

PROTOCOL PTK0796-ABSI-16301

Study Title A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

IND Number: 73,431 and 75,928

Protocol Number: PTK0796-ABSI-16301

Indication: Acute Bacterial Skin and Skin Structure Infection

Phase: 3

Investigational Product: Omadacycline (PTK 0796)

Dose Form: Oral

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TABLE OF CONTENTS

TABLE OF CONTENTS.....	2
LIST OF IN-TEXT TABLES.....	6
LIST OF APPENDICES.....	6
1 DISCLOSURE STATEMENT.....	7
2 CONTACTS.....	8
2.1 Emergency Contacts.....	8
2.2 Additional Contacts.....	8
3 SPONSOR SIGNATURE.....	9
4 INVESTIGATOR AGREEMENT.....	10
5 LIST OF ABBREVIATIONS.....	11
6 DEFINITIONS.....	14
7 PROTOCOL SYNOPSIS.....	15
8 STUDY FLOWCHART.....	23
9 INTRODUCTION.....	26
9.1 Background.....	26
10 STUDY OBJECTIVES.....	28
10.1 Primary Objectives.....	28
10.2 Secondary Objectives.....	28
11 STUDY DESIGN.....	29
11.1 Description.....	29
11.2 Rationale of Study Design.....	29
11.3 Rationale for Choice of Comparator.....	29
11.4 Approximate Duration of Subject Participation.....	29
11.5 Approximate Duration of Study.....	30
11.6 Approximate Number of Subjects.....	30
12 SELECTION OF SUBJECTS.....	30
12.1 Inclusion Criteria.....	30
12.2 Exclusion Criteria.....	31
12.3 Screen Failures.....	33
13 PRIOR AND CONCOMITANT TREATMENT.....	33
13.1 Prohibited Treatment.....	34
13.1.1 Concomitant Medications That May Interact With Linezolid.....	34
13.2 Permitted Treatments.....	35
13.2.1 Dressings.....	35
13.2.2 Topical Solutions.....	35
13.2.3 Surgical Procedures.....	35

14	PROCEDURES.....	35
14.1	Visit Schedule and Assessments.....	36
14.2	Screening Phase.....	36
14.2.1	Subject Demographics/Other Baseline Characteristics.....	37
14.2.1.1	Medical History Relating to the Infection Under Study.....	37
14.2.2	Physical Examination.....	37
14.2.3	Diagnosis of ABSSSI and Clinical Assessment of the Site of Infection.....	37
14.2.4	Assessment of Lesion Size.....	38
14.2.5	Subject Reported Outcomes.....	38
14.2.5.1	Numerical Rating Scale for Pain.....	38
14.2.5.2	SF-36v2 [®] Health Survey.....	39
14.2.6	Urine Tests.....	39
14.3	Double-blind Treatment Phase.....	39
14.3.1	Assessments While on Test Article.....	39
14.3.1.1	Treatment Phase.....	40
14.3.1.2	Management While on Oral Test Article.....	41
14.3.2	Permitted Dose Adjustments and Interruptions of Test Article.....	42
14.4	Follow-up Phase.....	42
14.5	Total Volume of Blood Collected.....	42
15	TEST ARTICLE AND ADMINISTRATION.....	42
15.1	Test Article Administration.....	42
15.1.1	Identity of the Investigational Product.....	43
15.2	Investigational and Comparator Test Article.....	43
15.2.1	Investigational Test Article: Omadacycline.....	43
15.2.2	Comparator Test Article: Linezolid.....	43
15.3	Dose Selection Rationale.....	43
15.4	Subject Compliance.....	44
16	SAFETY.....	45
16.1	Physical Examinations.....	45
16.1.1	Vital Signs.....	45
16.1.2	Laboratory Evaluations.....	46
16.1.2.1	Hematology.....	46
16.1.2.2	Clinical Chemistry.....	47
16.1.2.3	Other Laboratory Tests.....	47
16.1.3	Safety Studies to be Performed Locally.....	47
16.1.3.1	Electrocardiogram (ECG).....	47
16.1.3.2	Pregnancy and Assessments of Fertility.....	48
16.1.3.3	Blood Cultures.....	48
16.1.3.4	Additional Local Laboratory Tests.....	48
16.1.4	Appropriateness of Safety Measurements.....	48

17	EFFICACY	48
17.1	Clinical Assessment of the Site of Infection.....	49
17.2	Assessment of Lesion Size.....	49
17.3	Microbiological Assessment of the Site of Infection.....	49
17.4	Assessment of Clinical Outcome	50
17.4.1	Evaluation of the Infection Under Study at the Early Clinical Response Assessment.....	51
17.4.2	Clinical Evaluation of the Infection Under Study at EOT	51
17.4.3	Clinical Evaluation of the Infection Under Study at PTE.....	52
18	OTHER ASSESSMENTS	53
18.1	Resource Utilization.....	53
19	PHARMACOKINETIC PLASMA SAMPLES FOR OMADACYCLINE CONCENTRATION.....	53
19.1	Selection of Sites for PK Studies	53
19.2	Collection of PK Samples.....	53
19.3	Storing and Shipping of PK Samples.....	54
19.4	Analysis of PK samples	54
20	OTHER BIOMARKERS	54
21	SAFETY MONITORING.....	54
21.1	Definitions.....	54
21.1.1	Adverse Events	54
21.1.2	Serious Adverse Events	55
21.1.3	Other Reportable Information.....	56
21.1.4	Overdose	56
21.1.5	Medication Errors	56
21.2	Recording and Reporting	57
21.2.1	Serious Adverse Event Reporting.....	57
21.2.2	Assessment of Relatedness	57
21.2.3	Assessment of Severity	58
21.2.4	Laboratory Findings.....	58
21.2.5	Worsening or Progression of Qualifying ABSSSI	58
21.2.6	Pregnancies	59
22	DATA ANALYSIS.....	59
22.1	Analysis Populations.....	59
22.2	Subject Demographics and Other Baseline Characteristics.....	60
22.3	Treatments (Test Article, Rescue Medication, Other Concomitant Therapies, Compliance).....	61
22.4	Primary Efficacy Analysis	61

22.4.1	Early Clinical Response Efficacy Variable.....	61
22.4.2	Investigator’s Assessment of Clinical Response at PTE Efficacy Variable	61
22.4.3	Statistical Model, Hypothesis, and Method of Analysis.....	61
22.4.4	Additional Analyses of the Primary Efficacy Outcomes.....	62
22.5	Analysis of Secondary Variables.....	63
22.6	Analysis of Additional Efficacy Variables.....	63
22.7	Safety Outcome Measures.....	64
22.7.1	Adverse Events.....	64
22.7.2	Vital Signs.....	64
22.7.3	Electrocardiograms.....	65
22.7.4	Laboratory Tests.....	65
22.8	Resource Utilization.....	65
22.9	Pharmacokinetics.....	65
22.9.1	Population PK Modeling.....	66
22.10	Pharmacogenetics/Pharmacogenomics.....	66
22.11	Biomarkers.....	66
22.12	PK/PD.....	66
22.13	Sample Size Calculation.....	67
22.14	Interim Analyses.....	67
22.15	Handling of Missing Values/Censoring/Discontinuations.....	68
23	SUBJECT IDENTIFICATION.....	68
24	TEST ARTICLE ACCOUNTABILITY, RECONCILIATION, AND RETURN.....	68
24.1	Supply, Storage and Tracking of Test Article.....	69
25	RANDOMIZATION AND BLINDING.....	69
25.1	Treatment Assignment.....	69
25.2	Dispensing the Test Article.....	70
25.3	Treatment Blinding.....	70
25.4	Emergency Unblinding of Treatment Assignment.....	70
26	SUBJECT DISCONTINUATION OR WITHDRAWAL.....	71
27	STUDY SUSPENSION, TERMINATION, AND COMPLETION.....	72
27.1	Study Completion and Post-Study Test Article.....	72
27.2	Study Suspension or Termination.....	72
28	ETHICAL CONSIDERATIONS.....	73
28.1	Regulatory and Ethical Compliance.....	73
28.2	Informed Consent Procedures.....	73
28.3	Responsibilities of the Investigator and IRB/IEC/REB.....	73
29	PROTOCOL ADHERENCE.....	73
29.1	Protocol Amendments.....	74

30	QUALITY CONTROL AND ASSURANCE	74
31	DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING	74
31.1	Investigator	74
31.2	Sponsor	74
32	SUBJECT INJURY	75
33	PRESTUDY DOCUMENTATION.....	75
34	RECORDS RETENTION.....	76
35	PUBLICATION POLICY	76
36	REFERENCES (available upon request).....	77

LIST OF IN-TEXT TABLES

Table 1.	Treatment Regimens for Oral Test Article.....	41
Table 2.	Oral Formulation.....	43
Table 3.	Hematology Panel	46
Table 4.	Clinical Chemistry Panel.....	47
Table 5.	Additional Laboratory Tests	47
Table 6.	Sample Size and Power Calculations.....	67
Table 7.	Investigator’s Assessment of Clinical Response at PTE Determination Considering Missing Data	68

LIST OF APPENDICES

Appendix 1.	Allowed and Disallowed Prior Antibiotics	78
Appendix 2.	Equations and Conversion Factors.....	79

1 DISCLOSURE STATEMENT

Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the sponsor. You may disclose the contents of this document only to study personnel under your supervision, institutional review boards (IRBs)/independent ethics committees (IECs)/research ethics boards (REBs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, and/or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the sponsor of any such disclosure. All other nonpublic information provided by the sponsor and any information that may be added to this document also is confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this document.

2 CONTACTS

2.1 Emergency Contacts

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E-mail (not for emergencies):

Address:



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Phone (after business hours):

E-mail (not for emergencies):

Address:



2.2 Additional Contacts

Serious Adverse Event (SAE) contact information

E-Mail:

Fax:



3 SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.



Stephen Villano, MD
VP, Clinical and Medical Affairs
Paratek Pharma, LLC

29 Nov 2016

Date of Signature
(DD-MMM-YYYY)

15:00 ET

Time
(24-hour clock, time zone)

4 INVESTIGATOR AGREEMENT

I have read the protocol (PTK0796-ABSI-16301) and agree to the following:

The protocol contains all necessary details for carrying out this study;

I will conduct the study as detailed in the protocol and will abide by all its provisions;

I will conduct the study in compliance with the most current versions of International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP), all applicable government regulations and the requirements of the IRB/IEC/REB that approved the study.

I will train and supervise all individuals delegated to assist me in conducting this study, including providing copies of the protocol and all pertinent information and discussing the material with them to ensure they are fully informed regarding the investigational product, the protocol and their responsibilities and obligations.

I will use only the informed consent form (ICF) approved by PARATEK (or their designee) and by the IRB/IEC/REB responsible for this study.

I will fulfill all requirements for submitting pertinent information to the IRB/IEC/REB and to PARATEK, including reportable serious adverse events (SAEs).

I will provide PARATEK (or their designee) with access to any source documents from which case report form information may have been generated.

I understand that the information in this protocol and the referenced Investigator's Brochure is confidential and that its disclosure to any third parties (other than those involved in approving or conducting the study) is prohibited. I will take the necessary precautions to protect this information from loss, inadvertent disclosure or access by third parties.

I will complete the study within the time designated.

