- Comet analysis of liver cells from the same taurolidine-treated rats showed no evidence of DNA damage compared to vehicle controls.

GLP compliance: Yes

Test system: Sprague-Dawley rats (Hsd:SD)

Study is valid: Yes

5.5.3. Carcinogenicity

Carcinogenicity studies were not needed for Defencath because the product is not intended for systemic administration and clinical exposure to its components is negligible when used as directed.

5.5.4. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were waived for Defencath because the product is not intended for systemic administration and clinical exposure to its components is negligible when used as directed.

5.5.5. Other Toxicology Studies

Taurolidine (final concentration of 1.49 mg/mL after dilution in plasma) did not inhibit the heparin-mediated increase in prothrombin time or activated partial thromboplastin time in human plasma in vitro. Thus, it did not interfere with the anti-coagulant properties of heparin under the conditions of these studies.

Defencath did not cause hemolysis in human blood in vitro (0.12%) and activation of complement in human plasma was not observed at concentrations up to 0.2%.

Guinea pig studies with Defencath showed that the product was not irritating when injected intradermally and it was nonsensitizing in these animals.

6. Clinical Pharmacology

6.1. Executive Summary

No clinical pharmacology studies were conducted for this NDA. Defencath is a CLS that is not intended to be used systemically. The proposed doses were not determined based on clinical pharmacology information.

Defencath is a drug product that consists of active ingredients: taurolidine 1.35% (13.5 mg/mL) and heparin 1,000 USP units/mL. A volume of 2 to 3 mL of Defencath is instilled into an HD CVC lumen at the conclusion of each dialysis session for adult patients with kidney failure receiving HD. The drug product must be aspirated and discarded from the catheter lumen prior to beginning the next dialysis treatment.

There were no reported incidences of inadvertent systemic injection or accidental flushing of Defencath in the Phase 3 clinical trial. In the event of an unintended bolus injection of Defencath, it is not anticipated that taurolidine will pose any risk as the taurolidine dose in Defencath is approximately 74-fold below the taurolidine dose that was administered intravenously to 18 healthy subjects who did not experience any SAEs (Gong L). The heparin concentration in Defencath is a standard concentration used in clinical practice as a CLS, so there should not be an increased bleeding risk in patients (Bander SJ).

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

One Phase 3 clinical trial, LOCK-IT-100, was submitted in the NDA. LOCK-IT-100 compared the safety and efficacy of Defencath with an active comparator, heparin, in reducing CRBSIs in patients with kidney failure receiving HD through a CVC.

Table 5. Clinical Trial Reviewed in Defencath NDA

Trial Identity/ NCT No.	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Randomized	Study Population	No. of Centers and Countries
LOCK-IT-100 NCT02651428	Multicenter, double-blind, randomized, active-controlled trial in patients with kidney failure receiving HD through a CVC	Defencath and the active control, heparin, were packaged in single-use vials and used as a catheter lock solution (CLS) for HD catheters: Day 1: CLS was instilled into the catheter lumens following the index HD session. Subsequent HD sessions: CLS was removed and discarded prior to HD and instilled in the catheter lumens following the HD session	Primary endpoint: • Time to CRBSI Secondary endpoints: • Catheter removal • Loss of catheter patency	Patients were followed from randomization until either: development of a CRBSI; catheter removal; death; transfer to a nonstudy site; termination of dialysis, or the end of the study, whichever occurred first. Follow-up for adverse events occurred for up to 28 days after the date of last dose of study drug. AEs were followed until resolution or the AE was stable.	806 total patients randomized Defencath: 403 Heparin: 403	Adult subjects (≥18 years) with kidney failure undergoing chronic HD with a permanent, tunneled silicone or polyurethane catheter	70 study sites across the US

Controlled studies to support efficacy and safety

Abbreviations: AE = adverse event, CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, HD = hemodialysis

7.2. Review Strategy

The review of clinical efficacy and safety of Defencath for the indication of reduction of CRBSI in patients receiving HD via CVC was conducted using data from the LOCK-IT-100 Phase 3 trial.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

LOCK-IT-100 was entitled, “A Phase 3, prospective, multicenter, double-blind, randomized, active control study to demonstrate the safety and effectiveness of Defencath in preventing catheter-related bloodstream infections in subjects receiving hemodialysis therapy as treatment for end stage renal disease.”

8.1.1. LOCK-IT-100

Trial Design

The study was a Phase 3, prospective, multicenter, double-blind, randomized, active control study. It evaluated the efficacy and safety of Defencath (taurolidine 13.5 mg/mL and heparin 1,000 USP units/mL) as a CLS as compared to the active control, heparin (heparin sodium 1,000 USP units/mL, benzyl alcohol 9.45 mg/mL and sodium chloride 9.0 mg/mL), in preventing CRBSIs in subjects receiving HD for kidney failure. Heparin is the current standard of care as a CLS in the U.S. The Defencath lock solution matched the control lock solution in terms of volume, color, viscosity, and smell and was packaged in identical containers. The blind was not broken until all subjects completed the study and the database was locked.

The inclusion criteria were as follows:

- (1) Subject had ESRD (also referred to as kidney failure in this review) and undergoes chronic HD at least two times per week
- (2) Subject had an 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 CVC was placed in a jugular or subclavian vein, with the tip of the catheter typically sitting at the junction of the superior vena cava and right atrium
- (4) The subject was not expected to expire within 180 days
- (5) The subject was likely to require the use of a CVC for at least 60 days
- (6) The subject (or the legal guardian) understood the nature of the study and provided written informed consent prior to the study enrollment
- (7) The subject was willing to comply with specified follow-up evaluations and prescribed dialysis therapy

- (8) The subject was receiving adequate HD 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 who would not be required to use the required birth control methods are those who are:
 - Postmenopausal, defined as:
 - 12 months of spontaneous amenorrhea or
 - 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels >40 Units/mL or
 - Surgically sterilized (i.e., previous tubal ligation or hysterectomy).

The exclusion criteria were as follows:

- (1) Subjects who received antibacterial drugs 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 had received any thrombolytic treatment (i.e., tissue plasminogen activating factor [tPA] – Cathflo®) in their current catheter within 30 days of randomization
- (4) Fill volume of HD catheter was 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, nonhealing skin ulcers
- (9) Current requirement for systemic immunosuppression that would increase risk of infection; such as:
 - Steroid dose higher than 10 times the physiologic dose (>50 mg Prednisone/day)
 - Methotrexate dose sufficiently high to suppress WBC count below 5,000
 - Biologic immunomodulators (anti-TNF, anti-CD4, etc.) within 1 month
 - Azathioprine dose greater than 2.5 mg/kg/day (175 mg for average adult)
 - 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)
 - 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 was currently taking another medication with known systemic drug interaction with citrate, taurolidine, or heparin
- (15) Subject was 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 was 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 rendered 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.

Eligible subjects were randomized in a 1:1 ratio to receive either Defencath or heparin as a CLS. The assigned study medicine was instilled into the HD CVC at the end of all dialysis sessions and discarded prior to the initiation of the next dialysis session. All subjects received other standard of care consistent with current clinical guidelines for HD therapy during the study. Study visits occurred on HD treatment days. Every four weeks at one of these dialysis visits, a more extensive visit occurred including the collection of vital signs and labs. Subjects remained in the study until the occurrence of one of the following events, whichever occurred first: 1) development of a CRBSI, 2) catheter removal, 3) death, 4) transfer to a nonstudy site, 5) termination of dialysis, or 6) the end of the study. The primary efficacy endpoint was time to CRBSI.

The final assessment of CRBSI was made by a CAC. According to the CAC charter, the CAC members were blinded to the treatment assignment. The study was designed to continue until approximately 56 subjects had experienced a CRBSI. The interim analyses for efficacy and futility of the primary endpoint were planned to be conducted by an independent statistical team when 28 CAC-adjudicated CRBSI events occurred. The Data Safety Monitoring Committee periodically reviewed the accumulating study data. Their primary responsibilities were to monitor subject safety and study conduct, oversee the interim analysis, and make a recommendation to stop the study or not based on the interim analysis.

Study Endpoints

The primary efficacy endpoint was time to a CAC-adjudicated CRBSI. The definition of CRBSI was modified over the course of the trial but prior to unblinding (Appendix [16.4](#)), and the reasons for the changes are discussed in Section [3.2](#). The major changes appeared to be for clarification purposes.

According to the protocol, the definition of CRBSI required that the same organism be 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 were to be taken from two sites to enhance the validity of the culture testing results. One aerobic and one anaerobic blood culture bottle were to be taken from each site. If the subject had clinical symptoms, while on or off dialysis, blood cultures were to 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 was not available, as soon as the patient was evaluated, blood cultures could 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 received antibacterial drugs. Ten to 20 mL of blood were to be collected, without discarding any of the CLS.

Necessary clinical indicators for suspicion of infection included the following:

- One of the following symptoms:
 - Fever (defined as $\geq 37.8^{\circ}\text{C}$)
 - Rigors, defined as shivering from a feeling of being cold, often with copious sweating, as documented by a medical professional
- Two or more of the following symptoms:
 - Tachycardia defined as a heart rate greater than 100 beats per minute
 - Tachypnea defined as a respiratory rate greater than 24 breaths per minute
 - Low blood pressure defined as a systolic blood pressure less than 90, as measured by a clinician (RN or MD) with a blood pressure cuff, or a decrease in blood pressure greater than 30 mm Hg
 - An obvious change in mental status from previously documented baseline.

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

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

As mentioned in Section [3.2](#), the Applicant was concerned about the low event rate, thus a Clinical Adjudication Committee (CAC) (see section below) was established to adjudicate for CRBSI.

The two secondary efficacy endpoints were as follows:

- (1) catheter loss for any reason
- (2) loss of catheter patency defined as required use of a tPA or removal of the catheter due to dysfunction.

Clinical Adjudication Committee (CAC)

The CAC was composed of five members, two board-certified in internal medicine and nephrology, one board-certified in pediatrics and infectious diseases, one board-certified in internal medicine and infectious diseases, and one board-certified in medical microbiology. The CAC reviewed the clinical documentation and the blood culture results to determine if a suspicious case was a CRBSI. The trigger for clinical suspicion included the signs and symptoms as detailed in the section above PLUS a positive blood culture (one positive blood culture would suffice for any organism with the exception of coagulase-negative *Staphylococcus*, which required 2 positive cultures). Blood samples were obtained from a peripheral site (or either the arterial or venous catheter hub or the arterial or venous dialysis blood line). Subjects had to show signs and symptoms of CRBSI and no other apparent source of bloodstream infection.

The CAC was convened between the dates of December 2017 and October 2018 to review and adjudicate potential CRBSI cases used for the primary endpoint analysis. The committee evaluated the subjects for suspicious CRBSI events by reviewing the subjects' medical records to ensure that they met the clinical and microbiological criteria for a protocol-defined CRBSI event.

Statistical Analysis Plan

Analysis Sets

The primary efficacy analysis population was the full analysis population (FAP) including all randomized subjects who received at least one dose of study medication. Subjects were analyzed according to their allocated group determined by randomization. The safety population included all patients who took at least one dose of study medication. For this population, subjects were analyzed according to the treatment they actually received.

Control of Multiplicity

The Pocock method was used to derive the interim efficacy boundary. The two-sided significance level of 0.0294 was used for both interim and final analyses. The fixed sequence testing procedure was utilized in the efficacy analyses to control the overall type I error. The comparison of the secondary endpoint of catheter loss for any reason between the treatment groups was formally performed only if the analysis of the primary efficacy endpoint demonstrated that Defencath significantly reduced CRBSI, and the analysis of another secondary efficacy endpoint of loss of catheter patency was formally conducted only if the

analysis of catheter loss for any reason showed that Defencath significantly reduced the incidence of catheter loss.

Analysis of Primary Endpoint

For the primary efficacy endpoint of time to CAC-adjudicated CRBSI, if a subject had a CRBSI adjudicated by the CAC, then time to CRBSI was the number of days between randomization and the occurrence of a CAC-adjudicated CRBSI. Otherwise, a subject was censored at the earliest of the following dates: date of first catheter removal, date of last study drug dose plus three days, and date of study completion. Note that, according to the Applicant, three days was added to the last study drug dose because the study drug would be withdrawn at the next dialysis session, which would typically be about three days later.

A log-rank test was performed to evaluate the treatment difference. A Cox proportional hazard model was utilized to obtain the hazard ratio of Defencath over heparin and its 95% CI for the CAC-adjudicated CRBSI. The incidence rate of CAC-adjudicated CRBSI per 1,000 catheter-days was calculated for each treatment group. The 95% CI for the incidence rate of the event per 1,000 catheter-days was also computed based on the assumption that the number of catheter-days followed an exponential distribution.

Reviewer's comments: There were censored data because subjects completed the study due to catheter removal, death, being transferred to a nonstudy site, termination of dialysis, or when subjects withdrew early from the study. The Applicant assumed all censored data was noninformative, which implied that censoring was unrelated to the study treatment. This assumption may not be valid. The statistical reviewer conducted sensitivity analyses to evaluate the robustness of the study results by including death as an event in addition to CRBSI and also by considering nonpositive disposition events as events. These analyses will be presented in the Sections of Efficacy Results – Primary Endpoint and Additional Analyses Conducted on the Individual Trial.

Analysis of Secondary Endpoints

The secondary efficacy endpoints were analyzed as time to catheter removal for any reason and time to loss of catheter patency. Time to catheter removal for any reason was defined as the number of days between randomization and first catheter removal if a subject had a catheter removed; otherwise, a subject was censored at the study completion date or last study drug dose date plus three days. Similarly, time to loss of catheter patency was defined as the number of days between randomization and date of loss of catheter patency if a subject had an event; otherwise, a subject was censored at the earliest of the following dates: date of first catheter removal, date of last study drug dose plus three days, or date of study completion. The secondary efficacy endpoints were analyzed using the same statistical approaches as those for the primary endpoint.

Protocol Amendments

As mentioned in Section [3.2](#), there were seven protocol revisions. Key amendments included changing the definition of CRBSI, adding a CAC to assess CRBSI, increasing the sample size because of changes to the assumptions for the sample size calculation, and adding an interim analysis that would take place when 50% of the planned CAC-adjudicated CRBSIs occurred.

Reviewer's comments: As the primary endpoint was modified during the trial, the statistical reviewer conducted sensitivity analyses to evaluate the robustness of the study results to the various definitions of outcomes. The details regarding these analyses are presented in the Section Efficacy Results – Primary Endpoint.

8.1.2. Study Results

Compliance With Good Clinical Practices

The study was conducted in compliance with Good Clinical Practice. The statement of Good Clinical Practice is provided in Section 5.2 of the clinical study report.

Financial Disclosure

There were no financial interests to disclose.

Patient Disposition

[Table 6](#) displays patient disposition. In total, 806 subjects were randomized equally to the two treatment arms. The average time in the study was 197 days for the Defencath arm and 198 days for the heparin arm. Among the 806 randomized subjects, 797 subjects received at least one dose of assigned treatment. The most common reason for study completion was catheter removal in both groups. A higher proportion of subjects in the Defencath group had the catheter removed than in the heparin group (56.6% versus 48.4%). A detailed assessment of the reasons for catheter removal is presented in Section [8.2](#). In addition, a total of 44 subjects completed the study due to meeting the primary endpoint definition of CRBSI, with more subjects in the heparin arm than the Defencath arm. Of these 44 subjects, 2 (Subjects (b) (6) and (b) (6)) were not presented to the CAC for adjudication, both were in the heparin arm. Upon the Agency's request for additional information on these two subjects, the Applicant stated that both cases were mistakenly classified as "meeting definition of CRBSI" by the clinical sites and should be considered as "catheter removal (not due to CRBSI)." A detailed review of the two cases showed that neither met criteria for a CRBSI (Subject (b) (6) had only one positive blood culture for a coagulase-negative Staphylococcus species and therefore was not referred to the CAC for adjudication and Subject (b) (6) did not have any microbiology results.) The remaining 42 cases were submitted to the CAC for adjudication. Among them, 36 cases were adjudicated by the CAC as having a CRBSI (8 in the Defencath arm and 28 in the heparin arm), and the remaining 8 cases were adjudicated by the CAC as not having a CRBSI (1 in the Defencath arm and 7 in the heparin arm). A detailed evaluation of the CRBSIs is discussed in

Section 8.1.

Table 6. Patient Disposition (Randomized)

Parameter	Defencath N=403 n (%)	Heparin N=403 n (%)	Total N=806 n (%)
Total number randomized	403 (100)	403 (100)	806 (100)
Received at least one dose of assigned treatment ¹	398 (98.8)	399 (99.0)	797 (98.9)
Completed study	359 (89.1)	356 (88.3)	715 (88.7)
All assessments completed through study closure	74 (18.4)	76 (18.9)	150 (18.6)
CRBSI meeting primary endpoint definition	9 (2.2)	35 (8.7)	44 (5.5)
Catheter removal not due to CRBSI	228 (56.6)	195 (48.4)	423 (52.5)
Death	15 (3.7)	14 (3.5)	29 (3.6)
Transferred to a nonstudy site	29 (7.2)	32 (7.9)	61 (7.6)
Termination of dialysis ²	4 (1.0)	4 (1.0)	8 (1.0)
Early withdrawal	44 (10.9)	47 (11.7)	91 (11.3)
Physician decision (safety concern other than AE)	8 (2.0)	9 (2.2)	17 (2.1)
Adverse event	6 (1.5)	5 (1.2) ³	11 (1.4)
Subject withdrew consent	16 (4.0)	14 (3.5)	30 (3.7)
Protocol violation	2 (0.5)	12 (3.0)	14 (1.7)
Other	12 (3.0)	7 (1.7)	19 (2.4)

Source: Table 2 in LOCK-IT-100 clinical study report

¹ summarized by the statistical reviewer

² Termination of dialysis includes: subject received a renal transplant (n=2), subject recovered renal function (n=2), subject transferred to hospice care/electively terminated dialysis (n=2), subject switched to peritoneal dialysis (n=1), subject had a maturation of AVF (n=1).

³ Subject (b) (6) started treatment on (b) (6), stopped treatment on (b) (6), had catheter removal due to loss of patency on (b) (6), and withdrew from the study on (b) (6). The subject was classified as an early withdrawal due to AE in this table.

Abbreviations: AE = adverse event, CRBSI = catheter-related bloodstream infection.

Reviewer's comment: Patient disposition was likely determined prior to the CAC-adjudication, therefore the numbers in this table did not reflect the final CAC-adjudication outcome.

Protocol Violations/Deviations

As shown in Table 6 above, approximately 2% of subjects withdrew from the study early because of a protocol violation. A lower proportion of subjects in the Defencath group withdrew due to protocol violations compared with the heparin group (0.5% versus 3.0%). These subjects were censored in the primary analysis either at three days after their last study drug dosing date or at the time they withdrew from the study but were considered as events in a sensitivity analysis conducted by the reviewer.

The following is the summary of protocol deviations described in Section 10.2 in the clinical study report. The protocol deviations had limited impact on the overall results of the trial.

- Reconsent for amendments to the informed consent form that reflected relevant modifications to the protocol was not obtained in a timely manner in 38 subjects. According to the Applicant, the amendments to the informed consent form were not related to communicating new safety concerns to the study subjects, but reflected

administrative changes to the protocol, such as the planned number of study sites and subjects, as they were increased.

- There were seven protocol deviations regarding inclusion criteria and 18 deviations related to exclusion criteria.
- There were 17 protocol deviations related to study treatment administration where subjects had the CLS instilled from the incorrect kit or vial.
- Protocol deviations related to study treatment compliance occurred in approximately 21% of treated subjects. The deviations were varied and included subjects who missed consecutive doses due to prolonged hospitalization, who did not receive the CLS on the day of randomization, or who had the incorrect volume of CLS instilled into the catheter (over fill and under fill). Of note, more detailed information on treatment compliance is presented in the section of this review that discusses treatment compliance.
- There were 23 protocol deviations related to missing endpoint assessments, which involved 21 subjects (8 Defencath and 13 heparin).
 - Fifteen deviations occurring in 14 subjects were captured as potential CRBSIs and presented to the CAC: 10 were deemed to be CRBSIs (1 Defencath and 9 heparin) and 5 were not CRBSIs (2 Defencath and 3 heparin).
 - Eight deviations involving eight subjects (5 Defencath and 3 heparin) were not captured as potential CRBSIs.
 - One subject in the Defencath arm was documented as an exit site infection and not a CRBSI.
 - Three subjects had a negative blood culture (2 Defencath and 1 heparin).
 - One subject in the heparin arm had no concurrent symptoms.
 - Two subjects did not have blood cultures performed (1 Defencath and 1 heparin).
 - One subject in the Defencath arm had a blood culture drawn incorrectly.
- There were 10 deviations involving 9 subjects who met withdrawal or study completion criteria but were not withdrawn (4 Defencath and 5 heparin).
- There were 41 other protocol deviations, including lab processing errors and temperature excursions for storage of investigational product.
- There were eight other Good Clinical Practices deviations, including IVRS registration not performed on the day of visit, procedures performed by non-delegated staff, lab report not signed and research unit used for enrollment without prior assessment for adequacy.

Table of Demographic Characteristics

The patient demographics were balanced between the two arms except for sex. The percentage of female subjects in the Defencath group was approximately 8% higher than in the heparin group (45.7% versus 38.2%), and the difference was nominally significant. The median age of the study population was 63 years old and 63% were white.

Table 7. Patient Demographics (Randomized)

Parameter	Defencath N=403	Heparin N=403	Total N=806
Age (years)			
Mean (SD)	60.8 (14.2)	60.9 (14.4)	60.9 (14.3)
Median	63.0	63.0	63.0
Min, max	22, 94	21, 93	21, 94
Age category (years), n (%)			
<65	239 (59.3)	236 (58.6)	475 (58.9)
≥65 to <75	99 (24.6)	95 (23.6)	194 (24.1)
≥75	65 (16.1)	72 (17.9)	137 (17.0)
Sex, n (%)			
Male	219 (54.3)	249 (61.8)	468 (58.1)
Female	184 (45.7)	154 (38.2)	338 (41.9)
Race, n (%)			
White	248 (61.5)	262 (65.0)	510 (63.3)
Black or African American	126 (31.3)	112 (27.8)	238 (29.5)
Asian	15 (3.7)	18 (4.5)	33 (4.1)
American Indian or Alaska Native	3 (0.7)	2 (0.5)	5 (0.6)
Native Hawaiian or other Pacific Islander	10 (2.5)	4 (1.0)	14 (1.7)
Other	1 (0.2)	5 (1.2)	6 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	177 (43.9)	189 (46.9)	366 (45.4)
Not Hispanic or Latino	226 (56.1)	214 (53.1)	440 (54.6)

Source: Table 3 in LOCK-IT-100 clinical study report

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The baseline characteristics were balanced between the two arms. The majority of the subjects (97.6%) had HD treatment three times per week, and 48.3% had their catheter implanted within three months prior to randomization.