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the ICH Guideline for GCP, the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature

Date of Signature
(DD-MMM-YYYY)

Time (24-hour clock,
time zone)

Investigator Name and Title (print)

5 LIST OF ABBREVIATIONS

ABSSSI	acute bacterial skin and skin structure infection
ACM	all-cause mortality
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the (concentration/time) curve
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CABP	community-acquired bacterial pneumonia
cc	cubic centimeter
CD4	cluster of differentiation 4
CE	clinically evaluable
CFR	Code of Federal Regulations
CK	creatine phosphokinase
CI	confidence interval
C _{max}	maximum plasma concentration
CrCL	creatinine clearance
CRF	case report/record form
CSA	clinical study agreement
CSR	clinical study report
cSSSI	complicated skin and skin structure infection
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Agency for the Evaluation of Medicinal Products
EMA	European Medicines Agency
EOT	end of treatment
FDA	Food and Drug Administration
<i>g</i>	gravity
GCP	Good Clinical Practice
GI	gastrointestinal
β-hCG	beta-human chorionic gonadotropin
HDPE	high-density polyethylene
HIV	Human Immunodeficiency Virus
HPFB	Canadian Health Products and Food Branch

HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSA	Infectious Diseases Society of America
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat (population)
IUD	intrauterine device
iv	intravenous
IxRS	Interactive Voice Response System/Interactive Web Response System
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LDH	lactate dehydrogenase
MAO	monoamine oxidase
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
Micro-mITT	microbiological modified intent-to-treat population
mITT	modified intent-to-treat population
MRSA	methicillin-resistant staphylococcus aureus
NI	non-inferiority
PD	pharmacodynamics
PI	principal investigator
PK	pharmacokinetics
po	per oral
PT	preferred term (MedDRA)
PTE	post therapy evaluation (test of cure)
PVC	polyvinyl chloride
q12h	every 12 hours
q24h	every 24 hours
QTc	corrected QT interval
QTcB	QTc Bazett's correction formula
QTcF	QTc Fridericia's correction formula
REB	Research Ethics Board
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SD	standard deviation

SOC	system organ class (MedDRA)
spp	species (plural)
ss	steady state
TEAE	treatment-emergent adverse event
TFL	table, figure and listing
TGA	Therapeutic Goods Administration
Tmax	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cells

6 DEFINITIONS

Term	Definition
Regulation	The term <i>regulation</i> refers to all applicable regulations, laws, and guidelines. The regulations may be international, national, or local and may include but are not limited to the Code of Federal Regulations; the Good Clinical Practice: Consolidated Guideline (Canada); the International Conference on Harmonisation Guideline for Good Clinical Practice; the Therapeutic Goods Administration Annotated International Conference on Harmonisation Guidelines (Australia); the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.
Regulatory agency	The term <i>regulatory agency</i> refers to all health and regulatory agencies with oversight responsibility for the study. These may be international, national, or local and may include but are not limited to the Australian Therapeutic Goods Administration (TGA), the Canadian Health Products and Food Branch (HPFB), the European Agency for the Evaluation of Medicinal Products (EMA), the United States (US) Food and Drug Administration (FDA).
Sponsor	The term <i>sponsor</i> refers to, but is not limited to the Sponsor listed in the front of this document and any contract research organization that is being used for the study.
Test article	Any study drug, device, biologic agent, or comparator (including placebo) used in sponsor studies. For test article accountability, this term applies to the above articles when they are required by the protocol and supplied (shipped) by the sponsor (including diluents such as sterile water for injection).
Adverse event	An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study.

7 PROTOCOL SYNOPSIS

Study Title	A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)
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Clinical Phase	3
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Study Rationale	<p>Omadacycline, the first aminomethylcycline antibiotic, is a semi-synthetic derivative of the tetracycline class. As a class, the tetracyclines have been in use for approximately 70 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections.</p> <p>Omadacycline has demonstrated activity against the most common ABSSSI pathogens, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA). Omadacycline was evaluated in a Phase 2 study of 219 subjects with complicated skin and skin structure infection (cSSSI) and a sponsor-terminated Phase 3 study of 140 subjects with cSSSI. Omadacycline was well-tolerated and demonstrated efficacy similar to an established comparator (linezolid).</p> <p>In a global Phase 3 study comparing the safety and efficacy of intravenous (iv) and per oral (po) omadacycline to iv and po linezolid in the treatment of adult subjects with ABSSSI (PTK0796-ABSI-1108) omadacycline was non-inferior to linezolid and was well tolerated. In addition, a global Phase 3 study is currently being conducted to evaluate the safety and efficacy of iv and po omadacycline compared to iv and po moxifloxacin in the treatment of adult subjects with community-acquired bacterial pneumonia (PTK0796-CABP-1200).</p> <p>This study is intended to evaluate the safety and efficacy of po omadacycline as compared to po linezolid in the treatment of adult subjects with ABSSSI.</p>
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Study Objective(s)	<p>Primary objective:</p> <p>To demonstrate that omadacycline administered orally for 7 to 14 days is non-inferior to linezolid administered orally for 7 to 14 days in the treatment of adult subjects with ABSSSI known or suspected to be due to Gram-positive pathogens.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none">• To evaluate the safety of omadacycline in the treatment of adult subjects with ABSSSI.• To evaluate the Clinical Response according to the identified causative pathogen.• To evaluate the pharmacokinetics (PK) of omadacycline in adult subjects with ABSSSI.
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Study Design	This is a randomized (1:1), active comparator-controlled, double-blind, double-dummy, Phase 3 study comparing omadacycline and linezolid for the treatment of adult subjects with ABSSSI that is known or suspected to be due to a Gram-positive pathogen(s). The Schedule of Events for the study is shown in Section 8 . Enrollment of subjects with major abscess may be up to 30% of randomized subjects. Enrollment of subjects who have received a single dose of an allowed short-acting antibiotic (see Appendix 1) within the 72 hours prior to randomization will be limited to no more than 25% of randomized subjects.
Approximate Duration of Subject Participation	Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of po treatment with either omadacycline or linezolid. A follow-up office visit will occur approximately 7 to 14 days after the last dose of test article and a follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.
Approximate Duration of Study	The study is expected to be clinically complete in approximately 12 months.
Approximate Number of Subjects	704 randomized subjects.
Approximate Number of Study Centers	50 sites.
Diagnosis and Main Criteria for Inclusion	<ol style="list-style-type: none">1. Written and signed informed consent must be obtained before any assessment is performed.2. Male or female, age 18 years or older.3. Has a qualifying skin and skin structure infection. All qualifying lesions must be greater than or equal to 75 cm² in total surface area of contiguous involved tissue, calculated as the product of the maximum length (head-to-toe) multiplied by the maximum width (measured perpendicular to length) as measured by the investigator using a wound ruler. Involved tissue is defined as tissue exhibiting clear evidence of one or more of the following: erythema, edema or induration. <p>The classification of qualifying infections is shown below.</p> <ul style="list-style-type: none">• Wound infection – an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound.• Cellulitis/erysipelas – a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration.• Major abscess – an infection characterized by a collection of pus within the dermis or deeper with surrounding erythema, edema,

and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the abscess.

4. Has evidence of a systemic inflammatory response within the 24 hours prior to randomization, as indicated by ONE of the following:
 - Elevated white blood cell (WBC) count (greater than or equal to 10,000 cells/mm³) or leukopenia (less than or equal to 4,000 cells/mm³)
 - Elevated immature neutrophils (greater than or equal to 15% band forms, see % bands calculation in [Appendix 2](#)) regardless of total peripheral white blood cell (WBC) count
 - Lymphatic involvement: lymphangitis or lymphadenopathy that is proximal to and in a location that suggests drainage from the qualifying infection
 - Fever or hypothermia documented by the investigator (temperature greater than 38.0°C [100.4°F] or less than 36.0°C [95.5°F])
5. Females must have a negative pregnancy test at Screening and agree to comply with using an acceptable method of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through Post Therapy Evaluation (PTE). Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

Main Criteria for Exclusion

1. Has received 1 or more doses of a potentially effective systemic antibacterial treatment within the 72 hour period prior to randomization (a subject will be considered to have received a potentially effective systemic antibacterial treatment if the pathogen identified as causing the infection is shown to be susceptible to the antibacterial treatment given or, in the circumstance where a pathogen is not identified, if the antibacterial agent is approved for treatment of skin infections or is known to have activity against any of the leading Gram-positive causes of ABSSSI [eg, *Staphylococcus aureus*, *Streptococcus* species [spp.], *Enterococcus* spp.]). EXCEPTION: Subjects may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting, non-oxazolidinone antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see list in [Appendix 1](#)).
 2. Has, for any reason, used a topical antibacterial agent(s) with specific antibacterial activity (eg, mupirocin, retapamulin, fusidic acid) continuously within the 72 hour period prior to randomization, if applied to the skin for greater than or equal to 72 hours.
 3. Infections where the outcome is strongly influenced by factors other than protocol-defined treatment and procedures, that require antibacterial treatment for greater than 14 days, are associated with
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chronic skin lesions that may obscure determination of response even after successful bacterial eradication has been achieved, or are suspected or known to be caused by a pathogen resistant to either test article, eg:

- chronic (persistently present greater than 3 months) lesions, ulcers or wounds (eg, cellulitis contiguous with a diabetic foot ulcer)
 - association with chronic dermatitis or any other chronic inflammatory skin lesion (eg, psoriasis, eczema)
 - burns
 - peri-rectal abscess (eg, buttock or perineal lesion likely to communicate with the rectum) or perineal infection
 - infected decubitus (pressure) ulcers
 - necrotizing fasciitis (infections with rapidly progressive destruction of tissue at or below the fascia)
 - life-threatening infections, ie, require emergency surgery for the treatment (eg, progressive gangrene)
 - infections in an area requiring surgery that in and of itself would cure the infection or remove the infected site (eg, amputation for vascular insufficiency)
 - infections associated with severe vascular insufficiency (eg, peripheral vascular disease) or acute occlusion expected to require immediate revascularization
 - infections associated with acute compartment syndrome expected to require extensive surgery to provide decompression
 - infections accompanied by confirmed or suspected contiguous bone or joint infection (eg, osteomyelitis, septic arthritis, bursitis)
 - bacteremic infections associated with an intravascular foreign body
 - infections accompanied by another confirmed or suspected infection requiring systemic antibiotic therapy (eg, endocarditis, other endovascular infection, meningitis, visceral abscess, intra-abdominal infection, pneumonia, urinary tract infection)
 - human or animal bites (infections associated with insect bites are NOT excluded)
 - myonecrosis
 - complicated by an immune deficiency in the subject (eg, ecthyma gangrenosum in a neutropenic subject)
 - infections associated with the presence of a foreign body (eg, wood, metal, plastic, etc.) if the foreign body cannot be removed within 24 hours of first dose of test article
4. Inability to tolerate oral medication (eg, nausea, vomiting, diarrhea or any other condition that might impair ingestion or absorption of oral medication).
 5. Has known or is clinically suspected for one or more of the following prior to randomization:
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- Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) greater than or equal to 3 times the Upper Limit of Normal (ULN),
 - total bilirubin greater than 1.5 times the ULN, or
 - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.
 7. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
 8. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCL) of less than 30 mL/min, using the Cockcroft-Gault equation (see equation in [Appendix 2](#)).
 9. Evidence of significant immunological disease determined by any of the following:
 - Current or anticipated neutropenia defined as less than 500 neutrophils/mm³
 - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm³ within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness
 10. The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy, etc.) within the 3 months prior to Screening, or the receipt of systemic corticosteroids for more than 14 days in the 30 days prior to Screening.
 11. Requires acute pharmacologic intervention to stabilize blood pressure and/or adequate tissue perfusion, OR has evidence of septic shock, defined by ALL of the following:
 - Fever or hypothermia documented by the investigator (temperature greater than 38.0°C [100.4°F] or less than 36.0°C [95.5°F])
 - Heart rate greater than 90 beats/min (bpm)
 - Respiratory rate greater than 20 breaths/min
 - WBC greater than 12,000 cells/mm³ or less than 4,000 cells/mm³ or greater than 10% immature (band) forms, see % bands calculation in [Appendix 2](#), regardless of the total peripheral WBC count
 - Hypotension with systolic blood pressure (SBP) less than 90 mm Hg despite an iv fluid challenge of 20 to 30 cc/kg over a 30 minute period
 - Perfusion abnormalities that may include, but are not limited to, lactic acidosis (blood lactate concentration greater than or equal
-

	to 4 mmol/L), oliguria, or acute alteration in mental status
	12. Pregnant or nursing (breastfeeding) women.
	13. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any oxazolidinone (eg, linezolid, tedizolid).
	14. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
	15. Has a history of systemic lupus erythematosus or lupus-like syndrome.
	16. Has current evidence of pancreatitis.
	17. Has received a monoamine oxidase inhibitor within 14 days prior to Screening (eg, phenelzine, isocarboxazid, selegiline, moclobemide; which are typically used to treat depression or Parkinson's Disease).
	18. Use of other investigational drugs within 5 half-lives or within 30 days prior to Screening.
	19. Has previously been treated with omadacycline or previously enrolled in this study.
	20. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
	21. Has any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of adverse events (AEs), or completion of the expected course of treatment.