Table 8. Baseline Characteristics (Randomized)

Parameter	Defencath N=403	Heparin N=403	Total N=806
BMI at screening (kg/m ²)			
N	401	402	803
Mean (SD)	29.7 (7.9)	29.2 (10.3)	29.4 (9.2)
Median	28.4	27.2	27.7
Min, max	16.0, 63.3	16.9, 165.3	16.0, 165.3
Height (cm)			
N	401	402	803
Mean (SD)	166.6 (10.7)	167.6 (11.3)	167.1 (11.0)
Median	166.8	167.6	167.6
Min, max	117.5, 195.0	71.5, 198.1	71.5, 198.1
Predialysis weight at screening (kg)			
N	402	403	805
Mean (SD)	82.2 (22.5)	81.7 (23.7)	82.0 (23.1)
Median	78.3	76.2	77.1
Min, max	38.4, 167.7	39.2, 173.4	38.4, 173.4

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

Parameter	Defencath N=403	Heparin N=403	Total N=806
Postdialysis weight at screening (kg)			
N	402	403	805
Mean (SD)	80.4 (22.1)	79.7 (23.5)	80.1 (22.8)
Median	76.5	74.8	75.6
Min, max	37.3, 163.4	36.2, 168.1	36.2, 168.1
Frequency of dialysis treatment, n (%)			
2 times per week	4 (1.0)	5 (1.2)	9 (1.1)
3 times per week	395 (98.0)	392 (97.3)	787 (97.6)
4 times per week	4 (1.0)	5 (1.2)	9 (1.1)
Time from placement of study catheter to randomization (months) ¹			
N	397	401	798
Mean (SD)	6.5 (9.2)	6.0 (7.5)	6.2 (8.4)
Median	2.9	3.3	3.1
Min, max	0.2, 59.4	0.2, 66.7	0.2, 66.7
<3 months, n (%)	205 (50.9)	184 (45.7)	389 (48.3)
≥3 months, n (%)	1932 (47.1)	217 (53.8)	410 (50.9)
Missing, n (%)	5 (1.2)	2 (0.5)	7 (0.9)
Time since first dialysis treatment (months)			
N	403	402	805
Mean (SD)	21.2 (37.5)	19.8 (37.0)	20.5 (37.3)
Median	4.6	4.8	4.7
Min, max	0.2, 280.2	0.1, 254.8	0.1, 280.2
≤12 months, n (%)	272 (67.5)	276 (68.5)	548 (68.0)
>12 months, n (%)	131 (32.5)	126 (31.3)	257 (31.9)
Duration of previous dialysis (min)			
N	397	398	795
Mean (SD)	219.2 (28.9)	218.3 (31.3)	218.8 (30.1)
Median	214.5	215.3	215.0
Min, max	124, 378	4, 353	4, 378
Number of catheter cuffs at screening, n (%)			
0	6 (1.5)	7 (1.7)	13 (1.6)
1	118 (29.3)	100 (24.8)	218 (27.0)
2	116 (28.8)	126 (31.3)	242 (30.0)
3	4 (1.0)	3 (0.7)	7 (0.9)
Unknown	127 (31.5)	129 (32.0)	256 (31.8)
Missing	32 (7.9)	38 (9.4)	70 (8.7)
Port location at screening n (%)			
Jugular vein	371 (92.1)	365 (90.6)	736 (91.3)
Subclavian vein	30 (7.4)	31 (7.7)	61 (7.6)
Other	2 (0.5)	6 (1.5)	8 (1.0)
Baseline diabetes n (%)			
Yes	278 (69.0)	277 (68.7)	555 (68.9)
No	125 (31.0)	126 (31.3)	251 (31.1)
Previous infection with CV catheter, n (%)			
Yes	3 (0.7)	4 (1.0)	7 (0.9)
No	400 (99.3)	398 (98.8)	798 (99.0)

Parameter	Defencath N=403	Heparin N=403	Total N=806
Topical prophylaxis antibiotics at catheter exit site, n (%)			
Yes	34 (8.4)	38 (9.4)	72 (8.9)
No	369 (91.6)	364 (90.3)	733 (90.9)
SpKt/V at baseline			
N	381	386	767
Mean (SD)	1.7 (2.1)	1.7 (2.0)	1.7 (2.0)
Median	1.5	1.4	1.4
Min, max	0, 30.4	0, 26.9	0.0, 30.4

Source: Table 14.1.3 in LOCK-IT-100 clinical study report

¹ Summarized by the statistical reviewer

² Subject (b) (6) had catheter placed in (b) (6) and did not know the exact date. The subject was randomized on (b) (6), was excluded in calculation of descriptive statistics of time from placement of study catheter to randomization in months but was considered to having ≥3 months from placement of study catheter to randomization.

Abbreviations: BMI = body mass index; CV = central venous, SpKt/V = single pool Kt/V

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The mean number of doses administered was approximately 69 doses per subject in both arms. According to the Applicant, every effort was made by site personnel to ensure that the randomized study drug was administered at all visits starting from Day 1 through study completion unless contraindicated per investigator judgement. The Applicant calculated a subject's compliance rate as the proportion of the number of dialysis sessions at the study site at which the correct dosing was administered over the total number of dialysis sessions at the study site. The mean compliance rate was approximately 95% for both arms. The compliance rate was less than 80% for 6.5% of the Defencath-treated subjects and 7.8% of the heparin-treated subjects.

Among all randomized subjects who received at least one dose of the assigned treatment, 397 (99.7%) of Defencath subjects and 398 (99.7%) of Heparin subjects had at least one concomitant medication. The most common drug class for concomitant medications was for the blood and blood-forming organs (97.7% of Defencath subjects and 98.0% of Heparin subjects). Other common drug classes were for the cardiovascular system (96.2% of Defencath subjects and 94.7% of Heparin subjects) and alimentary tract and metabolism (91.2% of Defencath subjects and 93.0% of Heparin subjects).

There was no rescue medication use specified in the protocol. As outlined in the exclusion criteria, some systemic immunosuppression medications that would increase risk of infection were prohibited.

CAC Adjudication Results

Of the 795 subjects in the study, 19% (151 of 795 subjects) had blood cultures collected due to suspicion of CRBSI. [Table 9](#) shows the 151 subjects (60 Defencath, 91 heparin) who had blood cultures drawn, of which 69 subjects had one or more positive blood cultures. An additional 10 subjects, 6 in the Defencath arm and 4 in the heparin arm had negative blood cultures but had

catheter tips that were culture-positive. The CAC adjudicated 58 of the 69 subjects for a potential CRBSI event. Of note, 1 subject had 2 potential cases of CRBSI and thus the CAC adjudicated a total of 59 events in 58 subjects. The remaining 11 subjects who were not CAC-adjudicated included 9 subjects who had a single positive blood culture identified as *S. epidermidis* or coagulase-negative *Staphylococcus* (CoNS) but no confirmatory cultures (4 in the Defencath arm and 5 in the heparin arm), and two subjects in the heparin arm who had positive blood cultures but did not manifest clinical signs or symptoms of infection and thus did not meet the criteria for a protocol-defined CRBSI event.

Table 9. Subjects with Positive Blood Cultures in the LOCK-IT-100 Clinical Trial

Parameter	Defencath N=397 n (%)	Heparin N=398 n (%)	Total N=795 n (%)
Blood cultures assessed	60 (15.1)	91 (22.9)	151 (19.0)
Positive blood culture ¹	21 (5.3)	48 (12.1)	69 (8.7)
CAC adjudicated	17 (80.9)	41 (85.4)	58 (84.1)
Non-CAC adjudicated	4 (19.1)	7 (14.6)	11 (15.9)
Single positive (<i>S. epidermidis</i> or CoNS)	4	5	9
No clinical signs or symptoms ²	0	2	2

Source: 16265micro, 5354-cac-summaries-mins

¹ Ten subjects had negative blood cultures, but positive catheter cultures: 4 in the heparin arm (Subject# (b) (6)) and 6 in the Defencath arm (Subject# (b) (6)).

² Subject # (b) (6) (heparin): blood culture grew MRSA and Subject # (b) (6) (heparin): blood culture was positive for MSSA
Abbreviations: CAC = Clinical Adjudication Committee, CoNS = coagulase-negative staphylococci

[Table 10](#) provides data on the 59 CAC-adjudicated events that occurred in a total of 58 subjects. The CAC adjudicated 15 subjects as having “no CRBSI”, 2 subjects as “indeterminate”, and 41 subjects as having a “CRBSI” event. Most subjects who were classified as having “No CRBSI” had a known alternate source of infection, 5 in the Defencath arm and 3 in the heparin arm. There was one subject in the heparin arm who grew methicillin-resistant CoNS with no other confirmatory culture and two subjects who had positive cultures but no signs or symptoms of an infection. The remaining four subjects were adjudicated as “no CRBSI” and were described as “Other” in [Table 10](#) below. The details of these four subjects are as follows:

Subject# (b) (6) (Defencath) – The CAC noted that the subject had multiple catheter exchanges, removals, and placements prior to the CRBSI event in question. The CAC did not adjudicate the subject further and the assessment was classified as “no CRBSI.” This was considered a possible protocol violation.

Subject# (b) (6) (Defencath) – The subject had two blood cultures that grew MSSA; however, the catheter had been removed 10 days prior to the CRBSI event. The CAC noted that since the CRBSI event occurred after the catheter removal, the CRBSI could not be attributed to the initial (study) catheter since the patient was not receiving the investigational product at the time of the event.

Subject# (b) (6) (heparin) – The subject had two positive cultures. One blood culture (unknown source) grew *Streptococcus mitis/oralis* and the other blood culture (venous source) grew *Streptococcus gordonii*. The subject showed clinical signs and symptoms and no other source of infection was identified. The CAC adjudicated the two isolates as different organisms and classified the case as “no CRBSI.”

Subject# (b) (6) (heparin) – The subject presented to their family physician reporting a fever for 3 days as well as pain at the catheter site, headache, fatigue, nausea and cough. The two blood cultures taken at the family physician’s office from a tunneled peripherally inserted central catheter (PICC) line (nondialysis) grew CoNS. Repeat blood cultures at the HD center a day later from both the HD CVC and the PICC showed no growth. It is important to note that the PICC line was not the clinical study line. The CAC adjudicated the case as “no CRBSI”.

One subject each from the Defencath and heparin arms were adjudicated by the CAC as “indeterminate”:

Subject# (b) (6) (Defencath) – The subject presented with clinical signs and symptoms and had a blood culture (peripheral) that grew *Streptococcus sanguinis*. The exit site appeared normal. However, the subject had a sputum culture that grew a group B streptococci (*S. agalactiae*) and *Moraxella catarrhalis*. The CAC considered the case “indeterminate” because *S. sanguinis* is not commonly associated with CRBSI. Additionally, the patient had an alternative source of infection (the attending clinician noted that the subject may have had pneumonia in the eCRF).

Subject# (b) (6) (heparin) – The subject presented with clinical signs and symptoms (low grade fever and elevated white blood cell [WBC] count) and a single set of blood cultures (unknown source) grew MSSA. A repeat blood culture grew *S. epidermidis* and *Veillonella* spp. from the dialysis line. The exit site did not show signs of infection. The CAC summary noted that the blood cultures with *S. epidermidis* also had a *Lactobacillus* species. Additionally, the catheter tip culture showed no growth. There was also a question of whether the blood cultures with MSSA may have been obtained peripherally. A chest x-ray showed a possible retrocardiac infiltrate and vital signs showed a decreased oxygen saturation of 72% on admission suggesting a possible pneumonia. Initial antibacterial drug therapy included vancomycin and levofloxacin for line-associated infection and pneumonia. Due to the presence of a possible alternative source of infection (i.e., pneumonia) and the uncertainty of the CRBSI diagnosis, the CAC assessed the case as “indeterminate”.

Table 10. CAC-Adjudicated Subjects (N=58) in the LOCK-IT-100 Clinical Trial

	Defencath N=397	Heparin N=398	Total N=795
Parameter	n	n	n
CAC-adjudicated	17	41	58
CRBSI	9	32	41
No CRBSI	7	8	15
Known alternate source of infection ¹	5	3	8
Single positive (<i>S. epidermidis</i> or CoNS) ²	0	1	1
No clinical signs or symptoms ³	0	2	2
Other ⁴	2	2	4
Indeterminate	1	1	2

Source: 16265micro; 5354-cac-summaries-mins

¹ In Defencath arm: gall bladder (Subject# (b) (6)), Wound (Subject# (b) (6)), cellulitis (Subject# (b) (6)), graft infection (Subject# (b) (6)), cUTI (Subject# (b) (6)); heparin arm: perforated bowel (Subject# (b) (6)); right abdominal/pelvic abscess (Subject# (b) (6)) and AV graft infection (Subject# (b) (6)).

² Heparin arm: Methicillin-resistant CoNS (Subject# (b) (6)).

³ Subject# (b) (6) (heparin) had 2 positive blood cultures that grew *S. epidermidis* but did not have clinical signs or symptoms; the exit site grew MRSA. Subject# (b) (6) (heparin) was assessed 2 times by the CAC. In the first assessment, the blood culture grew alpha-hemolytic streptococci (non-Group D) and the clinical signs and symptoms were attributed to suspected community acquired pneumonia. In the 2nd assessment, the blood grew bacilli species; however, the subject did not show clinical signs or symptoms. It was noted that the subject had cellulitis of the foot and lower leg.

⁴ "Other" included the following subjects: - Defencath arm: Subject# (b) (6) and Subject# (b) (6); Heparin arm: Subject# (b) (6) and Subject# (b) (6).

Abbreviations: CAC = clinical adjudication committee, CoNS = coagulase-negative Staphylococcus infection, CRBSI = catheter-related bloodstream infection

Efficacy Results – Primary Endpoint

The planned interim analysis was conducted when 28 CAC-adjudicated CRBSIs had occurred. The results are summarized in [Table 11](#). The treatment difference was statistically significant in favor of Defencath. Subjects in the Defencath group had a 72% reduction in risk of CAC-adjudicated CRBSIs as compared to those in the heparin group. The Data and Safety Monitoring Board recommended early termination of the study based on the results of the interim analysis.

Additional subjects were randomized and treated between the date that the database was locked for the interim analysis and the date when the study was stopped. Also, additional subjects experienced CAC-adjudicated CRBSI events between the database lock and the date of the last patient completing the study. As shown in [Table 11](#), the results using all data through the study completion were similar to the findings from the interim analysis. [Figure 2](#) displays the cumulative incidence of the CAC-adjudicated CRBSIs at study completion per treatment group using the Kaplan-Meier approach generated by the statistical reviewer.

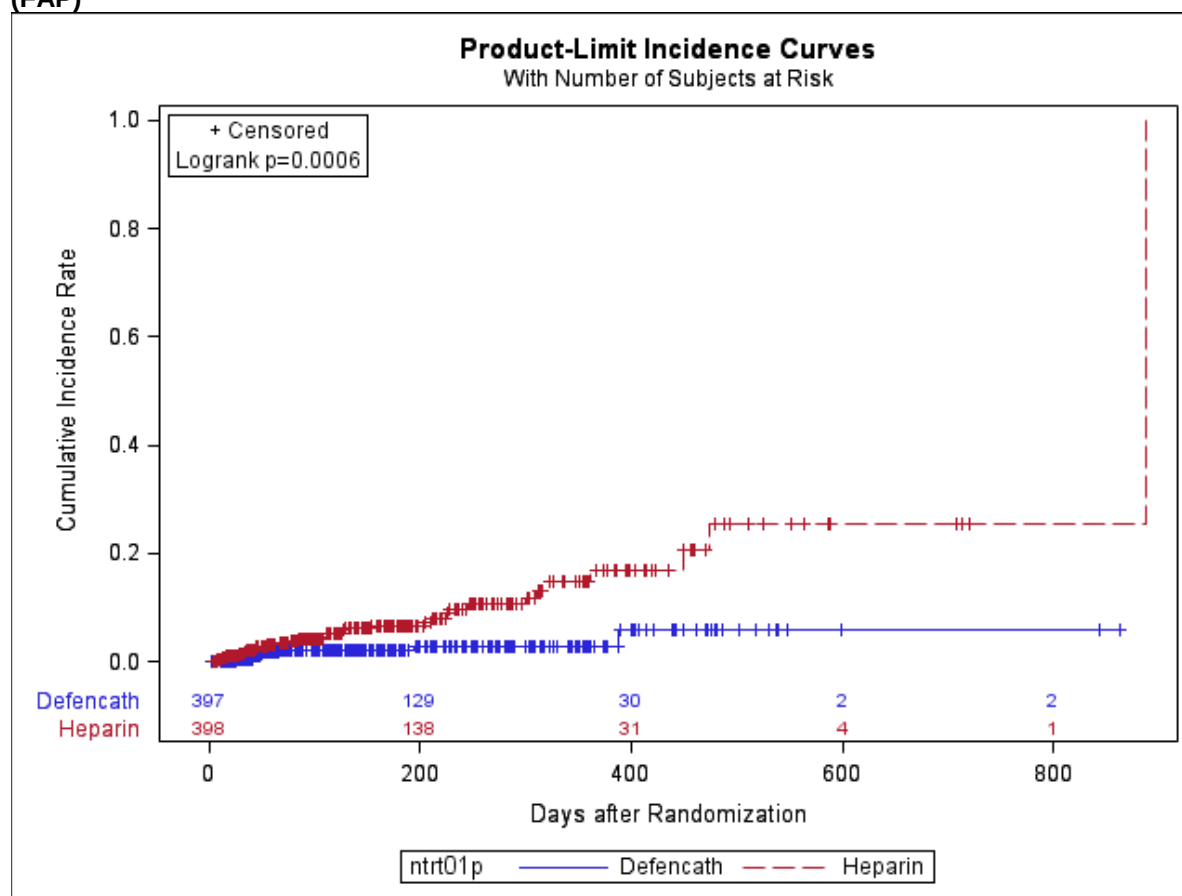
Table 11. Primary Analyses for Primary Efficacy Endpoint at Interim and Study Completion (FAP)

Parameter	Interim Analysis		Final Analysis	
	Defencath N=327	Heparin N=326	Defencath N=397	Heparin N=398
Number of subjects with CAC- adjudicated CRBSI, n (%)	6 (1.8)	22 (6.7)	9 (2.3)	32 (8.0)
Log-rank test p-value	0.0034		0.0006	
Hazard ratio (Defencath /Heparin) (95% CI)	0.28 (0.11, 0.70)		0.29 (0.14, 0.62)	
Event rate per 1,000 catheter- days (95% CI)	0.14 (0.06, 0.30)	0.49 (0.32, 0.75)	0.13 (0.07, 0.26)	0.46 (0.33, 0.66)

Source: Tables 5, 6, 7 and 8 in LOCK-IT-100 clinical study report

Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection; FAP = full analysis population

Figure 2. Kaplan-Meier Cumulative Incidence of CAC-Adjudicated CRBSI at Study Completion (FAP)



Source: statistical reviewer's plot

Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection, FAP = full analysis population

Reviewer's comments: There were two subjects, one for each group, who failed screening but were randomized into the study and received one day of allocated

study drug. The Applicant excluded them from the efficacy analysis and included them in the safety analysis. Based on the definition of the FAP, these two subjects should be included in the efficacy analysis as well. The reviewer conducted a sensitivity analysis including these two subjects and censoring them at Day 1 using all the data at study completion. The results were identical to those for the final analysis shown in [Table 11](#).

The protocol criteria to determine CRBSI were more stringent than the CAC's criteria. One of the Applicant's sensitivity analyses was to define the CRBSI based on the criteria in the protocol. Six cases met the protocol criteria, all in the heparin group. The results at study completion are displayed in [Table 12](#). The treatment difference was statistically significant at the nominal significance level of 0.0294.

Another sensitivity analysis the Applicant conducted was to classify two CRBSIs considered as indeterminate by the CAC as CRBSI. The results are summarized in [Table 12](#) as well and were similar to the primary analyses.

Table 12. Applicant's Sensitivity Analyses at Study Completion (FAP)

Analysis	Defencath N=397 n (%)	Heparin N=398 n (%)	Log Rank P-Value Hazard Ratio and 95% CI	Event Rate Per 1,000 Catheter-Days and 95% CI	
				Defencath	Heparin
CRBSI based on protocol definition	0 (0)	6 (1.5)	0.0251 0.0 (0.0, --)	--	--
CAC adjudicated CRBSI and indeterminate cases	10 (2.5)	33 (8.3)	0.0008 0.32 (0.16, 0.65)	0.15 (0.08, 0.27)	0.48 (0.34, 0.67)

Source: Tables 9, 10 and 14.2.4.3 in LOCK-IT-100 clinical study report

Abbreviations: CAC = Clinical Adjudication Committee, CRBSI = catheter related bloodstream infection, FAP = full analysis population

FDA Readjudication of CAC Cases

To confirm the validity of the CAC adjudication, the clinical review team re-evaluated the cases presented to the CAC. Two clinical reviewers, MW and HH, reviewed all 59 cases independently and were blinded to the CAC's assessment of the cases in order to arrive at a decision or to request more information from the Applicant. Any discrepant results were then discussed and if a consensus was not reached, a third clinician, PK, served as the tiebreaker. The results of the FDA-adjudication are presented in [Table 13](#). Three cases were discrepant between the FDA and CAC-adjudication of cases (noted with an asterisk in the first column).

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Table 13. FDA and CAC Adjudication Results by Study Arm and Patient ID

Study Arm	Patient ID	Adjudication (CAC)	Adjudication (FDA)
Heparin	(b) (6)	Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin*		Yes	Indeterminate
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		Yes	Yes
Heparin		No	No
Heparin*		No	Yes
Heparin		No	No
Heparin		No	No
Heparin		No	No
Heparin ^a		No	No
Heparin ^b		No	No
Heparin		No	No
Heparin		No	No
Heparin		Indeterminate	Indeterminate
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes
Defencath		Yes	Yes

Study Arm	Patient ID	Adjudication (CAC)	Adjudication (FDA)
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath	(b) (6)	No	No
Defencath*	(b) (6)	Indeterminate	No

* Discrepant results between FDA and CAC adjudication.

^a Subject (b) (6) was evaluated for two cases of potential CRBSI by the CAC. Case 1

^b Case 2

Abbreviations: CAC = clinical adjudication committee

The overall results of the adjudication for both the FDA and the CAC are presented in [Table 14](#). In total, 41 cases were adjudicated as having a CRBSI, 16 cases were adjudicated as not having a CRBSI, and 2 cases were adjudicated as indeterminate by both the FDA and the CAC. Both the FDA and the CAC adjudicated 9 cases in the Defencath arm and 32 cases in the heparin arm as CRBSIs. In the Defencath arm, 8 subjects were adjudicated as not having a CRBSI by the FDA while 7 subjects were adjudicated as not having a CRBSI by the CAC, with the remaining one subject adjudicated as indeterminate by the CAC. No subjects in the Defencath arm were adjudicated as indeterminate by the FDA. In the heparin arm, 8 subjects were adjudicated as not having a CRBSI by the FDA while the CAC adjudicated 9 subjects as not having a CRBSI. One case in the heparin arm was adjudicated as indeterminate by the CAC and two cases were adjudicated as indeterminate by the FDA.

Table 14. Results of CAC and FDA Adjudication Overall and By Study Arm

Analysis	Defencath			Heparin			Total		
	Yes CRBSI	No CRBSI	Indeterminate	Yes CRBSI	No CRBSI	Indeterminate	Yes CRBSI	No CRBSI	Indeterminate
CAC-Adjudication	9	7	1	32	9	1	41	16	2
FDA-Adjudication	9	8	0	32	8	2	41	16	2

Source: Clinical Reviewer's Analysis

Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection

Discrepant Results

Three cases were discrepant between the FDA and CAC adjudication of cases, Subjects (b) (6), and are discussed in further detail below.

Subject# (b) (6) (heparin) – The subject was assessed by the CAC as “no CRBSI”. The Agency classified the subject as having a “CRBSI.” As stated previously, this subject had two positive cultures that were CAC-adjudicated as growing different organisms in which one blood culture (unknown source) grew *Streptococcus mitis/oralis* and the other blood culture (venous source) grew *Streptococcus gordonii*. It is important to note that *S. mitis/oralis* and *S. gordonii* are viridans streptococci. There is difficulty in differentiating the two organisms because they are closely related without sending to a reference laboratory. Because the subject showed clinical signs and symptoms of

infection and no other source was identified, the Agency classified this subject as having a “CRBSI.”

Subject# (b) (6) (Defencath) – The subject was assessed by the CAC as “indeterminate”. The Agency classified the event as “no CRBSI.” The subject grew *S. sanguinis* from a single peripheral blood culture and a sputum culture grew *S. agalactiae* and *M. catarrhalis*. In the eCRF, the attending physician reported that the subject may have had pneumonia, thus indicating that there was a probable source for the positive blood culture. The subject’s CT scan on admission to the hospital showed bilateral effusions, ground glass and patchy opacities in the right upper lobe and right middle lobe, concerning for infection and the subject was noted to be unresponsive and apneic on arrival to the hospital and required intubation. The subject remained hospitalized for 4 days. He was discharged to a nursing home and was readmitted later that same day with worsening respiratory failure and died the following day. The Agency classified the subject as “no CRBSI” due to the suspected alternate source of infection.