Prior and Concomitant Treatment

No systemic prior or concomitant antibacterial therapy is allowed, other than a single dose of a short-acting antibacterial (see Exclusion Criterion number 1 and [Appendix 1](#)), within the 72 hours prior to randomization. No topical antibacterial therapy with a spectrum that is active against the known or potential infecting pathogen(s) responsible for the infection under study is allowed within the 72 hours prior to randomization or concomitantly through PTE. No monoamine oxidase (MAO) inhibitors within 14 days prior to Screening or concomitantly through Final Follow-up. All other medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.

Test Article(s)

Subjects will be randomized (1:1) to:

- Omadacycline
 - Linezolid
-

Dosage and Administration

- Omadacycline 450 mg po every 24 hours (q24h) for 2 doses followed by 300 mg po q24h
 - Linezolid 600 mg po every 12 hours (q12h)
-

Safety Evaluation

- Adverse events (AEs) and Serious Adverse events (SAEs)
 - Physical examinations
 - Vital signs
-

	<ul style="list-style-type: none">• 12-lead electrocardiograms (ECGs)• Laboratory assessments• Pregnancy assessments
Efficacy Evaluation	<ul style="list-style-type: none">• In order to satisfy different health authority requirements, the primary variables assessing efficacy will be tested with 2 response endpoints:<ul style="list-style-type: none">• Successful Early Clinical Response (48 to 72 hours after the first dose of test article) defined as survival with a greater than or equal to 20% reduction of lesion size compared to Screening measurements without receiving any rescue antibacterial therapy• Successful Investigator’s Assessment of Clinical Response at the Post Therapy Evaluation (PTE) visit defined as survival after completion of a test article regimen, with resolution or improvement of signs and symptoms of infection to the extent that further antibacterial therapy is not necessary• Lesion size• Microbiology of the infection
Health Outcomes Assessment	<ul style="list-style-type: none">• Resource utilization
Pharmacokinetics	<ul style="list-style-type: none">• Population pharmacokinetic (PK) analysis
Statistical Analysis	<p>A number of subject analysis populations have been defined for the various analyses of efficacy and safety, as follows:</p> <ul style="list-style-type: none">• The intent-to-treat (ITT) population will consist of all randomized subjects• The modified intent-to-treat (mITT) population will consist of all randomized subjects without a sole Gram-negative causative pathogen(s) at Screening• The clinically evaluable (CE) population will consist of all mITT subjects who received test article, have a qualifying ABSSSI, an assessment of outcome, and meet all other evaluability criteria detailed in the statistical analysis plan (SAP)• The microbiological modified intent-to-treat (micro-mITT) population will consist of subjects in the mITT population who have at least 1 Gram-positive causative pathogen(s) at Screening• The microbiologically evaluable (ME) population will include subjects in the CE population who have at least 1 Gram-positive causative pathogen(s) at Screening• The Safety population will consist of all randomized subjects who receive test article <p>A 2-sided 95% confidence interval (CI) approach for the difference in the</p>

rate of early clinical success in the mITT population (primary analysis for the United States [US] Food and Drug Administration [FDA]) will be used to test for non-inferiority (NI) of omadacycline arm compared to the linezolid arm. For the primary analysis for the European Medicines Agency (EMA), 95% CIs for the difference in the rate of clinical success at PTE in the mITT and CE populations will be used to test for the NI of omadacycline arm compared to the linezolid arm.

Safety will be assessed through the use of summary statistics and clinical review of reported AEs, changes in vital signs, ECGs and laboratory results obtained from blood and urine samples taken during the study.

**Rationale for
Number of
Subjects**

The study is designed to show NI in the primary efficacy outcome of Early Clinical Response at 48 to 72 hours following the first dose of test article in the mITT population. An NI margin of 10% will be used for the analysis in the mITT population. The NI margin was based on an analysis of the historical data regarding the treatment effect of antibiotics in ABSSSI.

The sample size determination is based on ensuring sufficient power for the secondary efficacy analyses of Investigator's Assessment of Clinical Response at PTE in the mITT and CE populations (co-primary efficacy outcomes for EMA) as well as the primary efficacy analysis of Early Clinical Response. For the Early Clinical Response primary efficacy endpoint, assuming an outcome rate of 79% for both treatment groups, NI margin of 10%, 90% power and a 1-sided alpha of 0.025, using the sample size determination method of Farrington and Manning¹², a total of 704 subjects are required.

Assuming an 85% outcome rate in both treatment groups, NI margin of 10%, and a 1-sided alpha of 0.025, with a total of 704 subjects, there is more than 90% power to show NI for Investigator's Assessment of clinical response at PTE in the mITT population. With an evaluability rate of 80%, there will be 564 subjects in the CE population. Assuming a 90% outcome rate in both treatment groups, NI margin of 10% and a 1-sided alpha of 0.025, 564 subjects provides more than 90% power to show NI in the CE population.

**Ethical
Considerations**

This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human use (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC)/research ethics board (REB) must review and approve the protocol and informed consent form (ICF) before any subjects are enrolled. The subject must be consented using the approved ICF before any procedures specified in the protocol are performed.

8 STUDY FLOWCHART

Study Phase	Screening ^a	Double-Blind Treatment Phase						Follow-up Phase	
		Day 1	Day 2	Day 3 (ECR 48- 72 hr after first dose)	Day 7	Day 10 ^c	EOT ^d	PTE ^e	Final Follow-up ^f Day 30-37
Signed Informed Consent ^g	X								
Demographics	X								
Medical/surgical history and current medical conditions	X								
Prior and concomitant medications ^h	X	X-----X							
Clinical assessment of the site of infection ⁱ	X	X	X	X	X	X	X	X	X
Assessment of lesion size ^j	X	X	X	X	X	X	X	X	X
Diagnosis of ABSSSI and photograph of the lesion site ^k	X								
Numerical Rating Scale for pain at the primary lesion site	X			X			X		X
SF-36v2 [®] Health Survey	X								X
Physical examination ^l	X						X		X
Vital signs									
Respiratory rate	X	X	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X	X	X
Blood pressure	X	X ^m	X ⁿ	X ⁿ	X	X	X	X	X
Pulse/heart rate	X	X ^m	X ⁿ	X ⁿ	X	X	X	X	X
12-lead ECG ^o	X						X		
Urine dipstick test ^p	X								
Local urine or serum pregnancy test ^q	X								
Central serum pregnancy test ^r	X						X		X
Hematology ^s	X ^t			X	X	X	X		X
Serum chemistry ^s	X ^t			X	X	X	X		X
Blood culture ^u	X	As Clinically Indicated						X ^v	X ^v

Study Phase	Screening ^a	Double-Blind Treatment Phase						Follow-up Phase	
		Day 1	Day 2	Day 3 (ECR 48- 72 hr after first dose)	Day 7	Day 10 ^c	EOT ^d	PTE ^e	Final Follow-up ^f Day 30-37
Culture of infection site & Gram stain	X	As Clinically Indicated						X ^v	X ^v
Adverse Events ^w	X	X-----X							
Review of Inclusion and Exclusion Criteria/Randomization (if Eligible)	X								
Test Article Administration and Accountability ^x		X ^y	X ^z	X ^{aa}	X	X			
Plasma samples (in heparin) for PK analyses ^{bb}			X	X					
Assessment of need to continue therapy ^{cc}					X	X			
Investigator's Assessment of Clinical Response							X	X	

ABSSI = Acute Bacterial Skin and Skin Structure infection; AE = adverse event; β-hCG = beta – human Chorionic Gonadotropin; ECG = electrocardiogram; ECR = Early Clinical Response; eCRF = electronic case report form; EOT = end of treatment; ICF = informed consent form; PK = pharmacokinetics; PTE = post therapy evaluation; SAE = serious adverse event.

- ^a Following the signing of an ICF, all Screening evaluations, with the exception of the blood culture sample collection, should be completed within the 24 hours prior to randomization. The blood culture sample collection should be completed within 24 hours prior to the first dose of test article.
- ^b Day 1 is the first day of test article administration. Subsequent study days are consecutive calendar days.
- ^c A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the EOT visit.
- ^d To be conducted on the calendar day of, or within 2 days following the last dose of test article. Should also be conducted for any subject who withdraws prematurely or terminates participation in the study before completion.
- ^e To be conducted 7 to 14 days after the subject's last day of study therapy.
- ^f To be conducted 30 to 37 days after the first dose of test article. The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, the visit must be conducted in person.
- ^g Written and signed ICF must be obtained before any assessment is performed.
- ^h Treatments that have been administered within the 7 days prior to the date of signing the ICF or during the Screening phase will be recorded in the eCRF. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the first dose of test article must be recorded in the eCRF.
- ⁱ Semi-quantitative description of infection features. Must be assessed within 48 to 72 hours after the first dose.
- ^j Measurement of the subject's lesion by ruler length × width. The Screening measurement must be collected within 4 hours prior to randomization. A lesion measurement must be completed within 48 to 72 hours after the first dose.
- ^k Diagnosis of the type of ABSSI (wound infection, cellulitis/erysipelas or major abscess) and anatomical location. A digital photograph of the infection site will be taken at Screening only.
- ^l A full physical examination will be completed at Screening; thereafter only changes from Screening measurements should be recorded as AEs in the eCRFs.