Subject# (b) (6) (heparin) – The subject was assessed by the CAC as having experienced a “CRBSI”. The Agency classified the event as “indeterminate.” Though the subject showed signs and symptoms of an infection and one blood culture (unknown source) grew *K. pneumoniae*, it was noted that the subject had multiple potential sources of infection. The subject presented with fever, chills, productive cough, vomiting, elevated blood pressure and heart rate, and a temperature of 39.6°C. A chest x-ray showed questionable confluent opacities in the left lower lung zone. The subject was also noted to have a right foot planter ulcer, and an MRI of the right foot showed cellulitis/myositis. The patient’s wound culture grew *S. saprophyticus*. Additionally, the subject was noted on admission to have a hematoma in the left arm arteriovenous fistula, raising the possibility of an infected hematoma. Additional information was requested from the Applicant for this subject, including a discharge summary, if available, or a catheter tip culture, if available. The Applicant responded to this request with hospitalization records and a discharge summary. There was no mention in the patient’s CRF of a catheter tip culture being taken. The patient’s operative notes from the hospitalization stated, “infected permanent catheter and right foot infected ulcer”. The patient’s discharge paperwork also noted the final diagnosis as pneumonia with *K. pneumoniae* bacteremia. Due to the confounding issues, the Agency assessed the subject as “indeterminate.”

Reviewer’s comments: As described above, the clinical reviewers re-evaluated the CAC-adjudicated CRBSIs. There were three discrepant cases between the clinical reviewers’ and CAC’s assessments, as described in detail above. The statistical reviewer performed a sensitivity analysis based on the FDA-adjudicated CRBSIs. Additionally, as the protocol definition of the primary endpoint of a CRBSI event changed to a CAC-adjudicated event as the study proceeded, the statistical reviewer conducted a variety of sensitivity analyses to assess how robust the

results were to the various outcome definitions used in the trial. The censoring rule in these sensitivity analyses was the same as the Applicant's for the primary efficacy endpoint. The findings from these sensitivity analyses consistently demonstrated a treatment effect for Defencath in reducing the incidence of CRBSI.

As noted in [Table 2](#), 8 of the 9 CRBSIs in the Defencath arm and 18 of the 32 CRBSIs in the heparin arm were due to gram-positive organisms, while gram-negative organisms accounted for 1 of the 9 CRBSIs in the Defencath arm and 14 of 32 CRBSIs in the heparin arm. These observations raised the possibility of differential activity of Defencath with more activity against gram-negative organisms vs. gram-positive organisms; however, the taurolidine MIC values were similar for gram-positive and gram negative organisms, and ranged from 64 to 1024 µg/mL against gram-positive bacteria and 512 to 1024 µg/mL against the gram-negative bacteria (see section [4.3 Clinical Microbiology](#) for additional details). A sensitivity analysis based on CAC-adjudicated CRBSI with gram-positive organisms did not show a statistically significant difference between the two arms ($p=0.0551$); however, the small number of CRBSI events in the study may be a factor. This result is consistent with previous studies in the literature, including a systematic review, which reported that taurolidine-based CLSs significantly decreased the incidence of CRBSIs due to gram-negative bacteria ($p=0.004$), but were associated with a nonsignificant decrease in gram-positive infections ($p=0.07$) (Liu 2013). One possible explanation for the difference in the number of CRBSIs due to gram-positive versus gram-negative organisms following treatment with a taurolidine-based lock solution may be related to whether the source of the CRBSI is an extra- or intraluminal source. CLSs combat intraluminal contamination and if the source is extra-luminal, for example, secondary to an exit-site infection from a gram-positive organism, the CLS may not be effective. The literature on intra-versus extraluminal sources of CRBSI is further discussed in section [16.3 Additional Clinical Microbiology Information](#). Additional sensitivity analyses with or without the inclusion of deaths are presented in [Table 15](#) and [Table 16](#).

Table 15. Reviewer's Sensitivity Analyses Without Considering Death as Event at Study Completion (FAP)

Analysis	Defencath N=397 n (%)	Heparin N=398 n (%)	Log Rank P-Value Hazard Ratio and 95% CI	Event Rate Per 1,000 Catheter-Days and 95% CI	
				Defencath	Heparin
CAC-adjudicated CRBSI with gram-positive organism	8 (2.0)	18 (4.5)	0.0551 0.45 (0.20, 1.04)	0.12 (0.06, 0.24)	0.26 (0.16, 0.41)
FDA-adjudicated CRBSI	9 (2.3)	32 (8.0)	0.0006 0.29 (0.14, 0.62)	0.13 (0.07, 0.26)	0.46 (0.33, 0.66)
FDA-adjudicated CRBSI + indeterminate	9 (2.3)	34 (8.5)	0.0003 0.28 (0.13, 0.58)	0.13 (0.07, 0.26)	0.49 (0.35, 0.69)
Cases presented to CAC to adjudicate ¹	16 (4.0)	41 (10.3)	0.0018 0.41 (0.23, 0.73)	0.24 (0.15, 0.39)	0.60 (0.44, 0.81)
Positive blood or catheter cultures (whether or not sent to CAC) ¹	26 (6.5)	52 (13.1)	0.0067 0.53 (0.33, 0.84)	0.39 (0.27, 0.57)	0.76 (0.58, 1.00)

Source: Statistical Reviewer's Analysis

¹ A subject who had a CRBSI 110 days after the first catheter was removed was not considered as having a CRBSI in the analysis. Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection; FAP = full analysis population

Table 16. Reviewer's Sensitivity Analyses Considering Death as Event at Study Completion (FAP)

Analysis	Defencath N=397 n (%)	Heparin N=398 n (%)	Log Rank P-Value Hazard Ratio and 95% CI	Event Rate Per 1,000 Catheter-Days and 95% CI	
				Defencath	Heparin
CRBSI based on definition in protocol definition + death	18 (4.5)	26 (6.5)	0.3294 0.74 (0.40, 1.36)	0.27 (0.17, 0.42)	0.38 (0.26, 0.55)
CAC-adjudicated CRBSI with gram-positive organism + death	26 (6.5)	35 (8.8)	0.2901 0.76 (0.46, 1.27)	0.38 (0.26, 0.56)	0.51 (0.36, 0.70)
CAC-adjudicated CRBSI + deaths	27 (6.8)	48 (12.1)	0.0250 0.59 (0.37, 0.94)	0.40 (0.27, 0.58)	0.70 (0.52, 0.92)
FDA-adjudicated CRBSI + death	27 (6.8)	48 (12.1)	0.0247 0.59 (0.36, 0.94)	0.40 (0.27, 0.58)	0.70 (0.52, 0.92)
CAC-adjudicated CRBSI + indeterminate + death	27 (6.8)	49 (12.3)	0.0191 0.57 (0.36, 0.92)	0.40 (0.27, 0.58)	0.71 (0.54, 0.94)
FDA-adjudicated CRBSI + indeterminate + death	27 (6.8)	50 (12.6)	0.0146 0.56 (0.35, 0.90)	0.40 (0.27, 0.58)	0.72 (0.55, 0.96)
Cases presented to CAC to adjudicate ¹ + death	32 (8.1)	56 (14.1)	0.0191 0.60 (0.39, 0.92)	0.47 (0.34, 0.67)	0.82 (0.63, 1.06)
Positive blood or catheter cultures (whether or not sent to CAC) ¹ + death	41 (10.3)	67 (16.8)	0.0237 0.64 (0.43, 0.95)	0.61 (0.45, 0.83)	0.98 (0.77, 1.24)

Source: Statistical Reviewer's Analysis

¹ A subject who had a CRBSI 110 days after the first catheter was removed was not considered as having event in the analysis. Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection; FAP = full analysis population

Data Quality and Integrity

Overall, the quality of the data was sufficient. It is possible to reproduce the efficacy endpoint and conduct sensitivity analyses from the original data source. It is noted that the statistical analysis plan and its addendum were completed after the interim analysis.

Efficacy Results – Secondary and Other Relevant Endpoints

[Table 17](#) and [Figure 3](#) present the results for the secondary efficacy endpoint of catheter removal for any reason. The proportion of subjects with catheter removal was comparable between the two treatment arms. The median time to catheter removal for the Defencath arm was shorter than for the heparin arm, but the treatment difference was not statistically significant. There were 34 subjects in the Defencath arm and 31 subjects in the heparin arm with “other” reasons for catheter malfunction which are detailed under [Table 17](#). There were 3 subjects in the Defencath arm and 2 subjects in the heparin arm which did not fall under the categories detailed in the table. The three subjects in the Defencath arm had the following reasons listed in their CRF as “other” reasons for catheter malfunction; “tubing leaking n[sic] top of the hub at the arterial site”, “right side of catheter was not functioning correctly”, and “CVC was exchange [sic] to a new CVC”. The 2 subjects in the heparin arm had the following reasons listed in their CRF as “other” reasons for catheter malfunction; “air leak in permanent catheter” and “catheter was possibly causing SVTs and was exchanged”.

In addition, the Applicant considered catheter removal due to “Catheter is no longer needed for hemodialysis” as a positive reason for catheter removal. In this category, 156 out of 162 Defencath subjects and 129 out of 132 heparin subjects had catheter removal due to maturation of the arteriovenous (AV) graft. The results of the analyses of catheter removal due to patients having a mature AV graft are summarized in [Table 18](#).

Table 17. Secondary Efficacy Endpoint of Catheter Removal for Any Reasons (FAP)

Parameter	Defencath N=397	Heparin N=398
Number of subjects with study catheter removal for any reason, n (%)	236 (59.4)	225 (56.5)
Reasons for catheter removal, n (%)		
As a result of CRBSI	8 (2.0)	29 (7.3)
Catheter malfunction	62 (15.6)	57 (14.3)
Loss of patency	28 (7.1)	26 (6.5)
Other	34 (8.6)	31 (7.8)
Catheter is no longer needed for hemodialysis ¹	162 (40.8)	132 (33.2)
Other ²	4 (1.0)	7 (1.8)
Time to study catheter removal for any reason		
Median time in days (95% CI)	197 (171, 224)	225 (187, 248)
P-value based on log-rank test		0.4161
Hazard ratio (95% CI)		1.08 (0.90, 1.29)
Event rate per 1,000 catheter-days (95% CI)	3.5 (3.1, 4.0)	3.2 (2.8, 3.7)

Source: Tables 18, 19, 20 and 14.2.8.5 in LOCK-IT-100 clinical study report

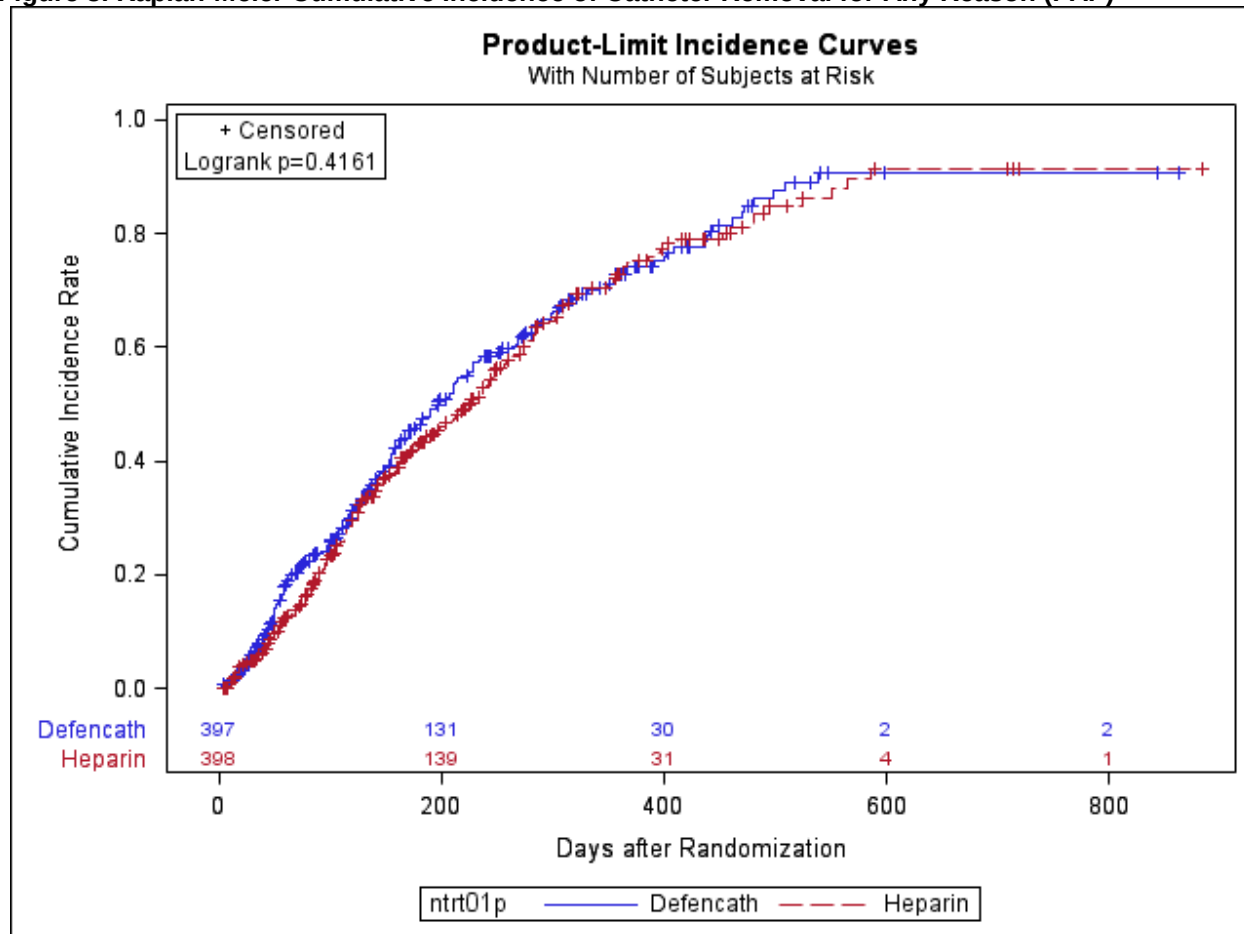
¹Including one subject who had improved renal function

²In the Defencath arm, “Other” included: catheter dislodgement/broken CVC (n=20); thrombosis in device (n=5); exit site infection (n=2); catheter malfunction not otherwise specified (n=4). In the heparin arm, “Other” included: catheter dislodgement/broken CVC

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(n=22); thrombosis in device (n=3); exit site infection (n=3); concern for CRBSI without positive cultures (n=1). In addition there were 3 subjects in the Defencath arm and 2 subjects in the heparin arm that did not fall into any of the categories. Abbreviations: CRBSI = catheter-related bloodstream infection, FAP = full analysis population

Figure 3. Kaplan-Meier Cumulative Incidence of Catheter Removal for Any Reason (FAP)



Source: Statistical reviewer's plot based on the Applicant's responses to an IR submitted on 12/04/2020
Abbreviations: FAP = full analysis population

Two post hoc analyses were conducted to assess whether there were any treatment differences in time to catheter removal due to a mature AV graft and time to catheter removal due to CRBSI. As shown in [Table 18](#) and [Figure 4](#), a higher proportion of subjects in the Defencath arm transitioned to an AV fistula, and the transition was faster although the treatment difference was not statistically significant.

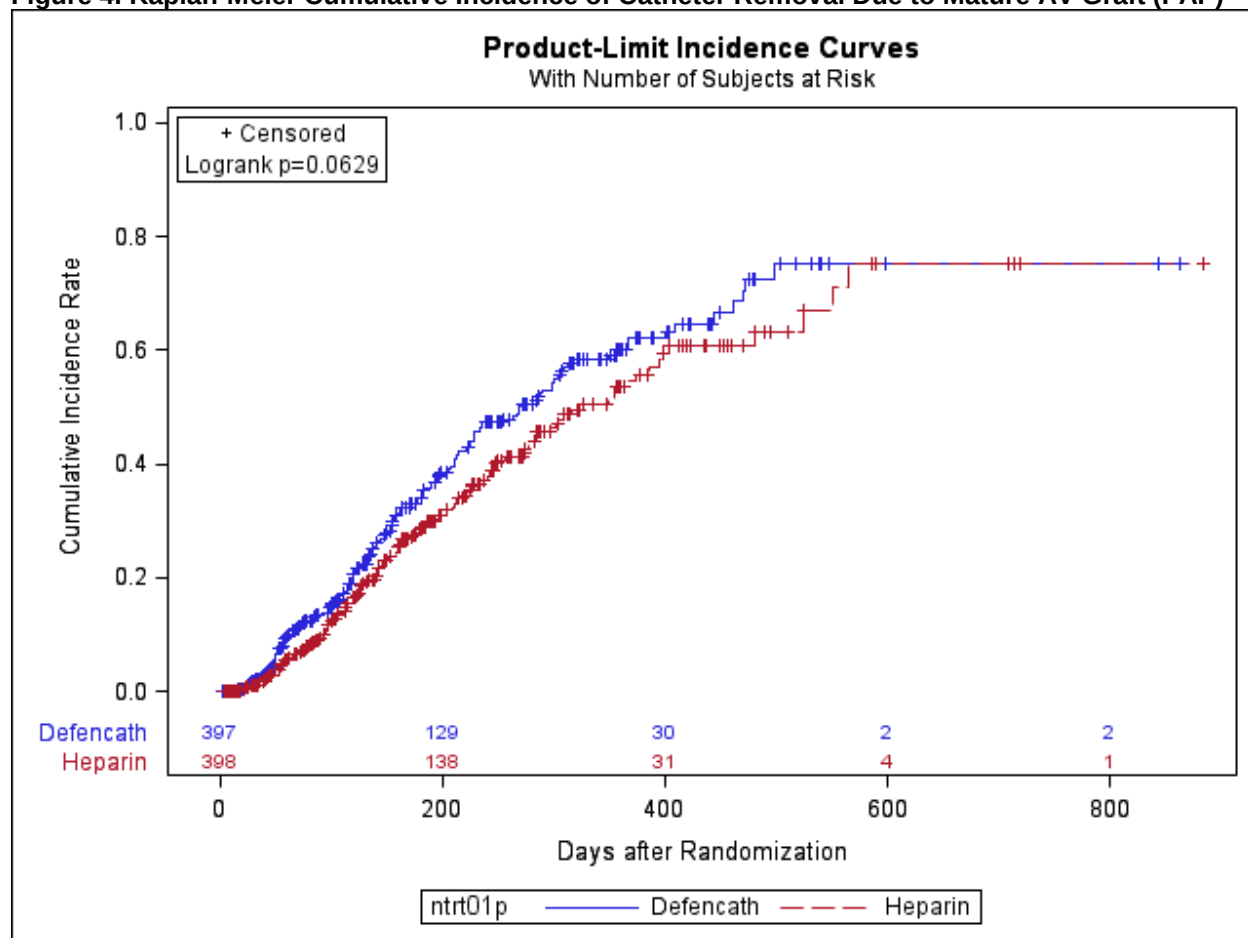
Table 18. Catheter Removal Due to Mature AV Graft (FAP)

Parameter	Defencath N=397	Heparin N=398
Number of subjects with catheter removal due to mature AV graft, n (%)	156 (39.3)	129 (32.4)
Time to catheter removal for mature AV graft		
Median time in days (95% CI)	268 (224, 309)	326 (277, 395)
P-value based on log-rank test	0.0629	
Hazard ratio (95% CI)	1.3 (1.0, 1.6)	
Event rate per 1,000 catheter-days (95% CI)	2.3 (2.0, 2.7)	1.9 (1.6, 2.2)

Source: Applicant's responses to an IR submitted on 12/04/2020

Abbreviations: AV = arteriovenous, FAP = full analysis population

Figure 4. Kaplan-Meier Cumulative Incidence of Catheter Removal Due to Mature AV Graft (FAP)



Source: Statistical reviewer's plot based on the Applicant's responses to an IR submitted on 12/04/2020

Abbreviations: AV = arteriovenous, FAP = full analysis population

Regarding time to catheter removal due to CRBSI, there was an insufficient number of CRBSI events to obtain the median time to catheter removal due to CRBSI, but the treatment difference was apparent, which was consistent with the results for the primary efficacy endpoint ([Table 19](#) and [Figure 5](#)).

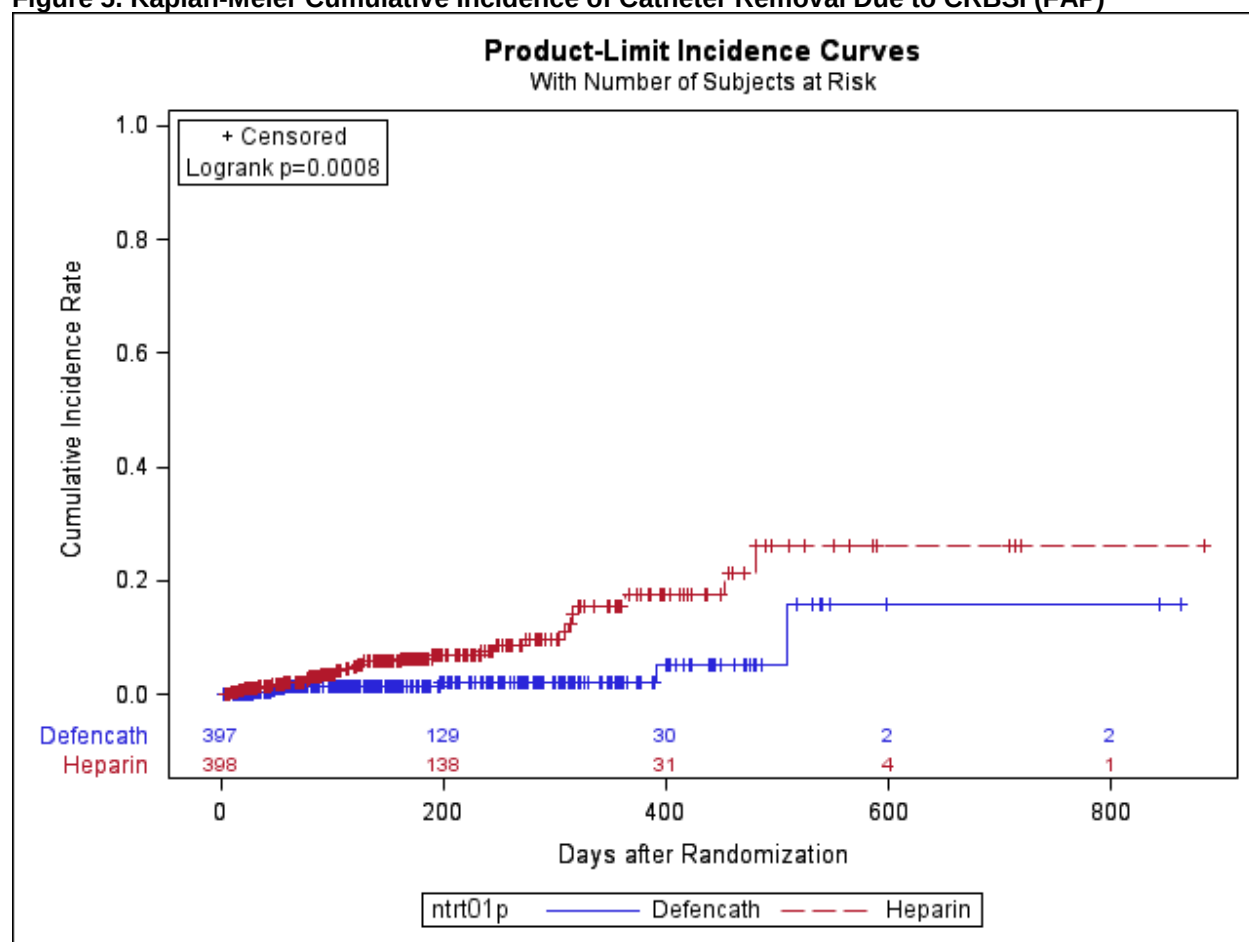
Table 19. Catheter Removal Due to CRBSI (FAP)

Parameter	Defencath N=397	Heparin N=398
Number of subjects with catheter removal due to CRBSI	8 (2.0)	29 (7.3)
Time to catheter removal due to CRBSI		
Median time in days (95% CI)	--	--
P-value based on log-rank test	0.0008	
Hazard ratio (95% CI)	0.3 (0.1, 0.6)	
Event rate per 1,000 catheter-days (95% CI)	0.1 (0.1, 0.2)	0.4 (0.3, 0.6)

Source: Applicant's responses to IR submitted on 12/04/2020

Abbreviations: CRBSI = catheter-related bloodstream infection, FAP = full analysis population

Figure 5. Kaplan-Meier Cumulative Incidence of Catheter Removal Due to CRBSI (FAP)



Source: Statistical reviewer's plot based on the Applicant's responses to an IR submitted on 12/04/2020

Abbreviations: CRBSI = catheter-related bloodstream infection, FAP = full analysis population

The results of another secondary efficacy endpoint of time to loss of catheter patency are summarized in [Table 20](#). The Defencath-treated subjects had a numerically higher proportion of loss of catheter patency events defined as either tPA usage for loss of patency or catheter removal due to loss of patency. This was driven by a higher proportion of subjects using tPA for loss of patency in the Defencath arm.

Table 20. Secondary Efficacy Endpoint of Loss of Catheter Patency at Study Completion (FAP)

Parameter	Defencath N=397 n (%)	Heparin N=398 n (%)	Log Rank P-Value Hazard Ratio and 95% CI	Event Rate Per 1,000 Catheter-Days and 95% CI	
				Defencath	Heparin
Subjects with loss of catheter patency	63 (15.9)	48 (12.1)	0.1224 1.34 (0.92, 1.96)	0.99 (0.27, 1.27)	0.74 (0.55, 0.98)
Subjects with use of tPA for loss of catheter patency	46 (11.6)	33 (8.3)	0.1220 ² 1.42 (0.91, 2.22) ²	0.72 (0.54, 0.97)	0.51 (0.36, 0.71)
Subjects with catheter removal due to loss of patency	28 (7.1)	26 (6.5)	0.7495 ² 1.09 (0.64, 1.86) ²	0.41 (0.29, 0.60)	0.38 (0.26, 0.55)

Source: Tables 14.2.9.1, 14.2.10.1, 14.2.10.3 and 14.2.10.5 in LOCK-IT-100 clinical study report

¹ Eleven subjects in each group used tPA for loss of catheter patency before removal of the catheter due to loss of patency.

² The log rank test p-value, hazard ratio and 95% CI were calculated by the statistical reviewer.

Abbreviations: FAP = full analysis population, tPA = tissue plasminogen activating factor

Dose/Dose Response

Not applicable

Durability of Response

Not applicable

Persistence of Effect

The primary efficacy endpoint was time to CAC-adjudicated CRBSI. This could be deemed to assess persistence of effect of Defencath in reducing the incidence of CAC-adjudicated CRBSI.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (Patient-Reported Outcome) Endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant calculated the incidence rates of CAC-adjudicated CRBSI per 1,000 catheter-days for the selected subgroups in LOCK-IT-100 ([Table 21](#)). Outcomes were generally favorable across all subgroups considered except for the subgroup consisting of patients with an HD port located at a site other than the jugular vein. However, the sample size for this subgroup was small and the results were highly variable.

Table 21. Subgroup Analysis for CAC-Adjudicated CRBSI at Study Completion (FAP)

Parameter	Defencath N=397			Heparin N=398		
	Number of Subjects	Number of Events ¹ n (%)	Event ¹ Rate Per 1,000 Catheter-Days (95% CI)	Number of Subjects	Number of Events ¹ n (%)	Event ¹ Rate Per 1,000 Catheter-Days (95% CI)
Age (years)						
<65	235	6 (2.6)	0.15 (0.07, 0.34)	233	14 (6.0)	0.36 (0.21, 0.60)
≥65 to <75	98	2 (2.0)	0.12 (0.03, 0.47)	94	10 (10.6)	0.63 (0.34, 1.16)
≥75	64	1 (1.6)	0.09 (0.01, 0.65)	71	8 (11.3)	0.58 (0.29, 1.17)
Race						
White	244	6 (2.5)	0.14 (0.06, 0.32)	259	19 (7.3)	0.41 (0.26, 0.65)
Black/African American	124	3 (2.4)	0.15 (0.05, 0.46)	110	9 (8.2)	0.50 (0.26, 0.96)
Other ²	29	0	--	29	4 (13.8)	0.82 (0.31, 2.18)
Gender						
Male	215	3 (1.4)	0.08 (0.03, 0.25)	246	14 (5.7)	0.33 (0.19, 0.55)
Female	182	6 (3.3)	0.19 (0.09, 0.43)	152	18 (11.8)	0.69 (0.44, 1.10)
Time since first dialysis						
≤12 months	267	5 (1.9)	0.13 (0.05, 0.30)	272	17 (6.3)	0.38 (0.24, 0.61)
>12 months	130	4 (3.1)	0.14 (0.05, 0.38)	126	15 (11.9)	0.62 (0.37, 1.03)
Age of catheter (prior to random.)						
<3 months	202	4 (2.0)	0.13 (0.05, 0.34)	183	11 (6.0)	0.35 (0.19, 0.63)
≥3 months	191	5 (2.6)	0.14 (0.06, 0.34)	214	21 (9.8)	0.56 (0.36, 0.86)
Port location						
Jugular vein	366	7 (1.9)	0.11 (0.05, 0.24)	361	31 (8.6)	0.50 (0.35, 0.71)
Other ³	31	2 (6.5)	0.37 (0.09, 1.48)	37	1 (2.7)	0.15 (0.02, 1.06)

Source: Tables 14.2.11.2 to 14.2.11.7 in LOCK-IT-100 clinical study report

¹ Event refers to the CAC-adjudicated CRBSI.

² Other races included Asian, American Indian or Alaska native, native Hawaiian or other Pacific Island, and other.

³ Other location included subclavian vein and other.

Abbreviations: CAC = clinical adjudication committee, CRBSI = catheter-related bloodstream infection, FAP = full analysis population

Additionally, as mentioned previously, the Applicant assumed all missing data were noninformative which could be invalid. The statistical reviewer conducted a sensitivity analysis considering nonpositive disposition events as nonpositive events in order to evaluate the robustness of the study results to the missing data. [Table 22](#) displays each individual disposition event as a nonpositive event or as censored in this sensitivity analysis. The results showed a numerically lower incidence rate for nonpositive events in the Defencath arm as compared to the heparin arm ([Table 23](#)).

Table 22. Patient Disposition at Study Completion (FAP)

Parameter	Nonpositive event or Censored	Defencath N=397 n (%)	Heparin N=398 n (%)
Completed study			
All assessments completed through study closure	Censored	74 (18.6)	76 (19.1)
CRBSI meeting primary endpoint definition	Nonpositive event	9 (2.3)	35 (8.8)
Catheter removal			
Malfunction/Dysfunction	Nonpositive event	62 (15.6)	56 (14.1)
No longer needed for hemodialysis	Censored	161 (40.6)	131 (32.9)
Other			
No longer needed for hemodialysis ¹	Censored	1 (0.3)	1 (0.3)
Other reasons	Nonpositive event	4 (1.0)	7 (1.8)
Death	Nonpositive event	15 (3.8)	14 (3.5)
Transferred to a nonstudy site	Nonpositive event	29 (7.3)	31 (7.8)
Termination of dialysis	Nonpositive event	4 (1.0)	4 (1.0)
Early withdrawal			
Physician decision (safety concern other than AE)	Nonpositive event	8 (2.0)	9 (2.3)
Adverse event	Nonpositive event	5 (1.3)	5 (1.3)
Subject withdrew consent	Nonpositive event	15 (3.8)	12 (3.0)
Protocol violation	Nonpositive event	1 (0.3)	10 (2.5)
Other	Nonpositive event	9 (2.3)	7 (1.8)

Source: Statistical Reviewer's Analysis

¹ Mature AV fistula/graft; or subjects renal function improved

Abbreviations: AE = adverse event, AV = arteriovenous, CRBSI = catheter-related bloodstream infection, FAP = full analysis population

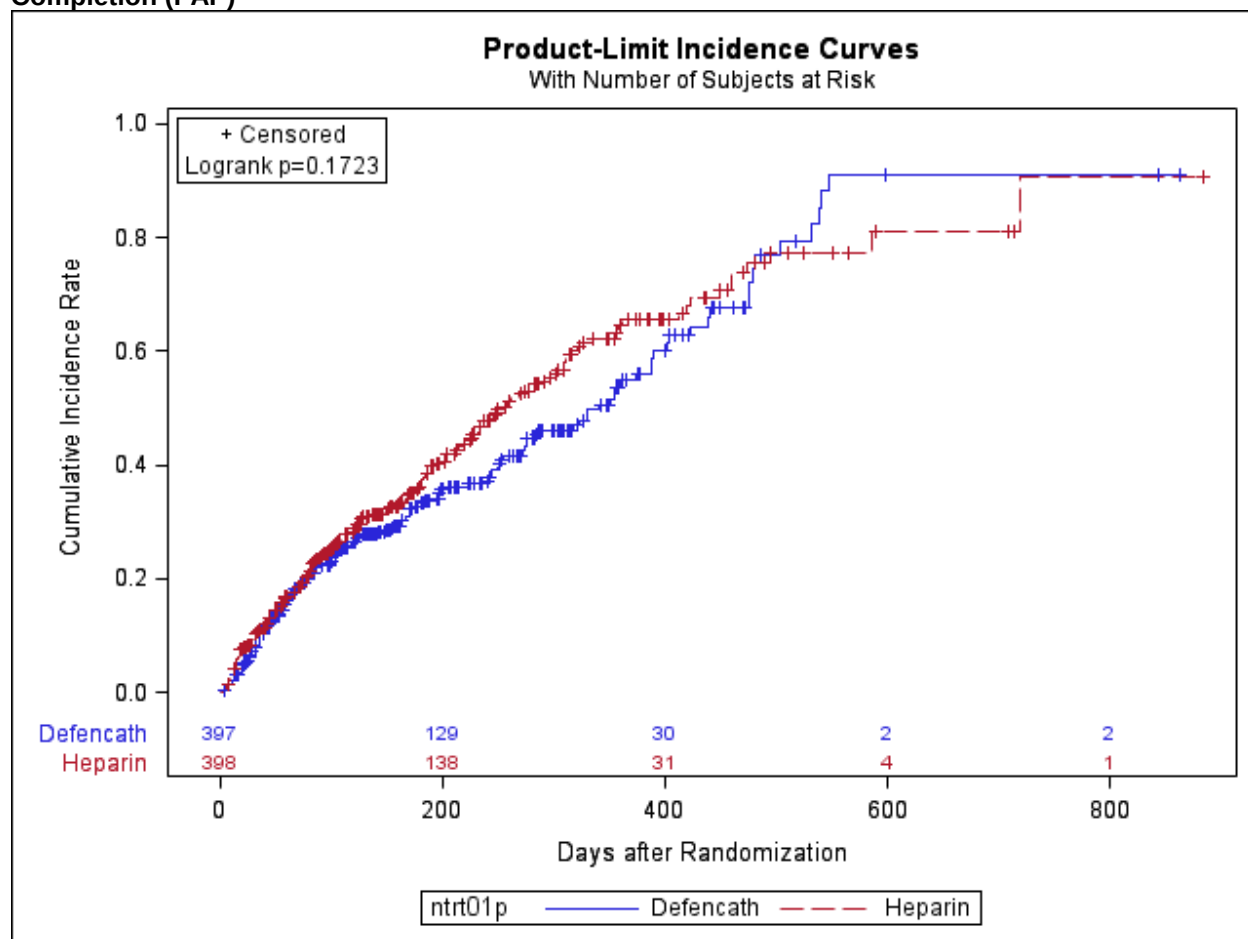
Table 23. Reviewer's Sensitivity Analyses for Nonpositive Disposition Events at Study Completion (FAP)

Parameter	Defencath N=397 n (%)	Heparin N=398 n (%)	Log Rank P-Value Hazard Ratio and 95% CI	Event Rate Per 1,000 Catheter-Days and 95% CI	
				Defencath	Heparin
Nonpositive events	161 (45.9)	190 (54.1)	0.1723 0.86 (0.70, 1.07)	2.4 (2.0, 2.8)	2.8 (2.4, 3.2)

Source: Statistical Reviewer's Analysis

Abbreviations: FAP = full analysis population

Figure 6. Kaplan-Meier Cumulative Incidence of Nonpositive Disposition Events at Study Completion (FAP)



Source: Statistical Reviewer's Analysis
Abbreviations: FAP = full analysis population

Integrated Review of Effectiveness

This was a double-blind, randomized, active control study. The results of the primary analysis demonstrated that Defencath achieved a statistically significant reduction in CRBSI events compared with heparin among subjects receiving HD for kidney failure. The treatment effect of Defencath was fairly consistent in the sensitivity analyses.

8.1.3. Assessment of Efficacy Across Trials

This section was not applicable since there was only one pivotal trial in the submission.

8.1.4. Integrated Assessment of Effectiveness

There was only one pivotal trial in the submission. No integrated assessment of effectiveness across studies was available.

8.2. Review of Safety

8.2.1. Safety Review Approach

The focus of the safety review is the single, Phase 3 trial, LOCK-IT-100. The secondary endpoints, catheter removal and loss of catheter patency were also considered as part of the safety review. Adverse events of special interest included adverse events associated with Defencath or any of its components (taurolidine, heparin, or the citrate excipient) in ex-U.S. postmarketing experience or clinical studies. These included gastrointestinal, hematologic, metabolic, and neurologic adverse events reported in the literature.

8.2.2. Review of the Safety Database

Overall Exposure and Adequacy of the Safety Database

A single, Phase 3 trial was conducted in support of the NDA for Defencath ([Table 25](#)). A total of 398 subjects were exposed to at least one dose of Defencath in LOCK-IT-100. The mean duration of treatment was 173 days and 175 days in the Defencath and heparin arms, respectively. The majority of subjects in both arms had a duration of treatment of under 6 months (63% in Defencath and 61% in the heparin arm). [Table 24](#) summarizes the overall exposure to study drug by duration of treatment in LOCK-IT-100.

Table 24. Overall Exposure to Investigational Product in LOCK-IT-100

	Defencath N=398	Heparin N=399
Duration of Treatment	n (%)	n (%)
>0-<3 months	141 (35.4)	139 (34.8)
≥3-<6 months	109 (27.4)	103 (25.8)
≥6-<9 months	59 (14.8)	71 (17.8)
≥9-<12 months	51 (12.8)	44 (11.0)
≥12-<15 months	20 (5.0)	23 (5.8)
≥15-<18 months	14 (3.5)	11 (2.8)
≥18-<21 months	2 (0.5)	4 (1.0)
≥21-<24 months	0 (0.0)	3 (0.8)
≥27-<30 months	2 (0.5)	1 (0.3)
Mean and SD (days)	173.10 (139.48)	174.80 (142.70)
Median (days)	137	140
Range (days)	4-863	4-884

Source: Clinical Reviewer's Analysis

Reviewer's Comment: There were no major differences noted in duration of drug exposure in the treatment arm compared to the control arm.

Table 25. Safety Database for Defencath

Safety Database for the Study Drug ¹ Individuals Exposed to the Study Drug in This Development Program N=398			
Trial	Defencath	Heparin	Total
Phase 3 Trial LOCK-IT-100	398	399	797

Source: Clinical Reviewer's Analysis

¹Study drug means the drug being considered for approval.

Reviewer's comment: The safety database of this single study was considered adequate as Defencath is being considered for use in a limited population of patients under the LPAD pathway.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The overall quality of the submitted data was adequate. A data traceability assessment was conducted in conjunction with the JumpStart service provided through the Office of Computational Sciences. There were minor findings identified through this assessment with the majority having either minimal or no impact on data analysis.

For additional assessment of the quality of the initial data collection and integrity, an OSI consult was obtained. Three clinical investigators, Drs. Murillo, Jamal, and Bien were inspected. The OSI report concluded that the study appears to have been conducted adequately based on the inspections, and the study data submitted are acceptable in support of the proposed indication (see Section [4.1](#)).

Categorization of Adverse Events

Adverse events in LOCK-IT-100 were defined as any untoward medical occurrence that did not necessarily have a causal relationship with the treatment. Collection of AE data began after a subject had signed the informed consent and ended 28 days (+7 days) after removal of the last dose of the investigational product. Treatment-emergent adverse events (TEAEs) were defined as AEs that started or worsened after the subject's first administration of investigational product. A serious adverse event was an adverse event that was fatal, life-threatening, led to a persistent or significant disability, congenital anomaly or birth defect, or required or prolonged an inpatient hospitalization. AEs were coded with MedDRA Version 21.0 in LOCK-IT-100.

Reviewer's comment: For the purposes of the Agency's analyses, AEs and SAEs were analyzed regardless of whether they were deemed related or unrelated by investigators to study drug. This may have resulted in a greater number of AEs being reported in the Agency's analysis. In situations where the relationship of the AE to the study drug was questionable given the mechanism of action of the

components of the study drug, case report forms, narratives, and verbatim terms, where available, were reviewed. Additional narratives and datasets were requested from the Applicant when required.

Routine Clinical Tests

As part of the LOCK-IT-100 protocol, routine blood laboratory studies were collected including, but not limited to, hematology tests (WBC count and differential, hemoglobin, hematocrit, platelet count) and blood chemistry tests (albumin, blood urea nitrogen, calcium, bicarbonate, creatinine, glucose, electrolytes, serum protein, serum bilirubin, liver transaminases).

8.2.4. Safety Results

Summary

TEAEs occurred in 79% of patients in both arms of the Phase 3 trial (Table 26). SAEs occurred in 40% (159/398) of subjects receiving Defencath and 42% (167/399) of subjects receiving heparin. Of these, one SAE, reported as a device malfunction in the Defencath arm, was considered treatment-related by the investigator.

Deaths occurred in 5% (18/398) of subjects in the Defencath arm and 5% (21/399) of subjects in the heparin arm. None of the deaths were attributed to the study drug.

Adverse reactions leading to discontinuation occurred in 17% (69/398) of subjects in the Defencath arm and 18% (72/399) of subjects in the heparin arm.

Table 26. Safety Summary for LOCK-IT-100, Safety Population

Parameter	Defencath N=398 n (%)	Heparin N=399 n (%)
Deaths due to adverse events	18 (4.5)	21 (5.3)
Serious adverse events (SAEs)	159 (39.9)	167 (41.9)
Treatment-related SAEs	1 (0.3)	0 (0)
Discontinuations of study drug due to SAEs	28 (7)	36 (9)
All treatment-emergent adverse events (TEAEs)	314 (78.9)	315 (78.9)
Discontinuation of study drug due to TEAEs	69 (17.3)	72 (18)
TEAEs related to study drug*		
Mild	258 (64.8)	241 (60.4)
Moderate	200 (50.3)	208 (52.1)
Severe	106 (26.6)	125 (31.3)
Life-threatening	22 (5.5)	21 (5.3)

Source: Clinical Reviewer's Analysis

* Relatedness assessment conducted by study site investigators and not by clinical reviewer.

Abbreviations: SAE = serious adverse event, TEAE = treatment-emergent adverse event

Reviewer's comment: Although there were numerically more deaths and SAEs reported in the heparin arm compared to the Defencath arm, the differences

were quite small and not considered to be clinically significant. The overall incidence of TEAEs was similar between the two arms. More moderate and severe TEAEs were reported in the heparin arm compared to the Defencath arm; however, these differences were considered small and not clinically significant.

Deaths

There were 39 deaths reported in LOCK-IT-100. Overall, the deaths were generally balanced between the two arms with 18 (4.5%) and 21 (5.3%) occurring in the Defencath and heparin arms, respectively ([Table 27](#)). Investigators did not attribute any of the deaths to the study drugs. The most commonly reported cause of death in both treatment arms was cardiac disorders, with five subjects (1.3%) in each treatment arm. Infections and infestations resulted in four deaths (1%), all occurring in the heparin arm. Other causes of death were less frequent, occurring in less than 1% of subjects, including injury, poisoning, and procedural-related deaths which occurred in two subjects (0.5%) in the Defencath arm; one death was due to a fall and another was reported as a postprocedural complication, which on further investigation was recorded as a postcholecystectomy complication.

Table 27. Adverse Events With an Outcome of Death By System Organ Class in LOCK-IT-100, Safety Population

TEAE Resulting in Death¹	Defencath N=398 n (%)	Heparin N=399 n (%)
General disorders and administration site conditions	5 (1.3)	2 (0.5)
Cardiac disorders	5 (1.3)	5 (1.3)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	2 (0.5)
Injury, poisoning and procedural complications	2 (0.5)	0 (0.0)
Renal and urinary disorders	1 (0.3)	2 (0.5)
Gastrointestinal disorders	1 (0.3)	2 (0.5)
Nervous system disorders	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)
Infections and infestations	0 (0.0)	4 (1.0)
Vascular disorders	0 (0.0)	2 (0.5)
All subjects with at least one TEAE reported leading to death	18 (4.5)	21 (5.3)

Source: Clinical Reviewer's Analysis

¹ Defined as any reported AEs with an outcome of death following first administration of the study drug.

Abbreviations: TEAE = treatment-emergent adverse event

A more detailed listing of adverse events with an outcome of death by preferred term (PT), as well as the age, sex, and race of each subject and treatment arm is presented in [Table 28](#).

Table 28. Detailed Listing of Adverse Events With Outcome of Death With Treatment Arm, Age, Sex and Race

Actual Arm	Age/Sex/Race	Adverse Event With Outcome of Death
Heparin	86 - M - White	End stage renal disease
Heparin	65 - M - White	Myocardial infarction
Heparin	86 - M - White	Pneumonia
Heparin	83 - F - White	Pulmonary edema
Heparin	55 - M - White	Cardiac arrest

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

Actual Arm	Age/Sex/Race	Adverse Event With Outcome of Death
Heparin	72 - M - Black/African American	Sepsis
Heparin	54 - M - Other	Death
Heparin	75 - M - White	Respiratory failure
<i>Heparin*</i>	<i>65 - F - White</i>	<i>Cardiac arrest</i>
<i>Heparin*</i>	<i>65 - F - White</i>	<i>Acute myocardial infarction</i>
Heparin	54 - F - White	Cardio-respiratory arrest
Heparin	53 - F - White	Staphylococcal sepsis
Heparin	48 - M - White	Hyperkalemia
Heparin	37 - M - White	Dumping syndrome
Heparin	73 - M - White	Arteriosclerosis
Heparin	71 - F - White	Aortic stenosis
Heparin	90 - F - White	Myocardial infarction
Heparin	80 - M - Black/African American	Hemorrhage intracranial
Heparin	64 - F - White	Device related sepsis
Heparin	59 - M - Black/African American	Renal failure
Heparin	63 - M - Black/African American	Esophageal varices hemorrhage
Heparin	75 - F - White	Death
Defencath	86 - M - Asian	Death
Defencath	77 - F - White	Intestinal infarction
Defencath	70 - M - White	Cardio-respiratory arrest
Defencath	88 - F - Black/African American	Cardiac failure congestive
Defencath	80 - M - White	Respiratory failure
Defencath	68 - F - Black/African American	Cardio-respiratory arrest
Defencath	88 - M - White	Death
Defencath	73 - F - White	Fall
Defencath	55 - F - White	Pulmonary embolism
Defencath	68 - M - White	Death
Defencath	85 - M - White	Death
Defencath	49 - M - White	Cardiac arrest
Defencath	79 - F - White	End stage renal disease
Defencath	76 - F - White	Lactic acidosis
Defencath	75 - M - White	Cardiac failure congestive
Defencath	46 - M - White	Cerebral hemorrhage
Defencath	48 - F - Asian	Death
Defencath	47 - F - White	Post procedural complication

Source: Clinical Reviewer's Analysis

* Subject (b) (6) had two AEs reported with an outcome of death: acute myocardial infarction and cardiac arrest.

There were five subjects in the Defencath arm and two subjects in the heparin arm with an AE of “death” reported as the cause of the event. Review of the CRFs and narratives for these subjects revealed that these deaths occurred at home or in a nursing facility where there was no further information available, no access to the death certificate, and no autopsy performed.

Deaths were reported more frequently in subjects 65 years of age and older, with 72% (13/18) of deaths in the Defencath arm and 57% (12/21) of deaths in the heparin arm.

Reviewer's comment: A detailed review of the death narratives and CRFs of each subject with an outcome of death was conducted. None of the deaths in LOCK-IT-100 appeared to be related to the study treatment given our knowledge of

adverse events associated with various components of the study drug and our understanding of the mechanism of action and lack of significant systemic exposure. A potential imbalance was noted in deaths occurring due to infections and infestations, which appeared to favor the Defencath arm, with zero deaths reported in the Defencath arm and four deaths reported in the heparin arm. Of these four deaths, three could potentially have been related to sepsis secondary to bacteremia with the causes of death detailed as sepsis, staphylococcal sepsis, and device-related sepsis.