- ^m Blood pressure and pulse rate should be measured within 30 min before, and approximately (\pm 15 minutes) 1 hour after and 3 hours after the completion of the first dose on Day 1.
- ⁿ Blood pressure and pulse rate should be measured within 30 min before, and approximately (\pm 15 minutes) 1 hour after and 3 hours after the completion of the odd numbered doses on Days 2 and 3. In the event that the subject takes the dose before arriving for the office visit, the site should collect the 1 and 3 hour post dose measurements if possible, if not then a single measurement should be made at any time during the visit and the date and time recorded.
- ^o A 12-lead ECG should be performed at screening, at the EOT visit, and as otherwise clinically indicated.
- ^p A urine dipstick test will be performed locally at Screening.
- ^q All women will have a local urine or serum pregnancy test at Screening.
- ^r All women will have blood collected for a serum β -hCG pregnancy test at the Central Laboratory at the Screening, EOT and PTE visits.
- ^s Blood will be collected for hematology (includes coagulation) and serum chemistry testing at the Central Laboratory at Screening and at the Day 3, Day 7, Day 10, EOT and PTE visits.
- ^t At the Screening visit, blood will be collected for local laboratory hematology and serum chemistry evaluations required for assessing subject eligibility.
- ^u If bacteria are isolated from blood cultures, repeat blood cultures should be collected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained.
- ^v At the EOT and/or PTE visit, blood cultures and infection site specimen cultures and Gram stains should be obtained only for subjects who are clinical failures and require alternative antibacterial treatment for the infection under study.
- ^w A subject's AEs and SAEs will be recorded and reported from signing of the ICF to the Final Follow-up assessment.
- ^x A 6 hour fast is required before and a 2 hour fast is required following all odd numbered doses. The total duration of test article therapy for all subjects will be 7 to 14 days. Test article may be dispensed and reconciled by blinded personnel. Subjects will be asked to return all unused test article and packaging at each visit. At the EOT visit subjects will return the test article packaging and site staff will perform accountability.
- ^y Subjects should receive their first dose of test article at the site within 4 hours after randomization.
- ^z Subjects should be instructed not to take the odd numbered dose on Day 2 until they return to the site for the Day 2 visit.
- ^{aa} Subjects should be instructed not to take the odd numbered dose on Day 3 until they return to the site for the Day 3 visit.
- ^{bb} At selected sites, subjects who have agreed to participate in PK evaluation and have signed a separate PK evaluation consent form will have up to 4 blood samples collected between Days 2 and 3. The PK sample collection schedule for the individual subject will be provided by the Sponsor.
- ^{cc} At the investigator's discretion, all therapy may be discontinued after the 7th day of treatment, when the infection is considered clinically cured (based on normalization of the clinical signs and symptoms of infection and the investigator's clinical assessment that continued systemic antibacterial therapy is no longer needed).

9 INTRODUCTION

9.1 Background

The investigational product – omadacycline (formerly named PTK 0796) – is the first member of the aminomethylcycline class of antibiotics, which are semi synthetic derivatives of the tetracycline class. As a class, the tetracyclines have been in use for approximately 70 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections. Omadacycline is being developed for clinical use by both intravenous (iv) and per oral (po) administration. The targeted indications encompass community-acquired bacterial pneumonia (CABP), acute bacterial skin and skin structure infections (ABSSSI), and urinary tract infection (UTI).

When first approved, the tetracyclines were an important component of the antibiotic armamentarium. Their clinical use declined in subsequent years, due to the increasing prevalence of tetracycline resistance and the availability of effective alternative therapies.

Over the past decade, Gram-positive bacteria with multi-drug resistance to a diverse range of antibiotics have emerged as a major treatment challenge. Two developments raise the specter that currently available antibiotics may become even less useful for treatment of infections caused by Gram-positive organisms. The first is the emergence of vancomycin resistance in *Enterococcus* species (spp.) and the subsequent transfer of those resistance elements to *Staphylococcus aureus*. Although vancomycin-resistant *Staphylococcus aureus* have not become epidemiologically significant, their very existence raises concern because vancomycin has been the agent of choice for infections caused by resistant Gram-positive pathogens.

The second important development is the appearance of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA).¹ These strains are increasingly becoming multi-drug resistant over time. In many areas of the world, MRSA infections represent the majority of sporadic staphylococcal infections with community-onset. These strains also have been associated with numerous outbreaks of localized (skin and skin structure) and invasive (bacteremic) infections.

Omadacycline is very active *in vitro* against most Gram-positive pathogens. It also exhibits activity against atypical pathogens (eg, *Legionella* spp.), and some anaerobic and Gram-negative pathogens. The drug is active against strains expressing both mechanisms of tetracycline resistance as well as strains that are resistant to currently available antibiotics, including methicillin, vancomycin, erythromycin, and ciprofloxacin.²

Omadacycline has been developed for both iv and po administration and to date over 700 subjects have received one or both formulations in clinical studies. Across the completed Phase 1 studies, more than 500 subjects were exposed to omadacycline.

Single iv doses up to 600 mg and single po doses up to 600 mg have been investigated. Multiple iv doses of 100 mg once daily and 200 mg once daily for up to 14 and 7 consecutive days, respectively, have been investigated. Multiple po doses of 200 mg once daily and 300 mg once daily for up to 10 consecutive days have also been investigated. In a Phase 2 study, 219 subjects

with complicated skin and skin structure infections (cSSSI) were treated with omadacycline (n = 111) or linezolid (n = 108); treatment was initiated with iv administration, with switch to po therapy at the discretion of the investigator. In this study the total duration of study treatment was a mean of 10 and maximum of 20 days. In a sponsor terminated Phase 3 study of similar design, 140 subjects with cSSSI were treated with omadacycline (n = 68) or linezolid (n = 72) for a mean of 10 and maximum of 20 days for omadacycline and 22 days for linezolid.

In Phase 1 studies of iv administration, modest and reversible alanine aminotransferase (ALT) increases were seen, most notably with iv doses of 300 mg or greater. Transient increases in heart rate (HR) were observed following administration of single and multiple doses of omadacycline, with a dose dependent mean increase of up to 15 to 20 beats per minute (bpm) compared to placebo. The increases in HR were rarely reported as adverse events (AEs) and not associated with any other cardiac findings. These increases were most evident within the 6 hours post-infusion. Following po administration, an increased incidence of gastrointestinal (GI) AEs, particularly nausea, was noted in early studies, which were most notable at po doses of 400 mg or greater. Of note, different po formulations evaluated in early studies (eg, capsule versus tablet) may have influenced the GI safety profile. In Phase 1 studies there were no discontinuations due to drug-related AEs in any subject who received multiple doses of omadacycline.

In the Phase 2 cSSSI study, the most frequently reported AEs were GI related occurring in 19% of omadacycline treated and 17% of linezolid-treated subjects. Nausea and vomiting were reported in 10% and 5%, respectively, of omadacycline-treated subjects primarily during po treatment, compared to 7 and 4%, respectively, of linezolid-treated subjects. Premature discontinuation of treatment due to an AE was very infrequent, occurring in 0.9% of omadacycline subjects and 1.9% of linezolid subjects. There was no pattern of adverse changes in laboratory safety parameters among subjects treated with omadacycline or linezolid. In particular, there was no clinical or statistical difference between the treatment groups in ALT values or in other liver enzymes.

An increase in mean HR was observed, but to a lesser extent than what was observed in Phase 1 studies. This effect was transient and no QT prolongation was observed, consistent with the negative findings from testing of omadacycline in a dedicated corrected QT interval (QTc) study. Three subjects treated with omadacycline had AEs of tachycardia; 1 other subject reported palpitations. All 4 of these AEs were mild in intensity, all were assessed as either unrelated or unlikely related to test article, and none resulted in discontinuation of study treatment.

In the sponsor-terminated Phase 3 cSSSI study, 140 subjects were treated prior to the sponsor's decision to discontinue the study (due to changing regulations regarding the endpoints). The overall incidence of reported AEs in this study was comparable between the 2 treatment groups. The most commonly reported AEs (greater than or equal to 10% frequency in either treatment group) were nausea (27% omadacycline, 26% linezolid), headache (24% omadacycline, 7% linezolid), vomiting (9% omadacycline, 15% linezolid), diarrhea (4% omadacycline, 18% linezolid), and dizziness (10% omadacycline, 8% linezolid). Creatine phosphokinase (CK) elevation was reported in 9% of omadacycline treated subjects compared to 3% for linezolid. Alanine Aminotransferase increases were reported as AEs in 1 omadacycline subject (2%)

compared to 4 linezolid treated subjects (6%). Rash was reported by 1 omadacycline subject (2%) and 6 linezolid subjects (8%). Serious adverse events (SAEs) were experienced by 3 omadacycline subjects (small bowel obstruction, large left pleural effusion, and worsening depression) and 1 linezolid subject (worsening right hand cellulitis).

In a completed Phase 3 study comparing omadacycline and linezolid for the treatment of adults with ABSSSI (PTK0796-ABSI-1108), subjects started therapy with omadacycline 100 mg iv every 12 hours (q12h) for 2 doses then 100 mg iv every 24 hours (q24h), or linezolid 600 mg iv q12h. Subjects could be switched to oral therapy (omadacycline 300 mg q24h or linezolid 600 mg q12h) after a minimum of 3 days of iv therapy; the total treatment duration was 7-14 days. Study results showed that omadacycline was non-inferior to linezolid. In the modified intent-to-treat population (mITT, total N=627) for omadacycline versus linezolid, respectively, clinical success based on a reduction of lesion size at 48-72 hours after the first dose was 84.8% versus 85.5% (95% confidence interval [CI]: -6.3, 4.9); clinical success based on investigator's assessment of clinical response at 7-14 days after the last dose was 86.1% versus 83.6% (CI: -3.2, 8.2). Omadacycline was well tolerated: treatment-emergent adverse events (TEAEs) were reported in 48.3% versus 45.7%; serious TEAEs in 3.4% versus 2.5% and discontinuation due to TEAE in 1.9% versus 2.2% of omadacycline and linezolid treated subjects, respectively.

In addition, a global Phase 3 study is currently being conducted to evaluate the safety and efficacy of iv and po omadacycline compared to iv and po moxifloxacin in the treatment of adult subjects with community-acquired bacterial pneumonia (PTK0796-CABP-1200).

Please refer to the current version of the omadacycline Investigator's Brochure for additional information.²

Omadacycline has demonstrated activity against the most common ABSSSI pathogens, including isolates resistant to standards of care. This study is intended to evaluate the safety and efficacy of po omadacycline as compared to po linezolid in the treatment of adult subjects with ABSSSI.

10 STUDY OBJECTIVES

10.1 Primary Objectives

To demonstrate that omadacycline administered orally for 7 to 14 days is non-inferior to linezolid administered orally for 7 to 14 days in the treatment of adult subjects with ABSSSI known or suspected to be due to Gram-positive pathogens.

10.2 Secondary Objectives

- To evaluate the safety of omadacycline in the treatment of adult subjects with ABSSSI.
- To evaluate the Clinical Response according to the identified causative pathogen.
- To evaluate the pharmacokinetics (PK) of omadacycline in adult subjects with ABSSSI.

11 STUDY DESIGN

11.1 Description

This is a randomized (1:1), double-blind, double-dummy, active comparator-controlled, Phase 3 study comparing omadacycline and linezolid for the treatment of adult subjects with ABSSSI that is known or suspected to be due to a Gram-positive pathogen(s). Enrollment of subjects with major abscess may be up to 30% of randomized subjects. Enrollment of subjects who have received a single dose of an allowed short-acting antibiotic (see [Appendix 1](#)) within the 72 hours prior to randomization will be limited to no more than 25% of randomized subjects. Subject randomization will be stratified across treatment groups by type of infection (wound infection, cellulitis/erysipelas or major abscess) and receipt of an allowed antibacterial therapy (see [Appendix 1](#)) in the 72 hours prior to randomization, as defined in the Interactive Voice Response System/Interactive Web Response System (IxRS) specifications and statistical analysis plan (SAP) (see [Section 25.1](#)).

The study will consist of 3 protocol-defined phases: Screening, Double-Blind Treatment and Follow-up. All Screening evaluations, with the exception of the blood culture, should be completed within the 24 hours prior to randomization. The blood culture should be completed within the 24 hours prior to the first dose of test article. Subjects who meet inclusion criteria, and do not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article at the site within 4 hours after randomization.