Serious Adverse Events

SAEs were reported in 159 subjects (39.9%) in the Defencath arm and 167 subjects (41.9%) in the heparin arm. SAEs reported in $\geq 2\%$ of subjects in either treatment group are summarized in [Table 29](#). The most frequently reported SAEs by system organ class (SOC) were infections and infestations, metabolism and nutrition disorders, cardiac disorders, respiratory and thoracic disorders, and vascular disorders. Relevant and related PTs across SOC were also pooled together if deemed necessary. The most frequently reported SAEs by PT were pneumonia, sepsis, device-related infection, fluid overload, hyperkalemia, cardiac failure congestive, acute myocardial infarction, respiratory failure, hypertension, and hemorrhage/bleeding (pooled term).

Table 29. SAEs Reported in $\geq 2\%$ of Subjects in LOCK-IT-100, Safety Population

SAE	Defencath N=398 n (%)	Heparin N=399 n (%)
All subjects with at least one serious adverse event (SAE)	159 (39.9)	167 (41.9)
Infections and infestations	69 (17.3)	79 (19.8)
Pneumonia	12 (3.0)	21 (5.3)
Sepsis	9 (2.3)	14 (3.5)
Device related infection	6 (1.5)	8 (2.0)
Metabolism and nutrition disorders	33 (8.3)	28 (7.0)
Fluid overload	14 (3.5)	12 (3.0)
Hyperkalemia	10 (2.5)	8 (2.0)
Cardiac disorders	29 (7.3)	47 (11.8)
Cardiac failure congestive	12 (3.0)	7 (1.8)
Acute myocardial infarction	5 (1.3)	13 (3.3)
Respiratory, thoracic and mediastinal disorders	28 (7.0)	25 (6.3)
Respiratory failure	7 (1.8)	9 (2.3)
Vascular disorders	26 (6.5)	35 (8.8)
Hypertension	4 (1.0)	10 (2.5)
Pooled terms*		
Hemorrhage/Bleeding ^a	17 (4.3)	17 (4.3)

Source: Clinical Reviewer's Analysis

*Terms pooled across SOC

^a Hemorrhage/bleeding includes Gastrointestinal hemorrhage, Hematemesis, Lower gastrointestinal hemorrhage, Upper gastrointestinal hemorrhage, Arteriovenous fistula site hematoma, Cerebral hemorrhage, Gastric ulcer hemorrhage, Hematoma, Hemobilia, Hemoptysis, Hemorrhagic anemia, Renal hematoma, Arterial hemorrhage, Cerebellar hemorrhage, Hemorrhage intracranial, Hemorrhagic stroke, Hemorrhoidal hemorrhage, Incision site hemorrhage, Esophageal ulcer hemorrhage, Esophageal varices hemorrhage, Subdural hematoma

Reviewer's comment: SAEs reported in LOCK-IT-100 were generally balanced between the two arms. The majority of SAEs reported were likely secondary to the subjects' underlying kidney failure and associated comorbidities and are common conditions in this population, including fluid overload, hyperkalemia, congestive heart failure, myocardial infarction, and respiratory failure. In the dialysis population, infections including pneumonia and sepsis are also common and not necessarily related to the study drug. Hemorrhage/bleeding was included as a pooled term due to the inclusion of heparin as one of the components of Defencath and includes the individual PTs listed above in [Table 29](#). Hemorrhage/bleeding was balanced between the two arms for SAEs with 4.3% of subjects in each arm reporting a hemorrhage/bleeding event; however, there was a slight imbalance in overall TEAEs reported with respect to hemorrhage/bleeding with more TEAEs reported in the heparin arm compared to the Defencath arm ([Table 31](#)).

Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations of study drug in LOCK-IT-100 occurred in 69 subjects (17.3%) treated with Defencath and 72 subjects (18%) treated with heparin ([Table 30](#)). Discontinuations of study drug due to SAEs occurred in 28 subjects (7%) treated with Defencath and 36 subjects (9%) treated with heparin ([Table 26](#)). The most frequently reported SOC for discontinuation of study drug were product issues and infections and infestations. The remainder of the SOC were reported in ≤1% of subjects. Product issues leading to discontinuation were reported more frequently in the Defencath arm (41 subjects, 10.3%) compared to the heparin arm (31 subjects, 7.8%). The product issues reported in more than one subject included hemodialysis catheter malfunction, device dislocation, device damage, and thrombosis in device.

Infections and infestations leading to discontinuation were reported more frequently in the heparin arm; 11 subjects (2.8%) in the Defencath arm and 31 subjects (7.8%) in the heparin arm had an infection or infestation reported as leading to discontinuation. The most frequently reported PTs under infections and infestations were sepsis, device-related infection, device-related sepsis, bacteremia, catheter site infection, and staphylococcal sepsis.

Of note, there was also one discontinuation in a subject due to heparin-induced thrombocytopenia (HIT) in the heparin arm.

Table 30. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment in LOCK-IT-100, Safety Population

Treatment-Emergent Adverse Event	Defencath N=398 n (%)	Heparin N=399 n (%)
All subjects with at least one adverse event leading to discontinuation	69 (17.3)	72 (18.0)
Product issues	41 (10.3)	31 (7.8)
Hemodialysis catheter malfunction ^a	28 (7.0)	20 (5.0)
Device dislocation	8 (2.0)	3 (0.8)
Device damage	3 (0.8)	2 (0.5)
Thrombosis in device	1 (0.3)	3 (0.8)
Device occlusion	1 (0.3)	1 (0.3)
Device breakage	0 (0.0)	1 (0.3)
Device leakage	0 (0.0)	1 (0.3)
Infections and infestations	11 (2.8)	31 (7.8)
Sepsis	4 (1.0)	4 (1.0)
Device related infection	3 (0.8)	6 (1.5)
Device related sepsis	2 (0.5)	4 (1.0)
Cellulitis	1 (0.3)	0 (0.0)
<i>Clostridium difficile</i> infection	1 (0.3)	0 (0.0)
Arteriovenous fistula site infection	1 (0.3)	0 (0.0)
Bacteremia	0 (0.0)	6 (1.5)
Catheter site infection	0 (0.0)	3 (0.8)
Staphylococcal sepsis	0 (0.0)	3 (0.8)
Endocarditis staphylococcal	0 (0.0)	1 (0.3)
Enterococcal bacteremia	0 (0.0)	1 (0.3)
Osteomyelitis	0 (0.0)	1 (0.3)
Staphylococcal infection	0 (0.0)	1 (0.3)
Streptococcal sepsis	0 (0.0)	1 (0.3)
Urosepsis	0 (0.0)	1 (0.3)
Tuberculosis	0 (0.0)	1 (0.3)
Gastrointestinal disorders	3 (0.8)	0 (0.0)
Pancreatitis	2 (0.5)	0 (0.0)
Duodenal ulcer	1 (0.3)	0 (0.0)
Cardiac disorders	3 (0.8)	2 (0.5)
Cardiac failure congestive	1 (0.3)	0 (0.0)
Cardio-respiratory arrest	1 (0.3)	0 (0.0)
Acute myocardial infarction	1 (0.3)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.3)
Myocardial infarction	0 (0.0)	1 (0.3)
Nervous system disorders	2 (0.5)	2 (0.5)
Cerebral hemorrhage	1 (0.3)	0 (0.0)
Syncope	1 (0.3)	0 (0.0)
Hemorrhage intracranial	0 (0.0)	1 (0.3)
Hypoxic-ischemic encephalopathy	0 (0.0)	1 (0.3)
Vascular disorders	2 (0.5)	3 (0.8)
Hypotension	1 (0.3)	0 (0.0)
Thrombosis	1 (0.3)	0 (0.0)
Arteriosclerosis	0 (0.0)	1 (0.3)
Aortic stenosis	0 (0.0)	1 (0.3)
Venous stenosis	0 (0.0)	1 (0.3)

Treatment-Emergent Adverse Event	Defencath N=398 n (%)	Heparin N=399 n (%)
Injury, poisoning and procedural complications	2 (0.5)	1 (0.3)
Fall	1 (0.3)	0 (0.0)
Post procedural complication	1 (0.3)	0 (0.0)
Subdural hematoma	0 (0.0)	1 (0.3)
Arteriovenous fistula site complication	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	2 (0.5)
Respiratory failure	1 (0.3)	1 (0.3)
Pulmonary embolism	1 (0.3)	0 (0.0)
Pleural effusion	0 (0.0)	1 (0.3)
Renal and urinary disorders	1 (0.3)	0 (0.0)
End stage renal disease	1 (0.3)	0 (0.0)
Investigations	1 (0.3)	0 (0.0)
International normalized ratio increased	1 (0.3)	0 (0.0)
General disorders and administration site conditions	1 (0.3)	4 (1.0)
Death	1 (0.3)	2 (0.5)
Feeling cold	0 (0.0)	1 (0.3)
Catheter site swelling	0 (0.0)	1 (0.3)
Feeling hot	0 (0.0)	1 (0.3)
Congenital, familial and genetic disorders	1 (0.3)	0 (0.0)
Protein C deficiency	1 (0.3)	0 (0.0)
Blood and lymphatic system disorders	1 (0.3)	1 (0.3)
Pancytopenia	1 (0.3)	0 (0.0)
Heparin-induced thrombocytopenia	0 (0.0)	1 (0.3)
Pregnancy, puerperium and perinatal conditions	1 (0.3)	0 (0.0)
Abortion spontaneous	1 (0.3)	0 (0.0)

Source: Clinical Reviewer's Analysis

^aIncludes device malfunction

Reviewer's comment: With the exception of some of the device-related issues, the adverse events leading to discontinuation were likely unrelated to the study drug and were likely related to the subjects' underlying kidney failure and comorbidities. Device-related issues including loss of catheter patency and catheter removals were also secondary endpoints in LOCK-IT-100 and are discussed in detail elsewhere (Section 8.1.2 Study Results). There were fewer infections and infestations, in particular sepsis, bacteremia, and device/catheter-related sepsis, reported in the Defencath arm, which is consistent with the findings described in the efficacy section (Section 8.1.2 Study Results).

Significant Adverse Events

Heparin-induced thrombocytopenia: HIT is a rare, serious, and potentially life-threatening condition that occurs as a result of exposure to heparin and can occur regardless of the route of administration or dose.

- HIT was reported in one subject in the heparin-treated arm and zero subjects in the Defencath arm. The study drug was discontinued in this subject as a result of HIT.

Reviewer's comment: Due to the serious and potentially fatal nature of HIT, and because Defencath also contains heparin, HIT will be included in the contraindications and warnings section of the Defencath label.

Serious Hypersensitivity Reactions: Anaphylactic reactions or other systemic hypersensitivity reactions to any of the components of Defencath (taurolidine, heparin, or the citrate excipient) were considered significant adverse events.

- Anaphylactic reaction was reported in one subject in the heparin-treated arm and zero subjects in the Defencath arm.
- Drug hypersensitivity reactions were reported in two subjects in the heparin-treated arm and zero subjects in the Defencath arm.
- Medical device site hypersensitivity was reported in one subject in the heparin-treated arm and zero subjects in the Defencath arm.

Reviewer's comment: The anaphylactic reaction occurred in the follow-up period in one subject in the heparin arm. The reaction was classified as severe in intensity. The investigator deemed the anaphylactic reaction as probably not related to the study drug. There were no narratives available to review for this particular adverse event. Given the timing of the reaction, this reaction was probably not related to the study drug, however in the absence of further information, it is not possible to completely rule out an association.

Treatment-Emergent Adverse Events and Adverse Reactions

The most common AEs reported in LOCK-IT-100 were infections and infestations, including pneumonia, cellulitis, urinary tract infection, sepsis, and device-related infection ([Table 31](#)). [Table 31](#) includes a comprehensive listing of TEAEs reported in $\geq 2\%$ of subjects in LOCK-IT-100 regardless of a causal relationship to the study drug. Gastrointestinal disorders including nausea and vomiting, as well as product issues including catheter malfunction and device occlusion were also frequently reported. The majority of TEAEs reported were deemed likely related to the subjects' kidney failure and associated comorbidities. AEs with a plausible causal relationship to the study drug are listed in [Table 32](#). To allow a more accurate analysis of similar preferred terms, some of these terms were pooled together to allow for a more meaningful analysis. Pooled terms included nausea, vomiting, musculoskeletal chest pain, and hemorrhage/bleeding.

Table 31. Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects in LOCK-IT-100, Safety Population

Treatment-Emergent Adverse Event	Defencath N=398 n (%)	Heparin N=399 n (%)
Infections and infestations	126 (32)	140 (35)
Pneumonia	18 (5)	28 (7)
Cellulitis	14 (4)	13 (3)
Urinary tract infection	12 (3)	15 (4)
Sepsis	11 (3)	21 (5)
Device related infection	10 (3)	17 (4)
Bronchitis	9 (2)	5 (1)
Upper respiratory tract infection	8 (2)	15 (4)
Osteomyelitis	8 (2)	5 (1)
Nasopharyngitis	8 (2)	3 (1)
Bacteremia	6 (2)	9 (2)
Catheter site infection	4 (1)	9 (2)
Gastrointestinal disorders	107 (27)	107 (27)
Diarrhea	38 (10)	30 (8)
Nausea ^a	28 (7)	44 (11)
Vomiting ^b	24 (6)	32 (8)
Abdominal pain	20 (5)	27 (7)
Constipation	18 (5)	17 (4)
Product issues	96 (24)	75 (19)
Hemodialysis catheter malfunction ^c	68 (17)	47 (12)
Device occlusion	9 (2)	9 (2)
Device dislocation	9 (2)	5 (1)
Thrombosis in device	8 (2)	16 (4)
General disorders and administration site conditions	95 (24)	118 (30)
Asthenia	15 (4)	12 (3)
Pyrexia	15 (4)	24 (6)
Musculoskeletal chest pain ^d	11 (3)	7 (2)
Edema peripheral	9 (2)	19 (5)
Peripheral swelling	9 (2)	9 (2)
Pain	7 (2)	10 (3)
Catheter site erythema	7 (2)	8 (2)
Chills	6 (2)	13 (3)
Fatigue	5 (1)	9 (2)
Metabolism and nutrition disorders	90 (23)	83 (21)
Hyperkalemia	27 (7)	26 (7)
Fluid overload	26 (7)	21 (5)
Hypoglycemia	14 (4)	10 (3)
Hyperglycemia	4 (1)	9 (2)
Injury, poisoning and procedural complications	90 (23)	97 (24)
Procedural hypotension	18 (5)	18 (5)
Fall	17 (4)	17 (4)
Arteriovenous fistula site complication	13 (3)	20 (5)
Vascular disorders	86 (22)	94 (24)
Hypotension	35 (9)	27 (7)
Hypertension	27 (7)	39 (10)
Hypertensive crisis	3 (1)	9 (2)
Nervous system disorders	77 (19)	73 (18)
Dizziness	22 (6)	16 (4)
Headache	22 (6)	22 (6)
Syncope	10 (3)	4 (1)

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Treatment-Emergent Adverse Event	Defencath N=398 n (%)	Heparin N=399 n (%)
Respiratory, thoracic and mediastinal disorders	73 (18)	87 (22)
Cough	21 (5)	30 (8)
Dyspnea	19 (5)	30 (8)
Respiratory failure	9 (2)	13 (3)
Pleural effusion	9 (2)	10 (3)
Pulmonary edema	6 (2)	8 (2)
Musculoskeletal and connective tissue disorders	66 (17)	80 (20)
Muscle spasms	23 (6)	36 (9)
Back pain	15 (4)	17 (4)
Pain in extremity	15 (4)	22 (6)
Arthralgia	3 (1)	10 (3)
Musculoskeletal pain	2 (1)	8 (2)
Cardiac disorders	62 (16)	81 (20)
Cardiac failure congestive	16 (4)	10 (3)
Bradycardia	12 (3)	11 (3)
Tachycardia	11 (3)	22 (6)
Angina pectoris	10 (3)	8 (2)
Atrial fibrillation	7 (2)	13 (3)
Acute myocardial infarction	6 (2)	14 (4)
Skin and subcutaneous tissue disorders	40 (10)	35 (9)
Skin ulcer	10 (3)	4 (1)
Investigations	33 (8)	31 (8)
Psychiatric disorders	31 (8)	34 (9)
Insomnia	9 (2)	7 (2)
Mental status changes	9 (2)	12 (3)
Blood and lymphatic system disorders	29 (7)	33 (8)
Nephrogenic anemia	10 (3)	8 (2)
Anemia	8 (2)	16 (4)
Thrombocytopenia	7 (2)	4 (1)
Pooled Terms*		
Hemorrhage/Bleeding ^e	27 (7)	34 (9)

Source: Clinical Reviewer's Analysis

* PTs pooled across 2 or more SOC categories

^a Includes nausea and procedural nausea

^b Includes vomiting and procedural vomiting

^c Includes device malfunction

^d Includes noncardiac chest pain, musculoskeletal chest pain, chest discomfort

^e Includes arterial hemorrhage, arteriovenous fistula site hematoma, arteriovenous fistula site hemorrhage, arteriovenous graft site hemorrhage, catheter site hematoma, catheter site hemorrhage, cerebellar hemorrhage, cerebral hemorrhage, conjunctival hemorrhage, eye hemorrhage, gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, hematoma, hematuria, hematuria traumatic, hemobilia, hemoptysis, hemorrhage intracranial, hemorrhagic anemia, hemorrhagic stroke, hemorrhoidal hemorrhage, incision site hemorrhage, lower gastrointestinal hemorrhage, mouth hemorrhage, esophageal ulcer hemorrhage, esophageal varices hemorrhage, periorbital hemorrhage, post procedural hemorrhage, procedural hemorrhage, rectal hemorrhage, renal hematoma, shock hemorrhagic, subdural hematoma, upper gastrointestinal hemorrhage, uterine hemorrhage, vaginal hemorrhage, venous hemorrhage

Reviewer's comment: The majority of AEs reported are conditions commonly seen in the kidney failure population. These include infections including pneumonia, cellulitis and sepsis, metabolic disturbances including hyperkalemia and fluid overload, and cardiac disorders such as congestive heart failure and arrhythmias. AEs of interest secondary to the study drug included device issues such as malfunction, occlusion and thrombosis in the device, as well as AEs that have

been reported with use of taurolidine, citrate, and heparin solutions in the literature and in postmarketing experience, including nausea, vomiting, musculoskeletal chest pain, thrombocytopenia, and dizziness and are discussed in additional detail below. While there were more product issues in general reported in the Defencath arm, including hemodialysis catheter malfunction, device occlusion, and device dislocation, thrombosis in the device was reported more frequently in the heparin arm in the adverse event dataset. A secondary endpoint analysis was conducted to evaluate loss of catheter patency in LOCK-IT-100 and is discussed in detail in Section 8.2.5.1 Catheter Thrombosis (safety) and Section 8.1.2 Study Results (efficacy). Loss of catheter patency as a secondary endpoint was noted to occur more frequently in the Defencath arm. It is not clear why thrombosis in device as an AE was reported more frequently in the heparin arm, however the secondary endpoint analysis was felt to be a more credible estimate of loss of catheter patency and catheter thrombosis in LOCK-IT-100.

Regarding the adverse events of special interest, hemodialysis catheter malfunction was noted to occur more frequently in the Defencath arm than in the heparin arm, with 68 subjects (17%) in the Defencath arm and 47 subjects (12%) in the heparin arm reporting hemodialysis catheter malfunction (Table 32). Catheter removal was a secondary endpoint and is further discussed in Section 8.1.2 of the review with additional details regarding the reason for catheter malfunction (Table 17). Hemorrhage/bleeding was reported in 27 subjects (7%) in the Defencath arm and 34 subjects (9%) in the heparin arm. Nausea was reported in 28 subjects (7%) in the Defencath arm and 44 subjects (11%) in the heparin arm. Dizziness was reported in 22 subjects (6%) in the Defencath arm and 16 subjects (4%) in the heparin arm. The remaining AEs, thrombocytopenia and musculoskeletal chest pain were reported in less than 5% of subjects in both arms and were relatively balanced between the two arms.

Table 32. Selected Treatment-Emergent Adverse Reactions Occurring in ≥2% of Subjects Receiving Defencath in LOCK-IT-100, Safety Population

Adverse Reactions	Defencath N=398 n (%)	Heparin N=399 n (%)
Product issues		
Hemodialysis catheter malfunction ^a	68 (17)	47 (12)
Blood and lymphatic system disorders		
Hemorrhage/Bleeding ^b	27 (7)	34 (9)
Thrombocytopenia	7 (2)	4 (1)
Gastrointestinal disorders		
Nausea ^c	28 (7)	44 (11)
Vomiting ^d	24 (6)	32 (8)
Nervous system disorders		
Dizziness	22 (6)	16 (4)
Musculoskeletal and connective tissue disorders		
Musculoskeletal chest pain ^e	11 (3)	7 (2)

Source: Clinical Reviewer's Analysis

^a Includes device malfunction

^b Includes arterial hemorrhage, arteriovenous fistula site hematoma, arteriovenous fistula site hemorrhage, arteriovenous graft site

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hemorrhage, catheter site hematoma, catheter site hemorrhage, cerebellar hemorrhage, cerebral hemorrhage, conjunctival hemorrhage, eye hemorrhage, gastric ulcer hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, hematoma, hematuria, hematuria traumatic, hemobilia, hemothysis, hemorrhage intracranial, hemorrhagic anemia, hemorrhagic stroke, hemorrhoidal hemorrhage, incision site hemorrhage, lower gastrointestinal hemorrhage, mouth hemorrhage, esophageal ulcer hemorrhage, esophageal varices hemorrhage, periorbital hemorrhage, post procedural hemorrhage, procedural hemorrhage, rectal hemorrhage, renal hematoma, shock hemorrhagic, subdural hematoma, upper gastrointestinal hemorrhage, uterine hemorrhage, vaginal hemorrhage, venous hemorrhage

^c Includes nausea and procedural nausea

^d Includes vomiting and procedural vomiting

^e Includes noncardiac chest pain, musculoskeletal chest pain, chest discomfort, neck pain

Reviewer's comment: Hemodialysis catheter malfunction was an AE of interest for LOCK-IT-100 due to the association of catheter malfunction issues, particularly loss of patency and increased use of thrombolytics with taurolidine-containing CLSs. Hemodialysis catheter malfunction was reported at an increased frequency in subjects receiving Defencath. The implication of loss of catheter patency and potential catheter removal or replacement are significant for the hemodialysis population due to the known vascular access issues in this population. The increased frequency of catheter malfunction seen in the Defencath arm compared to the heparin arm in LOCK-IT-100 will be included in the product label to help guide healthcare providers and patients in decision-making around the use of this product. Hemorrhage/bleeding and thrombocytopenia were included as AEs of interest and as having a plausible causal relationship to the study drug due to the inclusion of heparin in Defencath. Hemorrhage/bleeding was reported in >5% of subjects in both study arms and was slightly more frequent in the heparin only arm. Nausea, vomiting, dizziness, and musculoskeletal chest pain have all been associated with taurolidine use as a CLS in the literature and were all reported in ≥2% of subjects in the Defencath arm and are thus listed in [Table 32](#). These AEs will be discussed in the labeling for Defencath to inform healthcare providers and patients about the possibility of occurrence with the use of Defencath.

Laboratory Findings

The following laboratory parameters were evaluated:

- Hematology
 - WBC, neutrophils, lymphocytes, eosinophils, hemoglobin, hematocrit, leukocytes, platelets
- Chemistry
 - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, glucose, sodium, potassium, calcium, and albumin

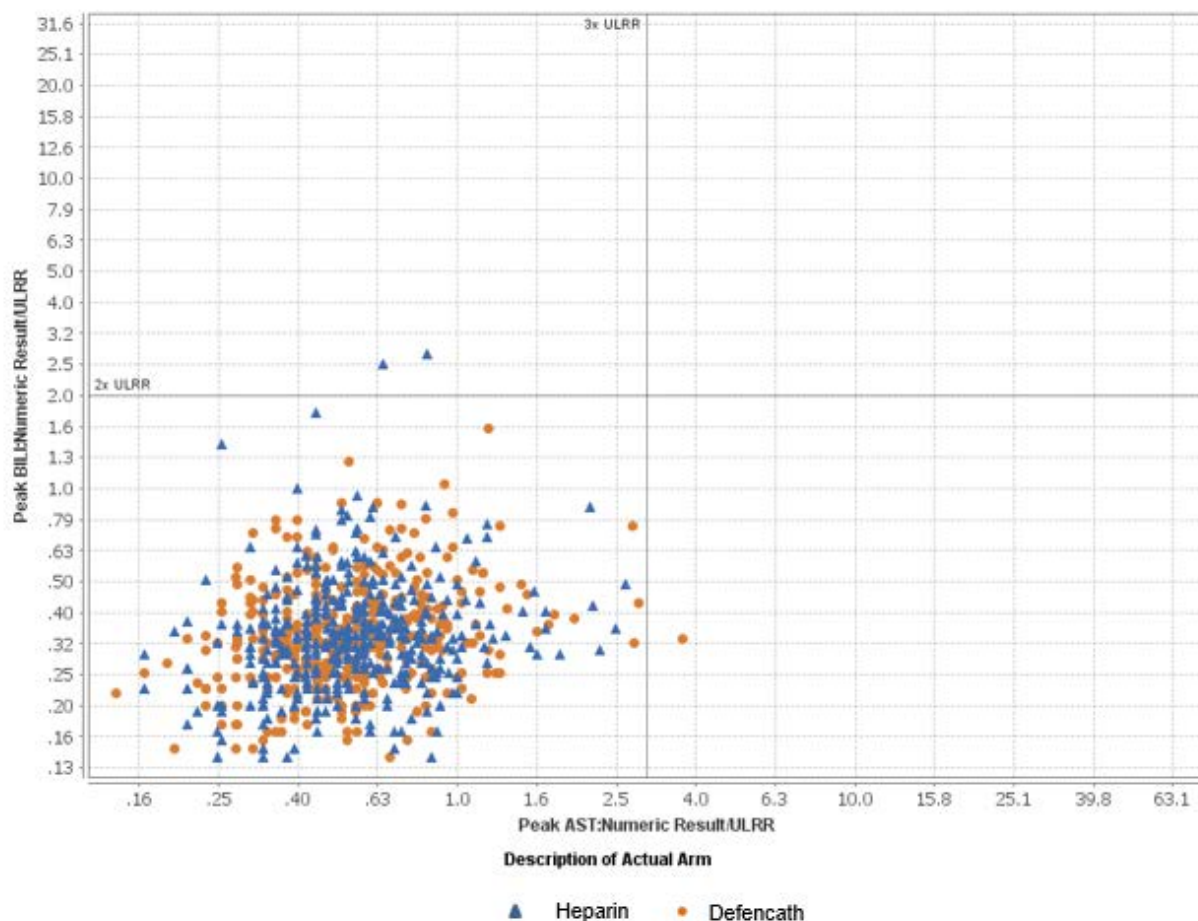
Differences between the mean values calculated per laboratory parameter were compared across visits and between treatment groups. The mean duration of treatment in LOCK-IT-100

was 173 days in the Defencath arm ([Table 24](#)) or approximately 6 months. Between Month 9 and 12, the number of subjects followed in the Phase 3 trial dropped off and there was slightly more variation noted in laboratory values due to the smaller number of subjects. Therefore, the laboratory analysis focused on the laboratory values obtained from baseline through Month 12. With the exception of occasional outliers and minor non-clinically meaningful differences, there were no significant changes from baseline across visits or between groups. As expected for this study population, certain laboratory parameters such as potassium, blood urea nitrogen, and creatinine values were elevated beyond what is seen in the general population. However, these changes were consistent between the two groups and throughout the 12-month duration assessed in this analysis.

Liver Transaminase Evaluation

- There were no cases of Hy's Law observed in LOCK-IT-100.
- Two subjects in the heparin arm had total bilirubin elevations >2x upper limit of normal (ULN).
- There were no subjects in the Defencath arm with total bilirubin elevations.
- One subject in the Defencath arm had an AST elevation ≥ 3 x ULN.
- One subject in the Defencath arm and two subjects in the heparin arm had ALT elevations ≥ 3 x ULN.

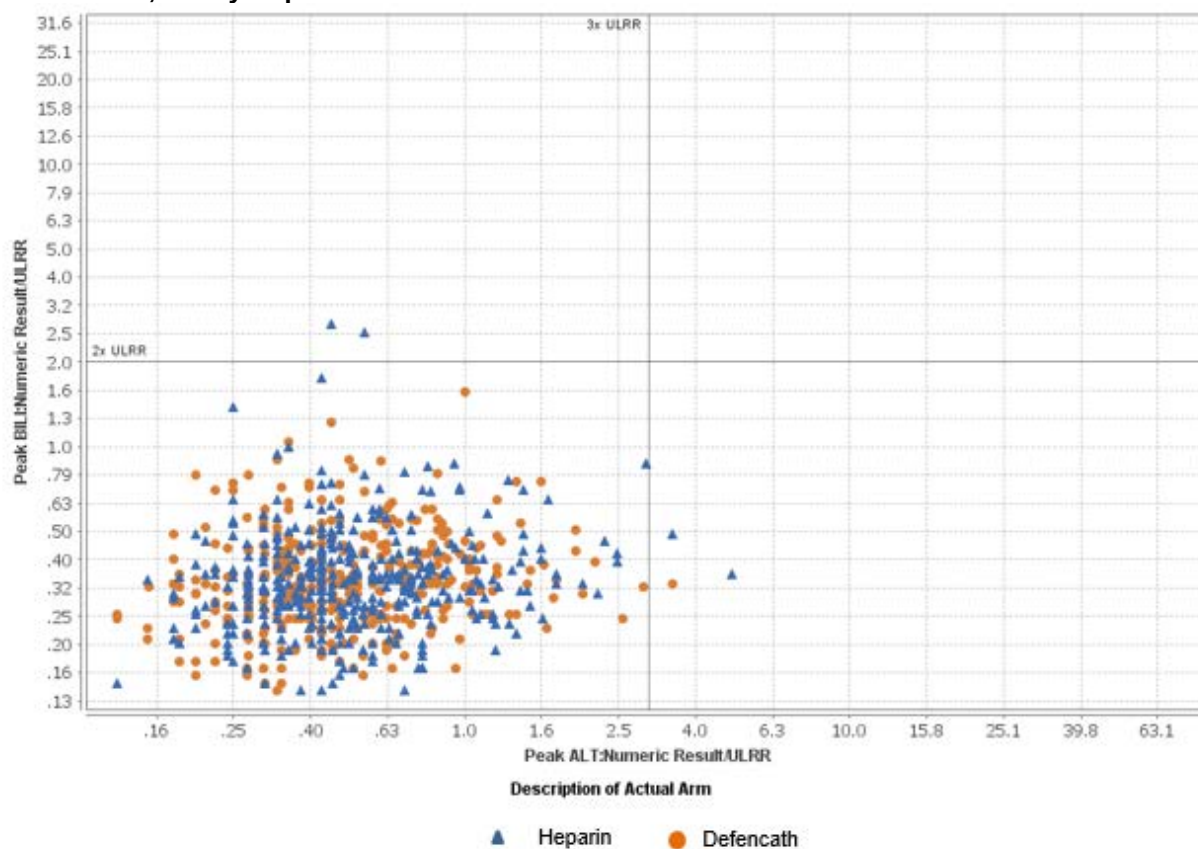
Figure 7. Elevations of AST and Total Bilirubin Among Subjects Receiving Defencath or Heparin in LOCK-IT-100, Safety Population



Source: Clinical Reviewer's Analysis

Abbreviations: AST = aspartate aminotransferase, ULRR = upper limit of the reference range, Neutrolin = Defencath

Figure 8. Elevations of ALT and Total Bilirubin Among Subjects Receiving Defencath or Heparin in LOCK-IT-100, Safety Population



Source: Clinical Reviewer's Analysis

Abbreviations: ALT = alanine aminotransferase, ULRR = upper limit of the reference range, Neutrolin = Defencath

Reviewer's comment: There were minimal liver enzyme abnormalities seen in LOCK-IT-100 in either treatment arm. Liver enzyme abnormalities have been reported in the literature with the use of systemic taurolidine. To our knowledge, there was no accidental flushing or systemic administration of Defencath that occurred in LOCK-IT-100, therefore liver enzyme abnormalities were not expected to occur in this study.

Vital Signs

The following vital signs were evaluated:

- Temperature
- Heart rate
- Respiratory rate
- Pre- and post-dialysis diastolic blood pressure
- Pre- and post-dialysis systolic blood pressure
- Pre- and post-dialysis weight

Differences between the mean values of calculated vital signs were compared across visits and between treatment groups. Vital sign measurements between the Defencath and heparin arms were comparable in LOCK-IT-100.

Reviewer's comment: There were no clinically significant differences in vital sign measurements seen between the two treatment arms.

Electrocardiograms

Electrocardiogram assessments were not performed in LOCK-IT-100.

QT

No clinical pharmacology studies, including a thorough QT study, were required to be conducted for this NDA (see Section [6](#)).

Immunogenicity

No immunogenicity/antigenicity evaluations were conducted as part of this development program.

8.2.5. Analysis of Submission-Specific Safety Issues

The following adverse reactions were considered adverse events of special interest due to their association with the components of Defencath in clinical trials or during postmarketing experience:

Taurolidine

- Catheter thrombosis/loss of patency
- Abnormal or metallic taste
- Oral paresthesia/dysesthesia
- Nausea/vomiting
- Chest pain

Heparin

- Bleeding complications
- HIT

Citrate

- Hypocalcemia

Additionally, catheter compatibility issues with the Defencath CLS were also evaluated as part of this NDA and the findings are summarized as part of this section as well.

8.2.5.1. Catheter Thrombosis

Catheter thrombosis was raised as a potential concern during the development program for Defencath due to reports in the literature of an increased need for thrombolytic treatment with the use of taurolidine lock solutions. The following secondary endpoints were added to LOCK-IT-100 to address this safety concern:

- Catheter removal
- Loss of catheter patency

A more detailed discussion of these secondary endpoints as they pertain to the efficacy analysis can be found in Section [8.1.2](#). Discussion here will be limited to the safety aspects.

Catheter Removal

There were 236 subjects (59%) in the Defencath arm and 225 subjects (56%) in the heparin arm who had a catheter removed during the study period for any reason ([Table 33](#)). Of these, the majority [161 subjects (41%) in the Defencath arm and 131 subjects (33%) in the heparin arm] had their catheters removed because they were no longer needed for hemodialysis. Catheter malfunction was the next most commonly cited reason for catheter removal: 62 subjects (16%) in the Defencath arm and 57 subjects (14%) in the heparin arm. Eight subjects (2%) in the Defencath arm and 29 subjects (7%) in the heparin arm had their catheters removed as a result of CRBSI.

Table 33. Study Catheters Removed by Study Arm in LOCK-IT-100, Safety Population

Reason for Catheter Removal	Defencath N=398 n (%)	Heparin N=399 n (%)
Total study catheters removed	236 (59.3)	225 (56.4)
Catheter is no longer needed for hemodialysis	161 (40.5)	131 (32.8)
Catheter malfunction	62 (15.6)	57 (14.3)
As a result of CRBSI	8 (2.0)	29 (7.3)
Other	5 (1.3)	8 (2.0)

Source: Clinical Reviewer's Analysis

Abbreviations: CRBSI = catheter-related bloodstream infection

Reviewer's comment: As noted above, increased need for thrombolytic treatment with taurolidine-containing CLS has been noted in a number of studies conducted outside of the U.S. Some studies have shown catheter replacement rates have stayed the same despite increased use of thrombolytics. The Applicant noted that heparin was included in the formulation for Defencath based on discussions with users in the European Union, suggesting that certain HD populations have increased thrombogenicity in the absence of heparin. The increased number of

study catheters removed in the Defencath arm in LOCK-IT-100 was attributed largely to catheters being no longer needed for hemodialysis and to a smaller extent to catheter malfunction. The majority of catheters being removed due to CRBSI were in the heparin arm and thus did not explain the disproportionate number of catheters removed in the Defencath arm. To further elucidate the reasons why a catheter was no longer needed for hemodialysis, the Applicant categorized the study catheter removal reasons as positive and negative as discussed below.

At the Agency’s request, the Applicant submitted additional detailed information regarding the “positive” reasons for catheter removal. The most common reason was a mature AV graft ([Table 34](#)), with 156 subjects (39%) in the Defencath arm and 129 subjects (32%) in the heparin arm.

Table 34. Detailed Positive Reasons for Study Catheter Removal in LOCK-IT-100, Safety Population

Reason for Catheter Removal	Defencath N=398 n (%)	Heparin N=399 n (%)
Total catheters removed	236 (59.3)	225 (56.4)
“Positive” reasons	162 (40.7)	132 (33.1)
Mature AV graft	156 (39.2)	129 (32.3)
Peritoneal dialysis	5 (1.3)	1 (0.3)
Renal function improved	1 (0.3)	0 (0)
Transplant	1 (0.3)	1 (0.3)

Source: Clinical Reviewer’s Analysis
Abbreviations: AV = arteriovenous

Reviewer’s comment: Catheter removals in LOCK-IT-100 were more frequently reported in the Defencath arm. While some of this discrepancy can be explained by catheter malfunction, including loss of patency, the largest difference in catheter removals was due to the increased number of subjects in the Defencath arm with mature AV grafts. It is not clear why there were more subjects in the Defencath arm that had mature AV grafts compared to subjects in the heparin arm. One possibility is that subjects in the Defencath arm were less likely to experience a CRBSI and thus were able to remain in the study long enough for their AV graft to mature.

Table 35. Negative Reasons for Study Catheter Removal in LOCK-IT-100, Safety Population

Reason for Catheter Removal	Defencath N=398 n (%)	Heparin N=399 n (%)
Study catheter removal (negative)	74 (18.6)	93 (23.3)
Catheter malfunction/dysfunction (other)	34 (8.5)	31 (7.8)
Catheter malfunction/dysfunction (loss of patency)	28 (7.0)	26 (6.5)
As a result of CRBSI	8 (2.0)	29 (7.3)
Patient developed fever, chills. Blood cultures obtained revealed no growth, so CRBSI could not be confirmed.	0 (0.0)	1 (0.3)
PI elected to exchange catheter due to positive blood culture resulting in gram variable bacilli	0 (0.0)	1 (0.3)
Catheter was removed during hospitalization due to recommendation of the infectious disease specialist of the hospital.	1 (0.3)	0 (0.0)
Nonurgent chip in CVC (no error with CVC, only physical dysfunction)	0 (0.0)	1 (0.3)
Catheter was suspected of nidus of infection, but blood cultures showed no growth	0 (0.0)	1 (0.3)
Catheter removed during hospitalization	1 (0.3)	0 (0.0)
Became displaced	0 (0.0)	1 (0.3)
Primary care physician removed catheter without consulting PI	1 (0.3)	0 (0.0)
Cloudy CVC	1 (0.3)	0 (0.0)
Catheter was removed while patient was in hospital for SAE of gastric ulcer hemorrhage	0 (0.0)	1 (0.3)
Persistent pain and irritation at catheter site.	0 (0.0)	1 (0.3)

Source: Clinical reviewer's analysis

Abbreviations: CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, PI = principal investigator, SAE = serious adverse event

Reviewer's comment: The negative reasons for catheter removal were largely due to either CRBSI or catheter malfunction, including loss of catheter patency. In the Defencath arm, catheter malfunction and loss of patency were reported more frequently while CRBSI was reported more frequently in the heparin arm. The positive reasons for catheter removal were all due to the catheter no longer being needed for hemodialysis.

Loss of Catheter Patency

Loss of catheter patency was defined as requiring the use of a thrombolytic agent, namely tPA, to maintain flow through the HD CVC or removal of the catheter due to malfunction/dysfunction. Loss of catheter patency was reported in 63 subjects (16%) in the Defencath arm and 48 subjects (12%) in the heparin arm ([Table 36](#)). Of these, 46 subjects (12%) in the Defencath arm and 33 subjects (8%) in the heparin arm required use of tPA for loss of patency.

Table 36. Loss of Catheter Patency in LOCK-IT-100, Safety Population

Loss of Catheter Patency	Defencath N=398 n (%)	Heparin N=399 n (%)
Loss of catheter patency	63 (15.8)	48 (12.0)
Use of a thrombolytic agent	46 (11.6)	33 (8.3)
Catheter malfunction/dysfunction	17 (4.3)	15 (3.8)

Source: Clinical Reviewer's Analysis

Abbreviations: tPA = tissue plasminogen activating factor

Reviewer's comment: Loss of catheter patency in this study population is a serious concern as patients with kidney failure may have limited options for vascular access in the absence of a mature AV graft or fistula. Loss of catheter patency and in particular, use of tPA to maintain flow through the HD CVC was reported more frequently in subjects in the Defencath arm. The mechanism by which taurolidine may affect loss of catheter patency is not clear; however, increased catheter malfunction/loss of patency and need for thrombolytic treatment has been noted in other trials with taurolidine-containing CLSs.

8.2.5.2. Abnormal or Metallic Taste

Three subjects (1%) in the Defencath arm and one subject (<1%) in the heparin arm reported dysgeusia.

Reviewer's comment: The reports of dysgeusia or an abnormal taste are consistent with literature reports and postmarketing experience outside the U.S. with taurolidine CLSs.

8.2.5.3. Oral Paresthesias/Dysesthesia

One subject (<1%) in the heparin arm reported hypoesthesia oral.

Reviewer's comment: Oral paresthesias were included as an AE of interest due to their association with taurolidine CLSs in the literature and in ex-U.S. postmarketing experience. There were no oral paresthesias or any related terms, reported in the Defencath arm in LOCK-IT-100. There was one subject with "hypoesthesia oral" reported in the heparin arm, however this was not thought to be related to the heparin, as similar reactions have not been reported with heparin alone previously. Paresthesia was included in the Defencath label because it has been noted as an adverse reaction reported in the ex-U.S. postmarketing experience.

8.2.5.4. Nausea/Vomiting

The preferred terms nausea and procedural nausea were pooled together (see Section [8.2.4 Treatment-Emergent Adverse Events](#)).

- Twenty-eight subjects (7%) in the Defencath arm and 44 subjects (11%) in the heparin arm had nausea.
- Twenty-four subjects (6%) in the Defencath arm and 32 subjects (8%) in the heparin arm had vomiting.

Reviewer's comment: There was a significant number of subjects reporting nausea and/or vomiting in the Defencath and the heparin arms. Given the multiple comorbidities associated with this study population and thus presumably multiple concomitant medications, it is possible that the nausea and vomiting reported are partly related to comorbidities, concomitant medications, and/or procedures. However, due to multiple reports in the literature associating gastrointestinal adverse events, such as nausea and vomiting with taurolidine-containing lock solutions, we felt it was prudent to inform healthcare providers and patients about the risk of nausea and vomiting reported in LOCK-IT-100 in the labeling for Defencath.

8.2.5.5. Musculoskeletal Chest Pain

The preferred terms noncardiac chest pain, musculoskeletal chest pain, and chest discomfort were pooled together under the term musculoskeletal chest pain (see Section [8.2.4 Treatment-Emergent Adverse Events](#)).

- Eleven subjects (3%) in the Defencath arm and seven subjects (2%) in the heparin arm reported musculoskeletal chest pain.

Reviewer's comment: The number of subjects reporting musculoskeletal chest pain were balanced between the Defencath and the heparin arms. Musculoskeletal chest pain has been reported with taurolidine CLSs but may be brief and associated with accidental flushing of the taurolidine lock solution. There were no reports of accidental flushing of Defencath during the Phase 3 trial.

8.2.5.6. Hypocalcemia

Four subjects (1%) in the Defencath arm and four subjects (1%) in the heparin arm had hypocalcemia reported.

- Three subjects (1%) in the Defencath arm and four subjects (1%) in the heparin arm reported hypocalcemia.
- One subject (<1%) in the Defencath arm reported blood calcium decreased.

Reviewer's comment: Hypocalcemia has been associated with the citrate component of Defencath, due to the ability of citrate to bind calcium. The number of subjects with reported hypocalcemia or decreased blood calcium was approximately 1% in both arms. This may be due to the small amount of citrate present in Defencath, as well as the lack of systemic exposure to Defencath when used as instructed. Because 1% of subjects in the Defencath arm did have reported hypocalcemia, hypocalcemia will be listed in Section 6 of the labeling for Defencath as a clinically significant adverse reaction that occurred in less than 1% of subjects receiving Defencath in LOCK-IT-100.

8.2.5.7. Bleeding Complications

The following list of terms were pooled together under hemorrhage/bleeding:

- Arterial hemorrhage
- Arteriovenous fistula site hematoma
- Arteriovenous fistula site hemorrhage
- Arteriovenous graft site hemorrhage
- Catheter site hematoma
- Catheter site hemorrhage
- Cerebellar hemorrhage
- Cerebral hemorrhage
- Conjunctival hemorrhage
- Eye hemorrhage
- Gastric ulcer hemorrhage
- Gastrointestinal hemorrhage
- Hematemesis
- Hematochezia
- Hematoma
- Hematuria
- Hematuria traumatic
- Hemobilia
- Hemoptysis
- Hemorrhage intracranial
- Hemorrhagic anemia
- Hemorrhagic stroke
- Hemorrhoidal hemorrhage
- Incision site hemorrhage
- Lower gastrointestinal hemorrhage
- Mouth hemorrhage
- Esophageal ulcer hemorrhage
- Esophageal varices hemorrhage

- Periorbital hemorrhage
- Post procedural hemorrhage
- Procedural hemorrhage
- Rectal hemorrhage
- Renal hematoma
- Shock hemorrhagic
- Subdural hematoma
- Upper gastrointestinal hemorrhage
- Uterine hemorrhage
- Vaginal hemorrhage
- Venous hemorrhage

Twenty-seven subjects (7%) in the Defencath arm and 34 subjects (9%) in the heparin arm had an adverse event of hemorrhage/bleeding.

Reviewer's comment: Defencath includes heparin as one of its active ingredients, thus hemorrhage or bleeding related adverse reactions were of special interest in LOCK-IT-100. Hemorrhage/bleeding can occur with heparin regardless of the route of administration and hemorrhage is included as a warning in the heparin labeling, including in heparin lock flush solutions. Because Defencath is not intended for use as a lock flush solution or via any other method of systemic administration, risk of hemorrhage/bleeding is expected to be lower when used as intended. For this reason, hemorrhage/bleeding will not be included as a warning in the Defencath label; however, it will be included in Section 6 Adverse Reactions as it met the criteria of occurring in $\geq 2\%$ of subjects in the study with a plausible causal relationship to the study drug. Due to the expected long duration of use of Defencath in subjects (the median duration of use in LOCK-IT-100 was 173 days), accidental flushing of the product and/or leaching from the catheter lock is theoretically possible.

8.2.5.8. HIT

One subject (<1%) in the heparin arm had an adverse reaction of HIT.

Reviewer's comment: HIT is a serious and potentially fatal disorder that can occur following exposure to heparin regardless of dose or route of administration. While there were no subjects who developed HIT in the Defencath arm in LOCK-IT-100, due to the report of HIT in a subject treated with heparin in LOCK-IT-100, a component of Defencath, HIT will be included as a warning in the Defencath label.

8.2.5.9. Hypersensitivity Reactions

Anaphylactic reaction, drug hypersensitivity, and medical device hypersensitivity were pooled together as hypersensitivity.

- Four subjects in the heparin arm (1%) and no subjects in the Defencath arm experienced a hypersensitivity reaction during the Phase 3 trial.
- On further evaluation, 2 subjects (0.5%) in the heparin arm experienced a hypersensitivity reaction during the treatment period: 1 subject had a drug hypersensitivity and 1 subject had a medical device hypersensitivity. The other 2 subjects developed their hypersensitivity reactions during the follow-up period rather than the treatment period: 1 subject had an anaphylactic reaction and 1 subject experienced a drug hypersensitivity reaction.

Reviewer's comment: Hypersensitivity reactions to any of the components of Defencath will be included as both a contraindication and a warning in the Defencath label. Although there were no reported subjects with hypersensitivity in the Defencath arm, two subjects treated with heparin, a component of Defencath, experienced a hypersensitivity reaction during the treatment period.

8.2.5.10. Catheter Compatibility With Lock Solution

Since Defencath is a CLS, its potential impact on HD catheters including, biocompatibility and catheter integrity were evaluated. Please refer to the Office of Pharmaceutical Quality (OPQ) review which discusses these issues in detail. In addition, in order to evaluate the Applicant's nonclinical testing for any potential impact of Defencath on the integrity of the HD catheters, additional input was sought from the Center for Devices and Radiological Health (CDRH). Dr. Qin Zhang and Mr. Richard Williams provided input from the perspectives of biocompatibility and mechanical integrity, respectively. Please refer to their consult reviews in DARRTS, dated January 26, 2021. The CDRH reviewers evaluated the Applicant's data submitted for two test HD catheter models (one silicone and one polyurethane): MC10143 (MedCOMP) and CENFP19K/A (Merit).