11.2 Rationale of Study Design

The study was designed in accordance with the United States (US) Food and Drug Administration (FDA)³ and European Medicines Agency (EMA)^{4,5} guidance on developing antimicrobial drugs for the treatment of ABSSSI, in addition to the guidelines of the Infectious Diseases Society of America (IDSA)⁶ and 2012 Update from the Biomarkers Consortium of the Foundation for the National Institutes of Health.⁷

11.3 Rationale for Choice of Comparator

The comparator drug, linezolid, is approved world-wide for the treatment of ABSSSI caused by Gram-positive pathogens and has an acceptable and well-defined safety profile. Linezolid can be administered orally and has regulatory approval for the treatment of ABSSSI caused by Gram-positive pathogens including MRSA.

11.4 Approximate Duration of Subject Participation

Subjects will participate in the study for approximately 30 days. Following Screening, eligible subjects will be randomly assigned to receive 7 to 14 days of po treatment with either omadacycline or linezolid. A follow-up office visit will occur approximately 7 to 14 days after the last dose of test article, and a follow-up telephone contact will occur approximately 30 to 37 days after the first dose of test article.

11.5 Approximate Duration of Study

This study is expected to be clinically complete in approximately 12 months.

11.6 Approximate Number of Subjects

Approximately 704 subjects will participate in this study at approximately 50 sites.

12 SELECTION OF SUBJECTS

Each subject must participate in the informed consent process and sign and date an institutional review board (IRB)/independent ethics committee (IEC)/research ethics board (REB) approved informed consent form (ICF) before any procedures specified in this protocol are performed.

12.1 Inclusion Criteria

To be eligible for randomization in this study, a subject must fulfill ALL of the following criteria:

1. Written and signed informed consent must be obtained before any assessment is performed.
2. Male or Female, age 18 years or older.
3. Has a qualifying skin and skin structure infection. All qualifying lesions must be greater than or equal to 75 cm² in total surface area of contiguous involved tissue, calculated as the product of the maximum length (head-to-toe) multiplied by the maximum width (measured perpendicular to length) as measured by the investigator using a wound ruler. Involved tissue is defined as tissue exhibiting clear evidence of one or more of the following: erythema, edema or induration.

The classification of qualifying infections is shown below.

- Wound infection – an infection characterized by purulent drainage from a wound with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the wound.
 - Cellulitis/erysipelas – a diffuse skin infection characterized by spreading areas of erythema, edema, and/or induration.
 - Major abscess – an infection characterized by a collection of pus within the dermis or deeper with surrounding erythema, edema, and/or induration extending at least 5 cm in the shortest distance from the peripheral margin of the abscess.
4. Has evidence of a systemic inflammatory response within the 24 hours prior to randomization, as indicated by ONE of the following:
 - Elevated white blood cell (WBC) count (greater than or equal to 10,000 cells/mm³) or leukopenia (less than or equal to 4,000 cells/mm³)
 - Elevated immature neutrophils (greater than or equal to 15% band forms, see % bands calculation in [Appendix 2](#)) regardless of total peripheral WBC count
 - Lymphatic involvement: lymphangitis or lymphadenopathy that is proximal to and in a location that suggests drainage from the qualifying infection

- Fever or hypothermia documented by the investigator (temperature greater than 38.0°C [100.4°F] or less than 36.0°C [95.5°F])
5. Females must have a negative pregnancy test at Screening and agree to comply with using an acceptable method of birth control (eg, abstinence, oral contraceptive, intrauterine device [IUD], barrier contraception [condom], tubal ligation, hysterectomy, bilateral oophorectomy, postmenopausal or vasectomized partner) from Screening through Post Therapy Evaluation (PTE). Males must agree to use an acceptable method of birth control with female partner(s) and must not donate sperm from Screening through PTE.

12.2 Exclusion Criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Has received 1 or more doses of a potentially effective systemic antibacterial treatment within the 72 hour period prior to randomization (a subject will be considered to have received a potentially effective systemic antibacterial treatment if the pathogen identified as causing the infection is shown to be susceptible to the antibacterial treatment given or, in the circumstance where a pathogen is not identified, if the antibacterial agent is approved for treatment of skin infections or is known to have activity against any of the leading Gram-positive causes of ABSSSI [eg, *Staphylococcus aureus*, *Streptococcus* species [spp.] , *Enterococcus* spp.]). EXCEPTION: Subjects may be eligible despite prior antibacterial therapy if they have been treated with a single dose of a short-acting, non-oxazolidinone antibacterial (ie, an antibacterial whose standard dosing regimen is more frequent than once per day, see list in [Appendix 1](#)).
2. Has, for any reason, used a topical antibacterial agent(s) with specific antibacterial activity (eg, mupirocin, retapamulin, fusidic acid) continuously within the 72 hour period prior to randomization, if applied to the skin for greater than or equal to 72 hours.
3. Infections where the outcome is strongly influenced by factors other than protocol-defined treatment and procedures, that require antibacterial treatment for greater than 14 days, are associated with chronic skin lesions that may obscure determination of response even after successful bacterial eradication has been achieved, or are suspected or known to be caused by a pathogen resistant to either test article, eg:
 - Chronic (persistently present greater than 3 months) lesions, ulcers or wounds (eg, cellulitis contiguous with a diabetic foot ulcer)
 - association with chronic dermatitis or any other chronic inflammatory skin lesion (eg, psoriasis, eczema)
 - burns
 - peri-rectal abscess (eg, buttock or perineal lesion likely to communicate with the rectum) or perineal infection
 - infected decubitus (pressure) ulcers
 - necrotizing fasciitis (infections with rapidly progressive destruction of tissue at or below the fascia)
 - life-threatening infections, ie, require emergency surgery for the treatment (eg, progressive gangrene)

- infections in an area requiring surgery that in and of itself would cure the infection or remove the infected site (eg, amputation for vascular insufficiency)
 - infections associated with severe vascular insufficiency (eg, peripheral vascular disease) or acute occlusion expected to require immediate revascularization
 - infections associated with acute compartment syndrome expected to require extensive surgery to provide decompression
 - infections accompanied by confirmed or suspected contiguous bone or joint infection (eg, osteomyelitis, septic arthritis, bursitis)
 - bacteremic infections associated with an intravascular foreign body
 - infections accompanied by another confirmed or suspected infection requiring systemic antibiotic therapy (eg, endocarditis, other endovascular infection, meningitis, visceral abscess, intra-abdominal infection, pneumonia, urinary tract infection)
 - human or animal bites (infections associated with insect bites are NOT excluded)
 - myonecrosis
 - complicated by an immune deficiency in the subject (eg, ecthyma gangrenosum in a neutropenic subject)
 - infections associated with the presence of a foreign body (eg, wood, metal, plastic, etc.) if the foreign body cannot be removed within 24 hours of first dose of test article
4. Inability to tolerate oral medication (eg, nausea, vomiting, diarrhea or any other condition that might impair ingestion or absorption of oral medication).
 5. Has known or is clinically suspected for 1 or more of the following prior to randomization:
 - Alanine Aminotransferase (ALT) or Aspartate aminotransferase (AST) greater than or equal to 3 times the Upper Limit of Normal (ULN),
 - total bilirubin greater than 1.5 times the ULN, or
 - evidence of end-stage liver disease (eg, ascites, hepatic encephalopathy)
 6. Has a known history of having experienced unstable cardiac disease (eg, unstable angina, myocardial infarction, acute congestive heart failure, unstable cardiac arrhythmia, etc.) within the 3 months prior to Screening.
 7. Requires any form of dialysis (eg, hemodialysis, peritoneal dialysis).
 8. History or evidence of severe renal disease or has a calculated creatinine clearance (CrCL) of less than 30 mL/min, using the Cockcroft-Gault equation (see equation in [Appendix 2](#)).
 9. Evidence of significant immunological disease determined by any of the following:
 - Current or anticipated neutropenia defined as less than 500 neutrophils/mm³
 - Known infection with Human Immunodeficiency Virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be less than 200 cells/mm³ within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness
 10. The receipt of cancer chemotherapy, radiotherapy, or potent, non-corticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy, etc.) within the 3 months prior to Screening, or the receipt of systemic corticosteroids for more than 14 days in the 30 days prior to Screening.

11. Requires acute pharmacologic intervention to stabilize blood pressure (BP) and/or adequate tissue perfusion, OR has evidence of septic shock, defined by ALL of the following:
 - Fever or hypothermia documented by the investigator (temperature greater than 38.0°C [100.4°F] or less than 36.0°C [95.5°F])
 - Heart rate greater than 90 bpm
 - Respiratory rate greater than 20 breaths/min
 - WBC greater than 12,000 cells/mm³ or less than 4,000 cells/mm³ or greater than 10% immature (band) forms, see % bands calculation in [Appendix 2](#), regardless of the total peripheral WBC count
 - Hypotension with systolic blood pressure (SBP) less than 90 mm Hg despite an iv fluid challenge of 20 to 30 cc/kg over a 30 minute period
 - Perfusion abnormalities that may include, but are not limited to, lactic acidosis (blood lactate concentration greater than or equal to 4 mmol/L), oliguria, or acute alteration in mental status
12. Pregnant or nursing (breastfeeding) women.
13. Has a history of hypersensitivity or allergic reaction (eg, anaphylaxis, urticaria, other significant reaction) to any tetracycline (eg, minocycline, doxycycline or tigecycline) or to any oxazolidinone (eg, linezolid, tedizolid).
14. Has a history of pseudotumor cerebri, or prior (within 2 weeks prior to Screening) or planned concomitant use of isotretinoin.
15. Has a history of systemic lupus erythematosus or lupus-like syndrome.
16. Has current evidence of pancreatitis.
17. Has received a monoamine oxidase (MAO) inhibitor within 14 days prior to Screening (eg, phenelzine, isocarboxazid, selegiline, moclobemide; which are typically used to treat depression or Parkinson's Disease).
18. Use of other investigational drugs within 5 half-lives or within 30 days prior to Screening.
19. Has previously been treated with omadacycline or previously enrolled in this study.
20. Any planned medical intervention that might interfere with the ability to comply with the study requirements.
21. Has any concomitant condition that, in the opinion of the investigator, is likely to interfere with evaluation of the response of the infection under study, determination of AEs, or completion of the expected course of treatment.

12.3 Screen Failures

Subjects who sign the ICF but withdraw or are withdrawn from the study before random assignment to double-blind treatment are defined as screen failures. All screen failures should be recorded on the subject master list. Limited information including reason for screen failure will be recorded on the electronic case report form (eCRF) or (IxRS) system for screen failures.

13 PRIOR AND CONCOMITANT TREATMENT

Treatments that have been administered within the 7 days prior to the date of informed consent, or during the Screening phase, will be recorded in the eCRF. The investigator is to instruct the

subject to notify the study site about any new medications he/she takes after the start of the test article. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with test article must be listed in the eCRF (see [Section 8](#)). In addition, for antibacterial agents, the dose, unit, frequency and route must be entered in the eCRF.

13.1 Prohibited Treatment

- Use of all non-study investigational medications or devices is prohibited during the 30 days prior to Screening through PTE.
- Systemic antibacterial agents potentially effective for ABSSSI are prohibited for 72 hours prior to randomization through PTE, except as rescue therapy in cases of clinical failure. A single dose of a short-acting potentially effective systemic antibacterial agent (see list in [Appendix 1](#)) administered within the 72 hours prior to randomization will be allowed for up to 25% of randomized subjects.
- Any topical antibacterial agent applied to the infection site with a spectrum that is active against the known or potential infecting pathogen(s) responsible for the infection under study within the 72 hours prior to randomization through PTE.
- MAO inhibitors. Linezolid is a reversible non-selective inhibitor of MAO. Therefore, subjects should not be enrolled who are either taking MAO inhibitors (eg, phenelzine, isocarboxazid), or have taken MAO inhibitors within 14 days prior to Screening. MAO inhibitors are prohibited from 14 days prior to Screening through the Final Follow-up assessment.
- Subjects will be instructed to avoid taking antacids and multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 6 hours before and 4 hours after all odd numbered doses.