From a biocompatibility standpoint, Dr. Zhang found the testing conducted acceptable for the two test catheters and not likely to raise an unacceptable toxicity concern to patients. From a mechanical integrity standpoint, Mr. Williams' review noted that the bench testing done with the two test catheters mentioned above was limited to the tensile test only. As testing was limited to only two catheter types, both reviewers had raised concern about the lack of data with other catheter types. Additional information was requested from the Applicant regarding the testing performed.

Based on the additional information provided by the Applicant and further discussions with CDRH, it was determined that use of the product will not need to be limited to only the two catheter types tested. This determination was based on the findings of the biocompatibility and

catheter integrity testing performed with the two types of catheters and the clinical data from the LOCK-IT-100 trial in which more than 100 different HD catheter brands were used, including the MedCOMP and Merit catheters. The most commonly used catheter brands were MedComp, Bard, Angiodynamics and Covidien. The most commonly reported catheter manufacturer brands are listed in [Table 37](#). The catheter manufacturer brands were balanced between the two study arms. There was no imbalance in clinical adverse events between the Defencath and heparin arms and no imbalance was seen in adverse events by catheter type/brand.

An analysis was performed to assess if a specific catheter brand was more likely to be associated with a reported AE of device malfunction. There were 68 subjects in the Defencath arm (17%) and 47 subjects in the heparin arm (12%) with a reported AE of device malfunction. The catheter brands most commonly reported to have a device malfunction were MedComp, Bard, Angiodynamics and Covidien ([Table 38](#)), which were also the most commonly used catheters overall. There did not appear to be any major differences in device malfunction by study arm and catheter manufacturer brand. Section 14 (Clinical Studies) section of the labeling includes a statement that multiple catheter types were studied in the LOCK-IT-100 trial.

Table 37. Catheter Manufacturers Reported in ≥2% of Subjects in LOCK-IT-100

Manufacturer Name	Defencath N=398 n (%)	Heparin N=399 n (%)
Medcomp	86 (21.6%)	83 (20.8%)
Bard	87 (21.9%)	76 (19.0%)
Angiodynamics	36 (9.0%)	36 (9.0%)
Covidien	32 (8.0%)	28 (7.0%)
Arrow	12 (3.0%)	10 (2.5%)
Unknown	5 (1.3%)	17 (4.3%)
Med comp	4 (1.0%)	14 (3.5%)
Palindrome	10 (2.5%)	5 (1.3%)
Teleflex	7 (1.8%)	6 (1.5%)
Glidepath	8 (2.0%)	2 (0.5%)

Source: Clinical Reviewer's Analysis

*Note: Manufacturer names reported verbatim from study clinical datasets provided by Applicant.

Table 38. Catheter Manufacturers Reported in ≥0.5% of Subjects Receiving Defencath and With a Reported Device Malfunction in LOCK-IT-100

Manufacturer Name	Defencath N=398 n (%)	Heparin N=399 n (%)
Medcomp	14 (3.5%)	16 (4.0%)
Bard	14 (3.5%)	11 (2.8%)
Angiodynamics	6 (1.5%)	2 (0.5%)
Covidien	2 (0.5%)	3 (0.8%)
Unknown	1 (0.3%)	3 (0.8%)
Angiodynamics duraflow	2 (0.5%)	1 (0.3%)
Medtronic	2 (0.5%)	1 (0.3%)
Ash access technology, inc.	2 (0.5%)	0 (0.0%)
Palindrome	2 (0.5%)	0 (0.0%)
Coviden	2 (0.5%)	0 (0.0%)
Ash	1 (0.3%)	1 (0.3%)
Bard vaccess	2 (0.5%)	0 (0.0%)

Source: Clinical Reviewer's Analysis

*Note: Manufacturer names reported verbatim from study clinical datasets provided by Applicant.

Based on the sum of information provided by the Applicant and that the Phase 3 trial enrolled patients with multiple catheter types, CDRH provided an addendum to the consult reviews (signed into DARRTS on 2/25/21) noting that: "...Multiple catheter types were studied in the LOCK-IT-100 trial and we are not restricting Defencath to use in only the two catheters with bench testing for the labeling."

Reviewer's comment: In order to evaluate the catheter brands used in the Phase 3 trial, we analyzed the most common catheter manufacturers reported in the study and whether any differences in reported AEs of device malfunction were noted. While overall there were more cases of device malfunction reported in the Defencath arm ([Table 32](#)), there were no noted differences between the two study arms in terms of the brands of catheters affected. Given the totality of evidence presented including the in vitro testing of the Merit and Medcomp catheters, as well as findings noted in the LOCK-IT-100 trial and existence of ex-U.S. clinical experience with marketing of the same product, known as Neutrolin, Defencath use will not need to be limited to only the two catheter types tested. Section 14 (Clinical Studies) section of the labeling will include a statement that multiple catheter types were studied in the Phase 3 trial.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

There were no clinical outcome assessment analyses conducted as part of this drug development program.

8.2.7. Safety Analyses by Demographic Subgroups

Demographic subgroup safety analyses were conducted by age group, sex, race, and ethnicity.

Age Group

In general, more AEs were reported in subjects <65 years of age than in subjects ≥75 years of age ([Table 39](#)) with the exception of hemorrhage/bleeding. Eight subjects (13%) ≥75 years, 7 subjects (7%) ≥65 to <75 years and 13 subjects (6%) ≤65 years reported hemorrhage/bleeding.

Table 39. Adverse Events Reported in >10% of Subjects Receiving Defencath or Heparin by Treatment Group and Age Group, Safety Population

Adverse Event	Defencath			Heparin		
	<u>< 65</u> N=236 n (%)	<u>≥65-<75</u> N=98 n (%)	<u>≥75</u> N=64 n (%)	<u>< 65</u> N=234 n (%)	<u>≥65-<75</u> N=94 n (%)	<u>≥75</u> N=71 n (%)
Hemodialysis catheter malfunction ^a	43 (18)	14 (14)	11 (17)	28 (12)	6 (6)	13 (18)
Diarrhea	20 (9)	13 (13)	5 (8)	20 (9)	8 (9)	2 (3)
Hypotension	19 (8)	13 (13)	4 (6)	19 (8)	6 (6)	4 (5)
Nausea*	19 (8)	5 (5)	5 (8)	25 (11)	15 (16)	6 (9)
Hypertension	19 (8)	7 (7)	2 (3)	26 (11)	12 (13)	1 (1)
Hemorrhage/bleeding*	13 (6)	7 (7)	8 (13)	12 (5)	9 (10)	13 (18)
Vomiting*	13 (6)	8 (8)	3 (5)	15 (6)	13 (14)	5 (7)
Pneumonia	10 (4)	3 (3)	5 (8)	11 (5)	8 (9)	9 (13)

Source: Clinical Reviewer's Analysis

^a Device malfunction

* Pooled Terms

Reviewer's comment: There were more subjects with hemorrhage and bleeding in the ≥75 years age group compared to those in younger age groups in both study arms. This is consistent with what we know about bleeding risk overall in older age groups. There were no other clinically significant differences noted in adverse events by age group. While slightly more adverse events overall were noted in the younger age groups, this was likely due to the greater number of subjects in the under 65 year age group in LOCK-IT-100 compared to those in the 65 to 75 year age group and those in the over 75 year age group ([Table 7](#)).

Sex

There were more male subjects randomized and enrolled in LOCK-IT-100 than female subjects ([Table 7](#)). Of the adverse events reported in >10% of subjects, more adverse events occurred in the male group in both treatment arms ([Table 40](#)). Hemodialysis catheter malfunction, diarrhea, hypotension, hypertension and nausea were the most frequently reported adverse events reported when stratified by sex.

Table 40. Adverse Events Reported in >10% of Subjects Receiving Defencath or Heparin by Treatment Group and Sex, Safety Population

Adverse Event	Defencath		Heparin	
	<u>Female</u> N=183 n (%)	<u>Male</u> N=215 n (%)	<u>Female</u> N=153 n (%)	<u>Male</u> N=246 n (%)
Hemodialysis catheter malfunction ^a	29 (16)	39 (18)	20 (13)	27 (11)
Diarrhea	15 (8)	23 (11)	12 (8)	18 (7)

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Hypotension	13 (7)	23 (11)	6 (4)	23 (9)
Hypertension	13 (7)	15 (7)	9 (6)	30 (12)
Nausea*	12 (7)	17 (8)	17 (11)	29 (12)

Source: Clinical Reviewer's Analysis

^a Device malfunction

* Pooled Terms

Reviewer's comment: Small differences were observed in adverse events reported by sex; however, these differences were not thought to be clinically significant. Of note, more males were randomized and enrolled in the Phase 3 trial compared to females ([Table 7](#)).

Race

A safety analysis by race is presented in [Table 41](#). The majority of subjects in LOCK-IT-100 were white or black/African American ([Table 7](#)). Thirty-three subjects (3%) were Asian, five subjects (0.5%) were American Indian or Alaska Native, 14 subjects (1.3%) were Native Hawaiian or Other Pacific Islander, and 6 subjects (0.6%) were listed as "other". Hemodialysis catheter malfunction, hypotension, vomiting, diarrhea, hypertension, muscle spasms, nausea and hemorrhage/bleeding were the most frequently reported adverse events reported when stratified by race. Hemodialysis catheter malfunction was reported more frequently in black/African American subjects compared to white subjects. In the Defencath arm, 29 black/African American subjects (23%) and 33 white subjects (14%) reported hemodialysis catheter malfunction. In the heparin arm, 17 black/African American subjects (15%) and 27 white subjects (10%) reported hemodialysis catheter malfunction.

Table 41. Adverse Events Reported in >10% of Subjects by Treatment Group and Race, Safety Population

Adverse Event	Defencath		Heparin	
	Black or African American	White	Black or African American	White
	N=125 n (%)	N=244 n (%)	N=111 n (%)	N=259 n (%)
Hemodialysis catheter malfunction ^a	29 (23)	33 (14)	17 (15)	27 (10)
Hypotension	13 (10)	20 (8)	7 (6)	17 (6)
Vomiting*	13 (10)	11 (5)	7 (6)	22 (9)
Diarrhea	12 (10)	25 (10)	11 (10)	17 (7)
Hypertension	12 (10)	15 (6)	13 (12)	23 (9)
Muscle spasms	11 (9)	15 (6)	12 (11)	21 (8)
Nausea*	7 (6)	21 (9)	11 (10)	32 (12)
Hemorrhage/bleeding*	7 (6)	19 (8)	12 (11)	22 (9)

Source: Clinical Reviewer's Analysis

^a Device malfunction

¥A total of 58 subjects reported a race besides white or black/African American. This included 33 subjects who were Asian, 5 subjects were American Indian or Alaska Native, 14 subjects were Native Hawaiian or Other Pacific Islander, and 6 subjects were

listed as “other”.

* Pooled Terms

Reviewer’s comment: Hemodialysis catheter malfunction was reported more frequently among black/African American subjects as compared to white subjects in both treatment arms. The difference was more pronounced in the Defencath arm (difference of 9% between black and white subjects) versus the heparin arm (difference of 5% between black and white subjects). It is not clear why black/African American subjects would experience greater rates of hemodialysis catheter malfunction and whether this is related to the study drug since the difference is noted in both arms and may reflect disparate health outcomes with regard to kidney disease in different racial populations and disparate access to healthcare. The differences noted in the remainder of the observed AEs were small and not thought to be clinically significant and were likely due to the greater number of white subjects in the study compared to black subjects.

Ethnicity

Adverse events reported in >10% of subjects by ethnicity and treatment group are presented in [Table 42](#). Relevant listed adverse events with a plausible causal relationship to the study drug include hemodialysis catheter malfunction, hemorrhage/bleeding, nausea, and vomiting. Of these, the largest difference was seen in subjects reporting hemodialysis catheter malfunction, with 20 Hispanic/Latino subjects (12%) and 48 nonHispanic/Latino subjects (21%) reporting hemodialysis catheter malfunction in the Defencath arm.

Table 42. Adverse Events Reported in >10% of Subjects by Treatment Group and Ethnicity, Safety Population

Adverse Event	Defencath		Heparin	
	Hispanic or Latino N=173 n (%)	Not Hispanic or Latino N=225 n (%)	Hispanic or Latino N=187 n (%)	Not Hispanic or Latino N=212 n (%)
Hemodialysis catheter malfunction ^a	20 (12)	48 (21)	16 (9)	31 (17)
Diarrhea	16 (9)	22 (10)	14 (8)	16 (8)
Hypotension	14 (8)	22 (10)	12 (6)	17 (8)
Fluid overload	14 (8)	12 (5)	13 (7)	10 (5)
Hemorrhage/bleeding*	12 (7)	16 (7)	7 (4)	27 (13)
Muscle spasms	11 (6)	15 (7)	10 (5)	26 (12)
Hypertension	11 (6)	17 (8)	16 (8)	23 (11)
Nausea*	11 (6)	18 (8)	20 (11)	26 (12)

Source: Clinical Reviewer’s Analysis

^a Device malfunction

* Pooled Terms

Reviewer’s comment: With the exception of the difference noted between Hispanic/Latino and nonHispanic/Latino subjects with regard to hemodialysis catheter malfunction, the remainder of AEs were generally balanced between Hispanic/Latino and nonHispanic/Latino subjects. The small differences seen were not thought to be clinically significant. It is entirely not clear why Hispanic/Latino subjects in both treatment arms

would report less hemodialysis catheter malfunction than non-Hispanic/Latino subjects, however one plausible explanation may be that black/African American subjects who are reported as non-Hispanic may be driving the increased number of hemodialysis catheter malfunction among non-Hispanics.

8.2.8. Specific Safety Studies/Clinical Trials

There were no specific safety studies or clinical trials conducted as part of the development program for Defencath.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Human carcinogenicity studies were not conducted because Defencath is not intended for systemic administration and exposure to its components is minimal when used as directed.

Human Reproduction and Pregnancy

There are no adequate and well-controlled studies of Defencath in pregnant women. A consult from the Division of Pediatric and Maternal Health (DPMH) was requested as part of this review and is summarized below.

There were two reports of pregnancies among the 806 subjects randomized in LOCK-IT-100. Both pregnancies were in the Defencath arm. One subject delivered a full-term, healthy baby. One subject had a spontaneous abortion and the study drug was withdrawn. There are no case reports of Defencath (marketed as Neutrolin in Europe) use in pregnancy from the ex-U.S. pharmacovigilance database provided by the Applicant.

Since Defencath is not intended for systemic administration, use in pregnant or lactating patients is not expected to result in fetal or infant exposure to the drug. There are no cases of accidental injection of Defencath in the clinical trial or ex-U.S. experience. No animal reproduction study was conducted due to lack of systemic administration of this drug. Because Defencath is not systemically administered, DPMH did not recommend a postmarketing pregnancy safety or clinical lactation study.

Because the available data in the clinical trial and ex-U.S. experience on the use of taurolidine in pregnant women did not contain any cases of accidental injection in pregnancy or during lactation, there is insufficient information to inform a drug-associated risk of major birth defects, miscarriage, and adverse maternal, fetal or newborn outcomes if taurolidine was administered intravenously.

Prolonged experience with heparin in pregnant women over several decades, based on published literature, controlled trials and observational studies, has not identified a drug-

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associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on its molecular weight, heparin is not expected to be excreted into human breast milk.

Defencath is not intended to be used systemically and therefore its use is not expected to result in any effects on fertility or interaction with hormonal contraception.

Pediatrics and Assessment of Effects on Growth

A deferral of pediatric assessment of Defencath for pediatric patients <18 years of age was requested by the Applicant. An initial Pediatric Study Plan (iPSP) was agreed upon. Additional details on the iPSP can be found in Section [10](#) Pediatrics.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdoses and drug abuse have not been reported in the Defencath clinical development program.

Reviewer's comment: Overdose and drug abuse, as well as withdrawal and rebound is unlikely with Defencath given the known biological properties of the components of Defencath and the mode of administration. There are no known reported cases of overdose or drug abuse in the postmarket setting.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A postmarketing experience study was conducted from 2014 to 2016 in 20 dialysis centers in Germany (Reidenberg et al. 2018). A total of 201 patients were followed as part of this study. Two patients experienced occasional transient dysgeusia and no adverse drug reactions leading to the discontinuation of Defencath were reported.

The Neutrolin label (2018-04 v3.0) for the CE marked product in Europe, lists no known serious adverse effects in humans due to the active ingredients at concentrations contained in the Neutrolin device when used as directed. It notes that as Neutrolin contains heparin, it could be associated with the development of heparin-induced thrombocytopenia. The label lists abnormal taste sensation (dysgeusia) and a tingling sensation (paresthesia) as adverse effects reported for Neutrolin.

Expectations on Safety in the Postmarket Setting

In addition to safety concerns identified in the postmarket setting in Europe and discussed above, including HIT, abnormal taste sensation (dysgeusia), and tingling sensations (paresthesia), safety concerns identified in LOCK-IT-100 include:

- Nausea and vomiting

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- Musculoskeletal chest pain
- Hypocalcemia
- Bleeding complications
- Hypersensitivity reactions

8.2.11. Integrated Assessment of Safety

A single Phase 3 study was conducted for this development program, therefore there was no integrated assessment of safety conducted.

8.3. Statistical Issues

There were no major statistical issues with the Phase 3 trial. A planned interim analysis was performed when 28 CAC-adjudicated CRBSIs had occurred. The results demonstrated a statistically significant treatment difference in the primary efficacy endpoint in favor of Defencath, and therefore the study was stopped early using an acceptable method for controlling the type I error. Additional subjects were randomized and treated between the interim analysis and termination of the study. The final analysis based on all data through the study completion yielded similar results to the interim analysis.

The primary endpoint was changed during the blinded study. The Division was notified of the change and agreed. However, the treatment effect of Defencath appeared consistent across various definitions of outcomes. Death is an important efficacy outcome. The additional analyses where the deaths were considered as part of the event were performed, and the results were consistent with the primary endpoint.

8.4. Conclusions and Recommendations

Defencath is being considered for approval under the LPAD pathway due to its potential to reduce the incidence of a serious and life-threatening infection in a limited population of patients, that is, kidney failure patients receiving HD through a CVC. Effectiveness in other populations has not been demonstrated. A streamlined approach involving a single Phase 3 trial was considered acceptable given the statistically persuasive results in the trial. For the purposes of this NDA, the safety database of 398 subjects exposed to Defencath was considered sufficient. The efficacy and safety review for this NDA focused on the Phase 3 trial.

Efficacy

The efficacy of Defencath was demonstrated in a single, randomized, controlled Phase 3 trial in a population of patients with kidney failure receiving HD through a CVC. The interim analysis, which was conducted when 28 CAC-adjudicated CRBSIs had occurred, showed 6 CRBSI cases in the Defencath arm and 22 CRBSI cases in the heparin arm, with a statistically significant difference in favor of Defencath ($p=0.0034$). The Data and Safety Monitoring Board recommended early termination of the study based on the results of the interim analysis. In the

final analysis, Defencath met the primary endpoint of time to CRBSI with 9 cases of CAC-adjudicated CRBSIs in the Defencath arm and 32 in the heparin arm ($p=0.0006$) and an event rate per 1,000 catheter-days of 0.13 and 0.46 in the Defencath arm and the heparin arm, respectively. An FDA re-adjudication of the CRBSI cases evaluated in this trial showed a few differences as compared with the CAC-adjudicated CRBSI cases; however, the overall results of the FDA re-adjudication were consistent with the CAC-adjudicated results. The treatment effect of Defencath remained consistent in several sensitivity analyses performed by the Agency and is further detailed in Section [8.1.2](#) Study Results.

Safety

The safety of Defencath was supported by the single Phase 3 trial.

The safety finding of concern in LOCK-IT-100 was the difference in loss of catheter patency, which occurred more frequently in the Defencath arm versus the heparin arm. Loss of catheter patency is a serious concern for patients with kidney failure who may have limited vascular access options. The mechanism by which taurolidine affects loss of catheter patency is not clear but has been noted previously and was a specific safety endpoint for LOCK-IT-100 due to this concern. The difference in rates of catheter removal between the Defencath arm and the heparin arm however, do not appear to be secondary to loss of catheter patency. Although there were differences in the rates of CRBSI between the two treatment arms, the main driver of the overall observed difference in catheter removal rates between the two arms was the greater number of CVC removals due to AV graft/fistula maturation in the Defencath arm.

Certain AEs, including HIT, hypersensitivity reactions, and hemorrhage/bleeding were noted more frequently in the heparin arm than the Defencath arm; however, because heparin is a component of Defencath, these AEs may potentially occur with Defencath administration and were thus highlighted in this review, and will be communicated in the Defencath labeling.

The remainder of the AEs occurring in LOCK-IT-100 with a plausible relationship to Defencath and its components were consistent with prior knowledge of the safety of taurolidine, heparin and the citrate excipient and included hemodialysis catheter malfunction, thrombocytopenia, nausea, vomiting, dizziness, musculoskeletal chest pain, hypocalcemia, and dysgeusia.

Overall, there were no major differences noted between the Defencath arm and the heparin comparator arm with regard to the number of reported AEs, SAEs, and discontinuations. No deaths in either treatment arm were attributed to the study drug.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was originally scheduled for this NDA on January 14, 2021. Based on the ongoing review and the Applicant's responses to the review team's information

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requests, the Agency's questions regarding the primary efficacy analysis were addressed. The review team concluded that the overall benefit/risk was clear and there were no issues that would benefit from Advisory Committee discussion. The decision to cancel the advisory committee meeting was communicated to the Applicant on November 16, 2020.

10. Pediatrics

There were no pediatric studies submitted with this NDA. An initial Pediatric Study Plan was submitted to IND 113764 to conduct an open-label, two-arm (Defencath vs. standard of care) study to observe time to CRBSI and evaluate safety in patients 0 to <18 years receiving HD via a CVC. The Division confirmed initial agreement with the iPSP on April 2, 2020.

The Applicant requested a deferral of the pediatric study in patients <18 years of age until initial evidence of safety and effectiveness were demonstrated in adult patients receiving HD via a CVC.

A review by the Pediatric Review Committee (PeRC) was conducted on January 26, 2021. PeRC agreed with granting the deferral as presented in the iPSP.

Please also see Section 13 of this review regarding the postmarketing requirement to study Defencath in pediatric patients receiving HD via a CVC

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Table 43. High Level Summary of Significant Labeling Changes (Not Necessarily Direct Quotations)

Section	Applicant Proposed Labeling	Labeling Changes
Highlights	- Did not provide an established Pharmacological Class for taurolidine. - Referred to the Phase 3 trial as “LOCK-IT-100”. - Referred to patients in the Phase 3 trial as having ESRD.	- New EPC provided for taurolidine: “thiadiazinane” antimicrobial. - Refer to the Phase 3 trial as “Trial 1” - Changed ESRD to kidney failure
1. Indications and usage	- Indicated for the prevention of CRBSI. - Did not include a limited population statement as required by the LPAD guidance.	- Amended indication to: “reduce the incidence of CRBSI”. This change was recommended to avoid implying a guarantee of success by use of the term “prevention.” - Added statement regarding use in a limited and specific population of patients as per the LPAD guidance.

Reviewer’s comment: The Applicant requested LPAD during the review cycle. The limited population statement was added according to the LPAD guidance. We recommended using the phrase “reduce the incidence of CRBSI” rather than “for the prevention of CRBSI.” Use of the term prevention implies a guarantee of success, whereas “reduces the incidence of” is a more accurate description of the therapeutic activity of Defencath. Other recently approved antimicrobial products used for “prevention” indications, including [REDACTED], follow the suggested format. To optimize sensitivity to patients and minimize stigma, we substituted “kidney failure” for “ESRD” throughout the labeling. The name of the Phase 3 trial was revised from “LOCK-IT-100” to “Trial 1” throughout the labeling to decrease clutter and improve readability.