All other medications not prohibited by the protocol and considered necessary for the subject's welfare may be administered and/or continued under the supervision of the investigator.

13.1.1 Concomitant Medications That May Interact With Linezolid

Adverse interactions between linezolid and serotonergic psychiatric medications, sympathomimetics, vasopressors, dopaminergic agents and dextromethorphan have been reported. Subjects who receive any of these classes of drugs concurrent with test article must be monitored closely for elevated blood pressure and other manifestations of serotonin syndrome which could include mental changes (eg, confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination, and/or fever.

All subjects will be instructed to avoid eating foods high in tyramine content while taking test article as recommended in the linezolid prescribing information.

The full prescribing information for linezolid will be provided to the investigator under separate cover.

13.2 Permitted Treatments

All other treatments not specified as prohibited are permitted during the study. A single dose of a short-acting potentially effective systemic antibacterial agent (see list in [Appendix 1](#)) administered within the 72 hours prior to randomization will be allowed for up to 25% of randomized subjects. Subjects requiring additional or alternative antibacterial therapy for the ABSSSI will be judged as Clinical Failures and test article will be discontinued. Further treatment for their infection is at the discretion of the investigator or the subject's health care provider and will be considered as a concomitant medication.

Subjects should be encouraged to contact site personnel before starting any new treatment.

For all treatments received by the subject during the study, relevant information must be recorded on the subject's eCRF.

13.2.1 Dressings

Wounds may be covered with any sterile non-adherent type dressing (not containing any specific antibacterial agents) chosen by the investigator.

13.2.2 Topical Solutions

Topical solutions with nonspecific activity such as povidone iodine can be used during dressing changes and as part of local care to lesions. However, solutions containing specific antibacterial agents (eg, mupirocin, retapamulin, fusidic acid) should not be used as part of the regimen involved in local infection site care.

13.2.3 Surgical Procedures

Adjunct surgical treatment is appropriate and necessary in many ABSSSIs. At Screening, all subjects should be carefully evaluated and a determination should be made as to whether 1 or more procedures are indicated. When indicated, planned procedures should be performed within 24 hours and no later than 48 hours after start of test article. The date and time of all planned or unplanned surgical procedures will be recorded.

14 PROCEDURES

Written, signed, and dated informed consent will be obtained before any study-related procedures have been performed. Upon signing the informed consent, the subject should then be assigned a study subject number. AEs must be recorded from the time the ICF is signed. Subjects who have been pre-screened on the telephone but who do not sign an ICF will not be assigned a subject number. The investigator will maintain a subject master list to document every subject who has signed an ICF. A copy of this list should be retained in the investigator's study files.

14.1 Visit Schedule and Assessments

Refer to [Section 8](#), for the study procedures and their time points. There are 3 protocol-defined phases of the study: Screening, Double-Blind Treatment, and Follow-up. The study will have the following protocol-defined evaluations:

- Day 1 visit
- Day 2 visit
- Day 3 visit (Early Clinical Response [ECR] must be conducted between 48 to 72 hours after the first dose of test article)
- Day 7 visit
- Day 10 visit (A Day 10 visit should be conducted for subjects with treatment extending beyond 9 days, unless this visit coincides with the End of Treatment visit)
- End of Treatment (EOT): to be conducted on the calendar day of, or within 2 days following the last dose of any test article. If a subject withdraws prematurely or terminates participation in the study before completion, the EOT visit should be conducted
- Post Therapy Evaluation (PTE): to be performed 7 to 14 days after the subject's last day of study therapy
- Final Follow-up assessment: Day 30 to 37 (after the first dose of test article)

Subjects who discontinue study treatment prematurely should have the EOT visit and the procedures listed in Section 8, a PTE visit and a Final Follow-up assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

14.2 Screening Phase

Due to the nature of the disease under study, the Screening phase should be completed within 1 day (24 hour period). The Screening phase will be used to establish subject eligibility and Baseline characteristics for each subject. Subjects are eligible for Screening if they present with ABSSSI signs and symptoms. Following the signing of an ICF, site personnel will collect the following information:

- Demographics
- Medical/surgical history and current medical conditions
- Physical examination
- Vital signs
- Review of inclusion/exclusion criteria
- Laboratory tests: hematology, chemistry, urine tests, pregnancy test (for women only)
- 12-lead electrocardiogram (ECG)
- Concomitant medications (past 7 days)
- AEs since the signing of the ICF

- Diagnosis of ABSSSI (cellulitis/erysipelas, wound infection, or major abscess), clinical assessment of the site of infection, and photograph of the infection site.
- Assessment of lesion size
- Numerical Rating Scale for pain at the primary infection site
- SF-36v2[®] Health Survey
- Microbiological assessments (blood culture, culture of the infection site, and Gram stains)

14.2.1 Subject Demographics/Other Baseline Characteristics

Subject demographic and Baseline characteristic data to be collected on all subjects include: date of birth, gender, race/ethnicity and childbearing potential. Medical history/current medical condition data includes data until the signing of informed consent. Whenever possible, diagnoses are to be recorded.

The investigator will perform a comprehensive history and physical examination at the Screening evaluation with particular attention to items indicated below.

14.2.1.1 Medical History Relating to the Infection Under Study

- Predisposing factors at the site of infection, eg, surgery, mechanical trauma, edema (acute or chronic), vascular insufficiency, prior infection, iv drug abuse
- All systemic antimicrobials and topical treatments (prescription, over-the-counter) from onset of the infection will be recorded under concomitant medications
- Procedures (eg, debridement, incision and drainage) performed within the week (7 days) prior to Screening, including surgical (operating room, procedure room) procedures, interventional radiology procedures and bedside procedures, but excluding routine wound care such as dressing changes will be collected
- Surgical procedure history for surgical wound infections (within 30 days prior to Screening)

14.2.2 Physical Examination

At Screening, the physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams may be performed. Height and body weight will be measured.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of test article must be included in the subject's eCRF.

14.2.3 Diagnosis of ABSSSI and Clinical Assessment of the Site of Infection

At the Screening evaluation, the type of ABSSSI will be recorded: wound infection, cellulitis/erysipelas or major abscess as defined in the inclusion criteria (see [Section 12.1](#)). To

qualify, there must be greater than or equal to 75 cm² in total surface area of contiguous involved tissue (ie, surrounding erythema, edema and/or induration).

The anatomical location of the primary site of infection should be recorded. For subjects with multiple non-contiguous areas of infection, the investigator will identify the most severely affected portion at Screening and designate that as the primary lesion site. The investigator should note the presence and nature of any foreign body (eg, wood, metal, plastic, etc.) present at the site of infection. Note that if the foreign body cannot be removed within 24 hours of initiation of test article the subject should not be enrolled in the study (see Exclusion criteria, [Section 12.2](#)).

The investigator will examine the primary site of infection and record the following information on source documents and the eCRFs:

- Presence of lymphadenopathy proximal to primary lesion site
- Presence of lymphangitis proximal to primary lesion site
- Presence of drainage from the primary lesion site and description (serous/serosanguineous, seropurulent, or purulent)

Semi-quantitative (none, mild, moderate, severe) description of infection for the following features:

- Tenderness
- Edema
- Erythema
- Induration

At the Screening evaluation the site of infection will be photographed using a digital camera provided by the sponsor; the subject number and date will be included in the field. Instructions for lesion photographs will be provided to the investigator.

14.2.4 Assessment of Lesion Size

The Screening evaluation measurement of lesion size must be collected within 4 hours prior to randomization. Surface area of lesions will be calculated by multiplying the head-to-toe maximum length of the total lesion and maximum width (perpendicular to maximum length) inclusive of contiguous involvement (erythema, edema and/or induration). Investigator ruler measurements will be used to document the lesion size. Instructions for ruler measurements will be provided to the investigator.

14.2.5 Subject Reported Outcomes

14.2.5.1 Numerical Rating Scale for Pain

At the Screening, Day 3 (ECR), EOT and PTE visits the subject will complete a numerical rating scale for pain⁸ at the primary ABSSSI lesion site. The numerical rating scale anchors will range

from 0 to 10, where 0 represents “No pain” and 10 represents “Pain as bad as you can imagine.” The subject will be asked to rate their pain at the primary site of infection under study: “Please rate your pain by circling the number that best describes the average pain caused by your primary skin infection over the last 24 hours, where 0 represents no pain and 10 represents pain as bad as you can imagine.”

14.2.5.2 SF-36v2[®] Health Survey

At the Screening and PTE visits the subject will complete a SF-36v2[®] Health Survey (Medical Outcomes Trust, Optum[™]). The SF-36v2[®] Health Survey asks 36 questions to measure functional health and well-being from the subject's point of view. It is a practical, reliable and valid measure of physical and mental health that can be completed in five to ten minutes. It is referred to as a generic health survey because it can be used across age (18 and older), disease, and treatment group, as opposed to a disease-specific health survey, which focuses on a particular condition or disease.

14.2.6 Urine Tests

A urine dipstick will be performed locally at Screening. Urine dipstick results will be recorded on the eCRF. A local urine (or serum) pregnancy test will be performed during Screening for all women and the results will be recorded on the eCRF.

14.3 Double-blind Treatment Phase

14.3.1 Assessments While on Test Article

The double-blind treatment period is 7 to 14 days in duration. Subjects who met inclusion criteria, and did not meet exclusion criteria will be randomly assigned to a treatment group, and should receive their first dose of test article at the site within 4 hours after randomization.

The following assessments (see [Section 8](#)) will be done:

- Vital signs
- AEs and SAEs
- Concomitant treatments
- Assessment of lesion size and clinical assessment of the site of infection
- Numerical Rating Scale for pain at the primary infection site
- Microbiological assessments
- Blood for Central Laboratory assessments: hematology, chemistry, pregnancy (for women only)
- Test article administration and accountability
- Assessment for need to continue therapy
- Investigator’s assessment of clinical response

14.3.1.1 Treatment Phase

The study will employ a double-blind, double-dummy design using omadacycline placebo comparator tablets of matching size and shape to active omadacycline tablets and matching over-encapsulated placebo and over-encapsulated active linezolid tablets. To maintain investigator and subject blinding, subjects on both arms will receive the same number of tablets as shown in [Table 1](#).

All doses of test article should be taken with water. There are fasting requirements for administration of the odd numbered doses due to effects of food on oral omadacycline (see [Table 1](#)). These fasting requirements should be considered when determining the time of day when subjects will take their doses.

In order to perform protocol-required procedures, Dose 1 and the odd numbered doses on Days 2 and 3 should be taken at the site. Ability to perform the study procedures and the fasting requirements for the odd numbered doses should be considered when determining when subjects visit the clinic on Days 2 and 3.

On Day 1, Dose 1 will be administered after the completion of all required Screening and Day 1 procedures and within 4 hours after randomization as outlined in [Section 8](#). On Day 1, a second dose should be taken provided that 1) it can occur a minimum of 8 hours after Dose 1, and 2) it can occur a minimum of 8 hours before the expected time of the next dose (ie, Dose 3); otherwise only Dose 1 should be taken that day. Starting on Day 2, test article will be taken twice daily, with approximately 12 hours (at least 8 hours) separating each dose.

Table 1. Treatment Regimens for Oral Test Article

Dosing		Omadacycline Arm	Linezolid Arm	Dosing Condition
Day 1	Dose 1	Three 150 mg omadacycline tablets and one over-encapsulated placebo tablet resembling linezolid	Three placebo tablets resembling omadacycline and one over-encapsulated 600 mg linezolid tablet	Fasting ^a
	Dose 2 ^b	One over-encapsulated placebo tablet resembling linezolid	One over-encapsulated 600 mg linezolid tablet	No restrictions
Day 2	Dose 3	Three 150 mg omadacycline tablets and one over-encapsulated placebo tablet resembling linezolid	Three placebo tablets resembling omadacycline and one over-encapsulated 600 mg linezolid tablet	Fasting ^a
	Dose 4	One over-encapsulated placebo tablet resembling linezolid	One over-encapsulated 600 mg linezolid tablet	No restrictions
Day 3 and all subsequent study days	Dose 5 and odd doses	Two 150 mg omadacycline tablets and one over-encapsulated placebo tablet resembling linezolid	Two placebo tablets resembling omadacycline and one over-encapsulated 600 mg linezolid tablet	Fasting ^a
	Dose 6 and even doses	One over-encapsulated placebo tablet resembling linezolid	One over-encapsulated 600 mg linezolid tablet	No restrictions

a Fasting: no food, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) or drink except water for at least 6 hours before dosing; after dosing, no food for 2 hours, no dairy products, antacids or multivitamins containing multivalent cations (eg, aluminum, magnesium, calcium, bismuth, iron, or zinc) for 4 hours

b On Day 1, Dose 2 should be taken provided that 1) it can occur a minimum of 8 hours after Dose 1 and 2) it can occur a minimum of 8 hours before the expected time of the next dose (ie, Dose 3); otherwise Dose 2 should be skipped.

14.3.1.2 Management While on Oral Test Article

While the subject is receiving therapy, the investigator should assess the subject at the visits specified in [Section 8](#) and choose ONE of the following actions:

- Continue test article
- Discontinue test article – this decision will prompt the EOT evaluation

The date, time and decision of the investigator will be recorded on source documents and the information transferred to eCRFs by study site personnel.

The investigator may use the culture and susceptibility results from the local microbiology laboratory to help guide therapy; however, decisions to continue or discontinue test article should be based on clinical response rather than susceptibility results (as omadacycline susceptibility testing is not available at the local site). If the ABSSSI is caused by a microorganism that is not susceptible to linezolid *in vitro*, the decision to continue or discontinue study treatment should be based on the subject's clinical course and the investigator's clinical judgment. These cases should be discussed with the Medical Monitor. The rationale for this decision should be recorded in source documents.

14.3.2 Permitted Dose Adjustments and Interruptions of Test Article

None.

14.4 Follow-up Phase

Subjects will be evaluated at 2 visits after the completion of treatment: at the PTE visit, 7 to 14 days after the subject's last day of study therapy, and at a Final Follow-up assessment, 30 to 37 days after the first dose of treatment (see [Section 8](#)). The Final Follow-up assessment may be conducted via telephone contact or by another interactive technology for subjects who were considered to be Clinical Successes and had no AEs or clinically significant laboratory or ECG abnormalities noted at or after the PTE visit. Otherwise, this assessment is to be performed with an in person study visit.

14.5 Total Volume of Blood Collected

The total volume of blood collected from each subject will be approximately 80 mL.

15 TEST ARTICLE AND ADMINISTRATION

Test articles will be supplied by Paratek Pharma, LLC (the sponsor). Test articles will be labeled according to regulations.

The test articles should be administered only to subjects who have provided informed consent and who meet all of the inclusion criteria and none of the exclusion criteria. Once the test article has been assigned to a subject, it must not be reassigned to another subject.

15.1 Test Article Administration

Subjects will be randomized (1:1) to 1 of the following 2 treatment arms:

- Investigational therapy: omadacycline, 450 mg po every 24 hours (q24h) for 2 doses, followed by 300 mg po q24h. Total treatment duration of 7 to 14 days.
- Reference therapy: linezolid, 600 mg po every 12 hours (q12h). Total treatment duration of 7 to 14 days.

15.1.1 Identity of the Investigational Product

Table 2. Oral Formulation

Name	Omadacycline Tablet, 150 mg
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]

15.2 Investigational and Comparator Test Article

15.2.1 Investigational Test Article: Omadacycline

- 450 mg po q24h for 2 doses followed by 300 mg po q24h
- Total treatment duration of 7 to 14 days

15.2.2 Comparator Test Article: Linezolid

- 600 mg po q12h
- Total treatment duration of 7 to 14 days

15.3 Dose Selection Rationale

The dosing regimen of omadacycline selected for this study is based on the totality of nonclinical and clinical experience to date, including *in vitro* antibacterial activity, PK characteristics, clinical efficacy in prior studies, and the overall safety and tolerability profile. Key considerations in dose selection are summarized below:

- Given the half-life of omadacycline (approximately 18 hours), if dosing were to occur once daily then several days of dosing would be required to reach steady-state plasma concentrations. Consequently, dosing regimens typically include a “loading-dose” strategy to reach steady-state more rapidly.

- In a completed Phase 3 study comparing omadacycline and linezolid for the treatment of adults with ABSSSI (PTK0796-ABSI-1108), subjects started therapy with omadacycline 100 mg iv q12h for 2 doses (ie, 2 doses on Day 1), then 100 mg iv q24h; after 3 days iv therapy subjects could be switched to oral therapy (300 mg po q24h). As described in [Section 9.1](#), omadacycline demonstrated good efficacy and tolerability in that study.
- It has been demonstrated that omadacycline administered as a 100 mg iv dose is bioequivalent (based on plasma area under the curve [AUC]) to a 300 mg oral dose. Therefore, one approach to the dosing regimen for this oral-only treatment study was to start omadacycline treatment with oral doses considered bioequivalent to the iv doses used in the completed Phase 3 study (ie, 300 mg po q12h for 2 doses, then 300 mg po q24h).
- Because of a known food effect, oral omadacycline should be administered in a fasted state. While this restriction is considered manageable for once daily dosing, it was recognized that adherence to a fasting window surrounding two doses in a given day (such as that associated with a “loading-dose” of two separate doses on Day 1) would be challenging.
- A recently completed Phase 1 study (PTK0796-MDPO-16105) evaluated multiple once daily oral regimens of omadacycline. Preliminary results from that study showed that oral dosing regimens of 300 mg q24h and 450 mg q24h had similar and favorable tolerability profiles. In addition, PK results based on that study and prior studies indicate that a regimen of 450 mg po q24h for 2 doses followed by 300 mg po q24h will achieve approximately the same steady state concentrations within the same time frame as a dosing regimen starting with 300 mg po q12h for 2 doses, then 300 mg po q24h. In both regimens, a total of 900 mg oral omadacycline is administered over the first 2 days.
- Therefore, in order to minimize the potential impact of food effects and maximize convenience with an oral dosing regimen that is expected to be well tolerated and achieve rapid target plasma concentrations, an omadacycline dosing regimen of entirely once daily dosing will be used (ie, 450 mg po q24h for 2 doses, then 300 mg po q24h). Note that because the study is double-blind and linezolid is dosed twice-daily, all study subjects will be dosed twice-daily (with either active or placebo tablets), as detailed in [Section 14.3.1.1](#).

15.4 Subject Compliance

Study personnel at the site, should monitor po test article compliance at each study visit, by comparing the returned test article with the dosing information reported in the subject charts and subject diaries. Discrepancies should be resolved with the subject during the visit. Compliance and any unresolved discrepancies will be documented in the source document and on the drug inventory record. The test article eCRF should reflect the reconciled dosing information provided by the subject charts and subject diaries.

16 SAFETY

Any subject who receives test article will be included in the evaluation for safety.

Safety is assessed by the following measures:

- Physical examinations
- AEs and SAEs
- Vital signs
- Laboratory assessments
- 12-lead ECG
- Pregnancy assessments

16.1 Physical Examinations

After Screening, a physical examination should be conducted on the study days indicated in [Section 8](#). Any abnormalities or changes in intensity noted during the review of the body systems should be documented in the source documents. If a new clinically significant finding occurs (ie, not noted at Screening) after the Screening exam, it must be captured as an AE. In addition, resolution of any clinically significant abnormal findings that have been reported as an AE will be noted in the medical record and the AE eCRF.

16.1.1 Vital Signs

Vital signs include BP, pulse/heart rate, body temperature, and respiratory rate. Vital signs should be recorded at all visits, with the exception of the Final Follow-up assessment (see [Section 8](#)).

- In addition, blood pressure and pulse rate should be measured within 30 min before, and approximately (\pm 15 minutes) 1 hour after and 3 hours after the completion of the first dose on Day 1
- Blood pressure and pulse rate should be measured within 30 min before, and approximately (\pm 15 minutes) 1 hour after and 3 hours after the completion of the odd numbered dose on Day 2
- Blood pressure and pulse rate should be measured within 30 min before, and approximately (\pm 15 minutes) 1 hour after and 3 hours after the completion of the odd numbered dose on Day 3

In the event that the subject takes the dose before arriving for the Day 2 or Day 3 office visit, the site should collect the 1 and 3 hour post dose measurements if possible, if not then a single measurement should be made at any time during the visit and the date and time recorded.

The subject's vital signs should be captured after at least 5 minutes of rest while in a non-standing position (supine or semi-recumbent, head of bed from 0° to 90°). Subsequent vital sign measurements should be captured in the same non-standing position.

Systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff.

Pulse will be measured using an automated validated device, when available. If not available, pulse will be measured manually.

In addition to the above, BP and heart rate may be measured whenever clinically indicated at the discretion of the treating physician. Any subject who experiences an AE of cardiac chest pain, palpitations, or tachyarrhythmia while on study should have an ECG and an evaluation by the investigator (see [Section 16.1.3.1](#)).

Temperature will be obtained using an electronic (rapid reading) device whenever possible. Respiratory rate will be determined by observation.

16.1.2 Laboratory Evaluations

Blood samples for hematology, serum chemistry and coagulation (prothrombin time only) should be drawn at the Screening, Day 3, Day 7, Day 10, EOT, and PTE visits (see [Section 8](#)). At Screening only, 1 sample will be analyzed at a local laboratory for confirmation of eligibility criteria and a second sample shipped to the Central Laboratory for analysis. All other visits should have samples shipped to the Central Laboratory for analysis.

The Central Laboratory will be used for safety analysis of all specimens collected. Details on the collection tubes and containers, shipment of samples and reporting of results by the Central Laboratory are provided to investigators in the Central Laboratory manual.

Because subject enrollment will not permit using Central Laboratory results to assess a subject's meeting inclusion/exclusion criteria, it is expected that local laboratory testing will be used in circumstances where this testing is needed to assess a subject's WBC count or differential, serum transaminase or bilirubin levels, serum creatinine or pregnancy testing (for women only).

16.1.2.1 Hematology

The analytes listed in the table below (Table 3) will be measured at the Central Laboratory.

Table 3. Hematology Panel

Hematocrit	White blood cell differential (as % cell counts)
Total red blood cell count	-Neutrophils
Hemoglobin	-Lymphocytes
Mean cell hemoglobin	-Monocytes
Mean cell hemoglobin concentration	-Eosinophils
Mean cell volume	-Basophils
White blood cell count	
Platelet count	

16.1.2.2 Clinical Chemistry

The analytes indicated in Table 4 below will be measured at the Central Laboratory.

Table 4. Clinical Chemistry Panel

Blood glucose	ALT	LDH
Urea	AST	CK
Creatinine	AP	(CK isoenzyme testing as required)
Sodium	Total bilirubin	Calcium
Potassium	Total protein	Phosphate
Chloride	Magnesium	Cholesterol
Bicarbonate	Albumin	Uric Acid
		GGT
		Amylase
		Lipase

ALT = Alanine aminotransferase; AP = Alkaline phosphatase; AST = Aspartate aminotransferase;
 CK = creatine phosphokinase; GGT = gamma-glutamyl transpeptidase; LDH = Lactate dehydrogenase.