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Section	Applicant Proposed Labeling	Labeling Changes
2. Dosage and administration	Did not include instructions to avoid administering the product as a systemic product or as a catheter lock flush.	- Revised section to specify use of product only as a CLS in HD CVCs. - Moved statement on avoiding systemic administration to section 2 from (b) (4). - Added a statement on avoiding use of the product as a catheter lock flush product.
<i>Reviewer's comment: Defencath is for use as a CLS and is not meant for systemic administration. Statements clarifying administration were moved to section 2.</i>		
3. Dosage forms and strengths	- Stated that Defencath is (b) (4). - Package type term proposed was (b) (4).	- Removed statement on Defencath being (b) (4). - Revised package type term to single-dose.
4. Contraindications	Included contraindication statements for HIT and for known (b) (4) to taurolidine, citrate or heparin.	- Replaced term (b) (4) with (b) (4) hypersensitivity." - Hypersensitivity to pork products was added as a contraindication since the heparin in this product is porcine-derived.
<i>Reviewer's comment: We agreed with the contraindications stated by the Applicant. However, we recommended replacing the term (b) (4) with the more all-encompassing term (b) (4) hypersensitivity", which is consistent with the MedDRA preferred term used in the trial and is consistent with labeling practices in the Division. Other heparin labels include pork products as a potential trigger for hypersensitivity reactions and this was added for consistency.</i>		
5. Warnings and precautions	Included a warning for HIT, however did not include the incidence of HIT reported in the Phase 3 trial.	- Added a warning for drug hypersensitivity. - Included the incidence of HIT and drug hypersensitivity reported in the Phase 3 trial. - Revised the advisory statement to discontinue DEFENCATH and institute appropriate supportive measures.
<i>Reviewer's comment: Drug hypersensitivity was included as a warning due to the potentially serious and life-threatening nature of hypersensitivity reactions. HIT and drug hypersensitivity reactions were reported in the heparin arm of the Phase 3 trial. There were no cases of HIT or drug hypersensitivity that were reported in the Defencath arm. Heparin is a component of Defencath, thus both HIT and drug hypersensitivity are included in the Defencath label as warnings.</i>		

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Section	Applicant Proposed Labeling	Labeling Changes
6. Adverse reactions	- Reported (b) (4) - Reported (b) (4) - No other information or tables on adverse reactions reported in the Phase 3 trial were provided in this section.	- Removed Applicant's statements regarding: (1) (b) (4), and (2) (b) (4) - Included statement on clinical trials experience and rates of adverse reactions as per FDA guidance on adverse reactions labeling. - Included an overview of the safety evaluation of Defencath with a description of the demographics of the safety population. - Included overall serious adverse reactions and adverse reactions leading to discontinuation per study arm reported in the Phase 3 trial. - Added Table 1, "Selected Adverse Reactions Occurring in Greater Than or Equal to 2% of Patients Receiving Defencath in Trial 1". - Added Table 2, "Loss of Catheter Patency in Trial 1" to highlight the primary safety finding in the Phase 3 trial, increased loss of catheter patency in the Defencath arm compared to the heparin arm. - Added a section on adverse reactions that occurred in less than 1% of patients receiving Defencath. - Added Section 6.2 Postmarketing Experience for adverse reactions reported during use of taurolidine outside of the United States.

Reviewer's comment: Extensive revisions were made to Section 6 based on the Adverse Reactions Section of Labeling (final guidance). Sections were added as discussed above to describe the demographics of the safety population, to report the deaths, overall numbers of serious adverse reactions, and adverse reactions leading to discontinuation that were reported in each study arm. The findings of the safety analysis and important safety signals that emerged were also reported in this section in Tables 1 and 2 of the labeling. The most important safety signal emerging in the Phase 3 trial was loss of catheter patency in the Defencath arm and this is described in Table 2 of the labeling.

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Section	Applicant Proposed Labeling	Labeling Changes
8.Use in specific populations	- Included a statement on (b) (4) pregnant and lactating woman and in pediatric patients. - Included an overview of geriatric patients enrolled in the Phase 3 trial.	- Revised section on pregnant and lactating women based on DPMH consult. Since Defencath is not intended for systemic administration, maternal use and use during breastfeeding are not expected to result in exposure to the fetus or infant. - Revised Pediatric Use and Geriatric Use sections for clarity and consistency.
12. Clinical Microbiology	(b) (4)	<u>Resistance</u> Time kill studies showed that taurolidine is bactericidal (>3 log₁₀ CFU reduction) at 1x to 4x MIC. The frequency of resistant mutants was <10⁻⁹ at 2x and 4x MIC for two strains each of <i>Escherichia coli</i>, <i>Staphylococcus aureus</i>, <i>Enterococcus faecalis</i>, <i>Enterococcus faecium</i>, and <i>Pseudomonas aeruginosa</i>.
13.Nonclinical toxicology	- No statements on Carcinogenesis or Impairment of Fertility in Section 13.1. - Details regarding (b) (4) were included. - No statement regarding mutagenicity testing of heparin. - Section (b) (4) with Defencath.	- Included statements indicating that carcinogenicity studies were not performed with taurolidine or heparin and that fertility studies were not conducted with Defencath due to negligible clinical exposure. - Details on genetic toxicity testing (b) (4) Only the outcome (positive or negative) is generally included. - Statement regarding lack of mutagenicity testing of heparin was added. - Deleted Section (b) (4)

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Section	Applicant Proposed Labeling	Labeling Changes
14. Clinical studies	• (b) (4) • (b) (4) • Discussion of secondary endpoint results.	• Removed references to (b) (4) • (b) (4) added a Table 3, “Results of Analyses of CAC-Adjudicated CRBSI...” with a summary of the number of CAC-adjudicated CRBSI per study arm, event rate per 1,000 days, hazard ratio and log-rank test p-value. • Added a sensitivity analysis with CAC-adjudicated CRBSI or death as the endpoint. • Included the number of CRBSI cases with gram-negative and gram-positive organisms isolated in each study arm. • (b) (4)
<i>Reviewer’s comment: Section 14 was edited for clarity, brevity and consistency. Information on (b) (4) is not relevant or informative for healthcare providers and was removed. Information on results of the statistical analysis, including p-values, were moved to a new Table 3 as described above. The discussion of (b) (4) as recommended in the guidance, Clinical Studies Section of Labeling for Human Prescriptions Drug and Biological Products.</i>		
16. How supplied/storage and handling	• Applicant proposed the statement: (b) (4)	• Statement was revised to read as: (b) (4)

12. Risk Evaluation and Mitigation Strategies

There are no risk evaluation or mitigation strategies planned for this NDA.

13. Postmarketing Requirements and Commitment

Should Defencath be approved in a future review cycle, the following postmarketing requirement would be required for this application under the Pediatric Research and Equity Act:

An open-label, two-arm (Defencath vs. standard of care) study to assess safety and time to CRBSI in subjects with kidney failure aged 0 to <18 years receiving hemodialysis via a central venous catheter.

Draft Protocol Submission: Submitted

Final Protocol Submission: (b) (4)

Study Completion: (b) (4)

Final Report Submission: (b) (4)

14. Division Director (Clinical) Comments

I concur with the review team's assessment and recommendations.

15. Office Director Comments

I concur with the review team's assessment and recommendations.

16. Appendices

16.1. References

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16.2. Financial Disclosure

Financial disclosure information was provided for the Phase 3 trial investigators. There were no financial interests or arrangements to disclose for the investigators.

Table 44. Covered Clinical Study (Name and/or Number): LOCK-IT-100

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>68</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Additional Clinical Microbiology Information

Further evidence of the nonspecific toxic mechanism of action is the relatively high concentration of taurolidine required for microbial inhibition and killing. Data from surveillance studies showed taurolidine minimum inhibitory concentration (MIC) values:

- Against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus aureus* (MSSA), streptococci (Groups A, B, C and G), viridans streptococci, *Pediococcus* spp., *Lactobacillus* spp., *Leuconostoc* spp., *L. monocytogenes*, and diphtheroids, ranged from 128 to 2048 µg/mL with modal values of 512 µg/mL (Report#19-CMX-01; Zimmermann and Preac-Mursic 1992; Torres-Viera et al. 2000; Shah et al. 2002; Olthof et al. 2013).

- Against *Enterobacteriales* isolates, including *E. coli*, *K. pneumoniae*, *E. aerogenes*, *C. freundii*, *S. marcescens*, *P. mirabilis*, *P. vulgaris*, and *M. morganii*, ranged from 256 to 2048 µg/mL with modal values of 512 µg/mL (Report#19-CMX-01 ; Torres-Viera et al. 2000; Shah et al. 2002; Olthof et al. 2013).
- Against *P. aeruginosa* ranged from 256 to 2048 µg/mL with a one-dilution shift in modal value of 1024 µg/mL (Report#19-CMX-01 ; Torres-Viera et al. 2000).
- Against other nonfermenters, including *Acinetobacter* spp., *S. maltophilia*, *B. cepacia*, other gram-negative isolates (*M. catarrhalis*), and anaerobes, ranged from 500 to 4,000 µg/mL (Zimmermann and Preac-Mursic 1992; Torres-Viera et al. 2000).
- Against fungal organisms, such as *C. glabrata* taurolidine, were 512 µg/mL; however, taurolidine showed less activity against *C. albicans* with 8-fold higher MIC_{50/90} values of 4096 µg/mL (Report#19-CMX-01 ; Olthof et al. 2013).
- Against other fungal organisms, such as *Cryptococcus neoformans*, *Aspergillus* species, *Trichophyton rubrum*, *Epidermophyton floccosum* and *Pityrosporum ovale*, ranged from 256 to 5,000 µg/mL.

Time kill studies showed that taurolidine is bactericidal (>3 log₁₀ CFU reduction) between 1 to 4x MIC. One group (Torres-Viera et al. 2000) tested 5 isolates with a taurolidine MIC of 500 µg/mL (*E. coli*, n=2); *E. faecalis*, n=1; *S. aureus*, n=2), and an *E. faecium* isolate with a MIC of 250 µg/mL. At the MIC, only 3 isolates showed a 0.1 to 3.2 log₁₀ reduction at 24 hours (2 *S. aureus* and 1 *E. coli* isolate). The remaining isolates had a 0.8 to 1.8 log₁₀ increase in growth (1 *E. coli*, *E. faecium*, *E. faecalis*). In contrast, at 4x MIC (2,000 µg/mL), five of the six isolates showed bactericidal activity, with the *E. faecium* isolate showing a 1.3 log₁₀ increase in growth. Similarly, (Traub et al. 1993) evaluated 37 isolates, including *S. aureus* (n=9), *E. faecium* (n=17) and Enterobacteriaceae (n=11), with taurolidine MICs <1250 µg/mL and showed that the minimum bactericidal concentrations corresponded to 1 to 2x MIC with the exception of 3 gram-negative isolates, which showed minimum bactericidal concentrations of 4x MIC.

A study by (Shah et al. 2002) evaluated the in vitro activity of taurolidine solution (containing either 0.675% or 1.35% taurolidine and citrate 2.61%) against bacterial pathogens. Taurolidine at a concentration of 675 µg/mL following 24 hours of exposure showed a >3 log₁₀ CFU reduction in bacterial load against *S. aureus*, *S. epidermidis*, and *P. aeruginosa* compared to controls (p<0.05). However, a 2 log₁₀ reduction was observed against *E. faecalis* compared to control (p<0.05). In contrast, taurolidine at a concentration of 13500 µg/mL resulted in a 4.2 log₁₀ reduction compared to controls after 24 hours exposure. Similar results were shown in the (Report# (b) (4)-10-6115-N14) using the Defencath formulation, which resulted in a 6.04 log₁₀ reduction against *S. aureus* and 6.28 log₁₀ reduction against *P. aeruginosa* at 18 to 24 hours compared to controls. In contrast, *E. faecalis* had a 3.32 log₁₀ reduction and *C. albicans* had a 2.78 log₁₀ reduction compared to controls after 18 to 24 hours.

A study (Traub et al. 1993) showed that taurolidine at a concentration of 2,000 and 1,000 µg/mL in the presence of bovine serum (65% v/v) and human serum (50% v/v) marginally affected the bactericidal activity against selected gram-positive and gram-negative isolates.

However, (Blenkharn 1990) reported an increase in taurolidine activity with up to a 4-fold reduction in MIC values when tested in the presence of 25% (v/v) pooled human serum against test strains of *S. aureus*, *E. coli*, and *P. aeruginosa*. It was not stated whether testing was conducted using fresh or frozen serum to ensure the preservation of all components of the complement system required for activation of the classical and/or alternative pathways.

The development of taurolidine resistance has not been reported in vitro or with other taurolidine lock solutions used in humans. One study (Torres-Viera et al. 2000) evaluated the emergence of resistant subpopulations of 6 selected organisms (*E. coli*, n=2; *E. faecalis*; *E. faecium*; *S. aureus*, n=2). No resistant subpopulations or mutants to taurolidine grew when organisms were plated on agar containing 1,000 µg/mL or 2,000 µg/mL taurolidine. The frequency of resistant mutants was $<10^{-9}$ at 2x and 4x MIC for two strains each of *E. coli*, *S. aureus*, *E. faecalis*, *E. faecium*, and *P. aeruginosa*. The authors failed to find bacterial resistance, despite attempts to induce bacterial resistance experimentally. However, a study by (Kummerle et al. 1996) reported resistance against the disinfectant formaldehyde, a breakdown product of taurolidine partially responsible for its mechanism of action, which is most often found in gram-negative bacteria, such as members of the *Enterobacteriaceae* family and *Pseudomonas* spp. This was demonstrated against the plasmid-mediated formaldehyde-resistant clinical *E. coli* strain, VU3695, which carries a glutathione and NAD-dependent formaldehyde dehydrogenase plasmid. Studies were not conducted to evaluate the in vitro activity of taurolidine against formaldehyde-resistant gram-negative isolates.

A study (Blenkharn 1987) evaluated taurolidine in combination with gentamicin, amikacin, piperacillin, cefuroxime, and ceftazidime against aerobic and facultative gram-negative isolates. The study showed an additive or indifferent effect, with a fractional inhibitory concentration index (FICI) ranging from 0.7 to 1.8. Against *B. fragilis*, taurolidine and metronidazole were additive (FICI 1.4). Against *S. aureus*, combinations of taurolidine and gentamicin or amikacin were synergistic (FICI 0.3 and 0.4, respectively) while combinations with vancomycin were antagonistic (FICI 2.3).

The use of taurolidine in CLSs for the prevention of CRBSIs has been studied over the last 25 years. The reported event rate of CRBSIs per 1,000 catheter-days in taurolidine CLSs (with or without an anticoagulant) ranged from 0 to 1.35 compared to 0.21 to 3.44 in heparin CLS (Liu et al. 2013), indicating a trend towards benefit in patients who received taurolidine CLS. Information on the type of microorganisms leading to CRBSIs was available from five published clinical trials.

- In the five studies, the number of CRBSI episodes due to gram-negative bacteria after taurolidine CLS use trended lower in incidence (range, 0 to 4) compared to heparin (0 to 11). One study (Betjes and van Agteren 2004) in hemodialysis patients reported no CRBSI episodes due to gram-negative bacteria in either the taurolidine or heparin CLS groups. This is in contrast to another study in a hemodialysis patient population (Solomon et al. 2010), which reported 2 and 9 gram-negative organisms in the taurolidine and heparin CLS arms, respectively. In this study the 2 infections in the

taurolidine CLS group were due to *E. coli*, whereas, the 9 in the heparin arm were caused by *Klebsiella oxytoca*, *Delftia acidovorans*, *Enterobacter aerogenes*, *Haemophilus parainfluenzae*, *Serratia* spp., and *Stenotrophomonas maltophilia*.

- The most predominant gram-positive bacteria was *S. epidermidis* followed by *S. aureus*. In the four trials, the number of CRBSI episodes due to gram-positive bacterial infection was not significantly different between the taurolidine or heparin CLS groups (range, 0 to 9 versus 4 to 13, respectively).
- The incidence of pathogenic organisms cultured from the exit sites were reported in two clinical trials (Betjes and van Agteren 2004; Solomon et al. 2010). (Betjes and van Agteren 2004) reported exit site infections at a similar frequency in both the taurolidine (n=2) and heparin (n=4) CLS groups. Of note, in the one taurolidine patient the *S. aureus* CRBSI episode was preceded by an exit site infection with *S. aureus*. One study (Solomon et al. 2010) reported seven positive exit site cultures in the taurolidine CLS group, with all cultures due to *S. aureus*. The heparin group included six positive exit site cultures: four were *S. aureus* and two were coliforms. Four of the 13 exit site cultures were associated with positive blood cultures for the same organism (2 taurolidine and 2 heparin). The finding of approximately equal numbers of positive blood cultures associated with exit site infections suggest that these CRBSIs may have a different pathogenesis. Bacteremia related to dialysis catheters can develop from an extra- or intraluminal source. CLSs combat intraluminal contamination and cannot be expected to eliminate bacteremia originating from the exit site.
- Three studies reported on intraluminal growth in the catheter at the time of removal. None of the studies showed a significant difference in bacterial growth on the catheters. A study (Dumichen et al. 2012) reported biofilm growth on the catheters in which 6 of 25 catheters in the taurolidine CLS and 7 of 26 catheters in the heparin CLS group were colonized by bacteria at the time of removal. Similarly, a study (Handrup et al. 2013) using scanning electron microscopy found no difference in the development of biofilm on catheters that contained taurolidine versus heparin CLS. In contrast, another study (Solomon et al. 2010) examined select catheters (4 taurolidine, 10 heparin) by transmission electron microscopy which showed bacteria in 2 catheters: 1 in the heparin arm had an *S. aureus* observed in the tunnel and tip segments; and in 1 catheter in the taurolidine arm, 1 gram-negative rod was observed among red blood cells at the tip, this was not associated with clinical or microbiological evidence of infection. There was no bacterial biofilm in any catheter; the authors stated it was not possible to determine whether taurolidine CLS destroys established bacterial biofilms.
- There have been no reports of bacterial resistance with taurolidine CLS treatment.

16.4. Change in Definition of CRBSI

Table 45. Change in Definition of CRBSI

Protocol Version	Definition of CRBSI
Version 1 (September 22, 2014)	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 • The arterial and venous catheter hub, or the catheter tip if/when the catheter is ultimately removed. If a peripheral site is not available when the subject is not on dialysis, then at the next dialysis session, the venous or arterial dialysis port blood line can be substituted, preferably prior to the study subject receiving antibacterial drugs. If the patient has symptoms of CRBSI while undergoing hemodialysis, as defined by the clinical indications below, blood from the hemodialysis circuit, both the arterial and venous dialysis port blood line, can substitute for a peripheral site collection. Necessary clinical indication for suspicion of infection includes the following: One of the following symptoms: • Fever (defined as $\geq 37.8^{\circ}\text{C}$) 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 mm Hg • 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 case definition is based on the criteria listed above. An alternate source of infection should not be clinically suspected.

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Protocol Version	Definition of CRBSI
Version 5 (December 21, 2015)	Reason for change: Clarification of timing of blood cultures if subject is not on dialysis Updated definition: The peripheral site is the preferred source for the blood culture sample. However, if a peripheral site is not available when the subject is not on dialysis, then as soon as the patient is evaluated, the venous or arterial hubs of the HD CVC can be substituted, preferably before the study subject receives antibacterial drugs. Antibacterial drugs should be administered as soon as possible when clinically indicated at the discretion of the treating physician, with collection of the blood samples prior to administration of antibiotics. If the subject has symptoms of CRBSI while undergoing hemodialysis, as defined by the clinical indications below, blood from the hemodialysis circuit, either the arterial and venous hubs of the HD CVC, can substitute for a peripheral site collection. Of note, the list of symptoms or signs were not updated.
Version 6 (February 5, 2016)	Reason for change: Clarify procedure for blood culture collection Updated definition: 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) or catheter tip if/when the catheter is ultimately removed. 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 antibacterial drugs. Ten to twenty mL of blood should be collected, without discarding any of the CLS.

Protocol Version	Definition of CRBSI
Version 8 (January 13, 2017)	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 antibacterial drugs. 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 $\geq 37.8^{\circ}\text{C}$) • 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 mm Hg • 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. <u>An alternate source of infection should not be clinically suspected.</u>

Source: Dr. Christopher Kadoorie's review for original protocol (IND113764_1113.pdf), 1611-protocol-change-docom.pdf and protocol version 8 submitted in this NDA

Abbreviations: CLS = catheter lock solution, CRBSI = catheter-related bloodstream infection, CVC = central venous catheter, HD = hemodialysis

16.5. Additional Literature Reviewed

16.5.1. Randomized Controlled Trials

NDA Multidisciplinary Review and Evaluation – NDA 214520 Defencath (taurolidine 1.35% and heparin 5,000 units/5 mL (1,000 Units/mL))

Randomized controlled trials with taurolidine containing CLSs and published in the literature were reviewed in additional detail (Table 46).

Table 46. Randomized Controlled Trials Comparing Taurolidine to Heparin CLSs in the Published Literature

Reference	Study Type	Participants	Interventions	Study Location	No. of Patients	Follow-Up Days	Definition of CRBSI	CRBSI Events N
1	Single center, randomized (1:1), control study	Hemodialysis patients	1.35%T +4%C H (5,000 Units/mL)	Netherlands	58	59	Symptom, culture, source	T+C =0 H=4
2	Open label, randomized (1:1), control study	HPN patient	2%T H (150 Units/mL)	Netherlands	30	344	Symptom, culture, source, both positive	T=1 ^a H=10
3	Single center, randomized (1:1), control study	Pediatric oncology patients	1.35%T +4%C H (100 Units/mL)	Germany	71	194	Symptom, culture, source	T+C =2 H=9
4	Open label, single center, randomized (1:1), control study	Pediatric oncology patients	1.35%T +4%C H (100 Units/mL)	Denmark	112	349	Symptom, culture, source, both positive, time difference	T+C =7 H=26

Source: Adapted from (Liu et al. 2013)

^a One infection was due to *Candida albicans*

1 (Betjes and van Agteren 2004)

2 (Bisseling et al. 2010)

3 (Dumichen et al. 2012)

4 (Handrup et al. 2013)

Both positive = a positive blood culture from the CVC and peripheral vein for the same organism; Culture = positive blood culture; Source = no other source of infection; Symptom = clinical signs and symptoms; Time difference = growth of microbes from a blood sample drawn from a catheter at least 2 hours before blood sample a peripheral vein

Abbreviations: C = citrate, CD = catheter-days, CRBSI = catheter related bloodstream infection, H = Heparin, T = Taurolidine

Reviewer Comment: There is some evidence suggesting efficacy of taurolidine lock solutions based on relatively small, open label, randomized trials from the literature. Studies 2, 3, 4 referenced in Table 46 evaluated taurolidine lock solutions in non-HD populations. Study 1 was conducted in an HD population similar to Defencath, however, it had several limitations including that the study enrolled a small number of patients at a single-center and was unblinded. Additionally, the formulations of the taurolidine CLSs used in these studies differed from the formulation of Defencath, limiting generalizability of the study findings.

16.5.2. Observational Studies

The Applicant proposed using the results from two observational studies reported by Murray et al. (2014) and Solomon et al. (2012) to support the efficacy of a combined taurolidine and heparin CLS in reducing the risk of CRBSI.

The Murray study evaluated the effect of a heparin CLS versus a combined taurolidine and heparin CLS on the rate of staphylococcal bacteremia. Data for 565 patients on chronic HD were obtained from the UK National Health Service Greater Glasgow and Clyde and the National Health Service Forth Valley Renal Unit Patient Record database. The information on incident staphylococcal-positive blood cultures was collected for 27 months between April 1, 2011 and June 30, 2013. The first 15 months of observation evaluated the incidence of bacteremia while heparin was used as the CLS. On July 1, 2012, a combined taurolidine and heparin CLS replaced heparin and the incidence of bacteremia was assessed for an additional 12 months. The results demonstrated that the bacteremia rate per 1,000 HD days was higher before the introduction of the combined taurolidine and heparin CLS as compared with after its initiation of use (0.69 [95% CI: 0.51, 0.87] versus 0.40 [95% CI: 0.25, 0.54], respectively).

The Solomon study assessed whether a combined taurolidine and heparin CLS reduced the incidence of CRBSIs in patients with HD. All 106 patients in the study received the combined taurolidine and heparin CLS at a clinical site in the UK. The incidence rate of CRBSI per 1,000 HD days in these patients was then compared with 34 patients who received a heparin CLS in a prior randomized clinical trial. The results showed that the rate in the patients who received the combined taurolidine and heparin CLS was less than half of the rate observed in the patients who received the heparin CLS (1.33 versus 3.25).

Reviewer's comments: Both studies were observational and single-arm studies. Because neither study contained a randomized control, we cannot be sure that other differences did not exist between the test group and the control group that might be the reason for some or all of the differences seen. Additionally, patient level data were not supplied so we were unable to conduct additional analyses to explore the potential for bias.

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