16.1.2.3 Other Laboratory Tests

Table 5. Additional Laboratory Tests

Category	Test	Note
Coagulation	INR	Prothrombin time only
Female endocrinology	β -hCG (for women only)	See Section 16.1.3.2 below. Done both locally (urine) and centrally (serum)

β -hCG = beta-human Chorionic Gonadotropin; INR = international normalized ratio.

16.1.3 Safety Studies to be Performed Locally

16.1.3.1 Electrocardiogram (ECG)

A standard 12-lead ECG should be obtained using equipment provided by the sponsor. The ECG will be obtained after the subject has been in a semi-recumbent position for approximately 10 minutes at the following times:

- Screening
- At the EOT visit
- In any case in which a subject develops an AE of cardiac chest pain, palpitations, tachyarrhythmia or as otherwise clinically indicated (see [Section 16.1.1](#))

Reading and interpretation of the ECG will be performed centrally and provided to the investigator. The investigator is responsible for reviewing interpretations and for retaining hard copies of the reports.

16.1.3.2 Pregnancy and Assessments of Fertility

All women will have a local urine or serum pregnancy test at the site at the Screening visit. Urine pregnancy test kits will be provided by the sponsor through the Central Laboratory. If a positive urine or serum pregnancy test result is obtained at the site, the woman is not to be randomized. A serum sample for β -hCG testing will be collected at the Screening visit and sent to the Central Laboratory for confirmation of the local urine or serum pregnancy test results. Serum samples for β -hCG testing at the Central Laboratory also will be collected at EOT and PTE. If a positive β -hCG result is reported by the Central Laboratory after a woman is enrolled, test article administration should be discontinued (see [Section 21.2.6](#)).

16.1.3.3 Blood Cultures

Two sets of blood cultures (1 set = 1 aerobic bottle + 1 anaerobic bottle) should be collected within the 24 hours prior to the first dose of test article. Each set of blood cultures should be collected by direct venipuncture from independent body sites at least 15 minutes apart. Blood cultures should be collected for subjects that are clinical failures at the EOT and/or PTE visit. If bacteria are isolated from blood cultures, repeat blood cultures should be collected. If subsequent blood cultures are also positive, repeat the blood cultures as necessary until negative blood cultures are obtained (see [Section 8](#)). Blood culture isolates should be sent to the Central Laboratory (see [Section 17.3](#)).

16.1.3.4 Additional Local Laboratory Tests

The investigator may order additional local laboratory tests consistent with his/her routine standard of care.

16.1.4 Appropriateness of Safety Measurements

The safety assessments selected are standard for this indication and subject population.

17 EFFICACY

The following is a list of key assessments that will be performed:

- Clinical assessment of the site of infection
- Assessment of lesion size
- Assessment of the need for adjunct surgical procedures
- Microbiological assessment of the infection
- Assessment of clinical response by the investigator
- Assessment of all-cause mortality

Each is described in further detail below.

17.1 Clinical Assessment of the Site of Infection

The clinical assessment of the site of infection should be conducted at Screening and every scheduled evaluation with the exception of the Final Follow-up assessment (see [Section 8](#)). A clinical assessment of the site of infection must be performed within 48 to 72 hours after the first dose. The investigator will examine the primary site of infection and record the following information on source documents and the eCRFs:

- Presence of drainage from the primary lesion site and description (serous/serosanguineous, seropurulent, or purulent)

Semi-quantitative (none, mild, moderate, severe) description of infection for the following features:

- Tenderness
- Edema
- Erythema
- Induration

17.2 Assessment of Lesion Size

Lesion measurements by ruler should be performed by the Investigator at Screening, and every scheduled evaluation with the exception of the Final Follow-up assessment (see [Section 8](#)).

Surface area of lesions will be calculated by multiplying the head-to-toe maximum length of total lesion and maximum width (perpendicular to maximum length) inclusive of contiguous involvement (erythema, edema and/or induration). Investigator ruler measurements will be used to document lesion size. Instructions for ruler measurements will be provided to the investigator.

17.3 Microbiological Assessment of the Site of Infection

At the Screening visit, material should be collected from the site of infection and submitted to site's local microbiology laboratory for Gram stain and culture. The type of specimen submitted will be recorded on source documents at the microbiology laboratory. Laboratory reports on Gram stains should include a semi-quantitative description of the number of polymorphonuclear leukocytes per low power field (ie, 100×) and a description of bacteria seen.

It is critical, especially at Screening, that the best possible specimen be obtained.

As the site of infection responds to therapy, repeated cultures may not be clinically appropriate and/or there may be no material for culture. At the EOT and/or PTE visit, infection site specimen cultures and Gram stains should be obtained only for subjects who are clinical failures and require alternative antibacterial treatment for the infection under study.

The following types of specimens are considered acceptable in order of preference⁶:

- biopsy of involved cutaneous or subcutaneous tissue, preferably from the advancing margin of the lesion;
- debrided tissue;
- tissue scraping (using curette or scalpel);
- needle aspirate of involved, nonpurulent cutaneous or subcutaneous tissue;
- pus or infected tissue collected during an incision and drainage procedure;
- pus aspirated into a syringe;
- deep swab of purulent material (only if collected from infected tissue that has been incised or is draining).

Surface swabs of wounds, inflamed skin, or drainage (including purulent material) are not acceptable and should not be submitted. For subjects with cellulitis/erysipelas, a skin/subcutaneous tissue punch biopsy at the ‘leading edge’ (not the center) of the involved area is preferred. If this cannot be done, a needle aspirate of the ‘leading edge’ of the cellulitic area should be performed.

All specimens submitted to the site’s local laboratory are to be evaluated for aerobic and, where appropriate, anaerobic culture. Culture results are to include a semi-quantitative description of the organisms on the primary culture plate and identification of all isolates to the level of genus and species. Susceptibility testing for linezolid can be performed locally using a standard method chosen by the laboratory. Results of this testing can be used by investigators along with clinical findings to help guide therapy.

All bacterial isolates identified by the local laboratory from infection site specimens or blood will be submitted to the Central Laboratory for verification of genus and species and for standardized minimum inhibitory concentration (MIC) testing performed for omadacycline, linezolid and a panel of currently approved antibiotics. In the event that local laboratory genus and species identification are not consistent with Central Laboratory results, a back-up isolate should be sent to the Central Laboratory.

The investigator is to check the laboratory microbiology specimen results. If there is evidence of a Gram-negative or anaerobic microorganism, or microorganism that is non-susceptible to linezolid, the decision to continue or discontinue test article and change the antibacterial regimen is made based on the investigator’s clinical judgment and should be recorded in the source documents.

Details concerning Gram stains and cultures will be provided in the Clinical Microbiology Laboratory Manual.

17.4 Assessment of Clinical Outcome

Assessment of clinical outcome will occur at the Early Clinical Response assessment (programmatically), EOT, and PTE as described below.

17.4.1 Evaluation of the Infection Under Study at the Early Clinical Response Assessment

The formal determination of the response to therapy at the Early Clinical Response assessment (48 to 72 hours after the first dose of test article) will be done programmatically using lesion measurement values entered into the eCRF. The investigator is not responsible for categorizing subjects as Clinical Success, Failure, or Indeterminate at the Early Clinical Response assessment.

Clinical Success at the Early Clinical Response assessment will be defined as meeting all 3 of the following:

- The subject is alive
- The size of the primary lesion has been reduced greater than or equal to 20% compared to Screening measurements, without receiving any alternative (rescue) antibacterial therapy.
- The subject does not meet any criteria for Clinical Failure or Indeterminate (see below for definitions)

Clinical Failure will be defined as meeting any of the criteria below:

- The size of the primary lesion has not been reduced by greater than or equal to 20% compared to Screening measurements
- Investigator discontinued test article and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed
- The subject received antibacterial therapy that may be effective for the infection under study for a different infection from the one under study
- The subject developed an AE that required discontinuation of test article prior to the Early Clinical Response assessment and alternative (rescue) antibacterial therapy was needed
- Death prior to Early Clinical Response assessment

Indeterminate

The clinical response to test article could not be adequately inferred because:

- Subject was not seen for Early Clinical Response assessment because they withdrew consent, were lost to follow-up, other reason (specify)
- Other, specify

17.4.2 Clinical Evaluation of the Infection Under Study at EOT

At the EOT visit (on the day of or within 2 days following the last dose of test article), the investigator will indicate the clinical status of the infection under study as detailed below.

Clinical Success at the End of Treatment assessment will be defined as meeting the following:

- The subject is alive

- The infection is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic)

Clinical Failure will be defined as meeting any of the criteria below, the primary reason for clinical failure will be designated:

- Investigator discontinued test article and indicated that the infection had responded inadequately such that alternative (rescue) antibacterial therapy was needed
- The subject received antibacterial therapy that may be effective for the infection under study for a different infection from the one under study
- The subject developed an AE that required discontinuation of test article prior to completion of the planned test article regimen and alternative (rescue) antibacterial therapy was needed
- Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the infection under study
- The subject died before evaluation
- Other, specify

Indeterminate The clinical response to test article could not be adequately inferred. The investigator will mark all that apply:

- The subject was not seen for EOT assessment because they withdrew consent, were lost to follow-up, other reason (specify)
- Other, specify

17.4.3 Clinical Evaluation of the Infection Under Study at PTE

At the Post Therapy Evaluation PTE visit (7 to 14 days after the subject's last day of study therapy) the investigator will indicate ONE of the following outcomes relating to the primary infection under study:

Clinical Success at the Post Therapy Evaluation assessment will be defined as meeting the following:

- The subject is alive
- The infection is sufficiently resolved such that further antibacterial therapy is not needed. These subjects may have some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic)

Clinical Failure will be defined as meeting any of the criteria below, the primary reason for clinical failure will be designated:

- The infection required additional treatment with alternative (rescue) antibacterial therapy

- The subject received antibacterial therapy between EOT and PTE that may be effective for the infection under study for a different infection from the one under study
- Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the infection under study between EOT and PTE
- The subject died before evaluation
- Other, specify

Indeterminate The clinical response to test article could not be adequately inferred. The investigator will mark all that apply:

- The subject was not seen for PTE assessment because they withdrew consent, were lost to follow-up, other reason (specify)
- Other, specify

18 OTHER ASSESSMENTS

18.1 Resource Utilization

The number of emergency room visits and hospitalizations including number of days hospitalized during the study period will be calculated.

19 PHARMACOKINETIC PLASMA SAMPLES FOR OMADACYCLINE CONCENTRATION

19.1 Selection of Sites for PK Studies

PK data will be analyzed using a population PK model. In order to maximize the number of subjects who participate so that this analysis is optimal, during site selection the site's ability to participate in the PK portion of the study will be assessed. Not all sites will participate in the PK portion of the study. To assure the quality and accuracy of the PK samples, samples will be obtained only from subjects participating at a center that has the appropriate facilities and capabilities and has been specifically trained by the sponsor.

19.2 Collection of PK Samples

At selected sites, subjects who have agreed to participate in PK evaluation and have signed a separate PK evaluation consent form will have blood samples collected for PK analysis. PK samples will be collected using a sparse sampling method for the population PK model. The number of samples and collection schedule will vary for individual subjects. The sponsor will notify the site of the PK sample collection schedule for the individual subject. Up to 4 blood samples will be collected per subject between Days 2 and 3 (see [Section 8](#)).

The sponsor will provide heparin tubes for the collection of PK blood samples and will provide freezer tubes for storing the plasma. Blood will be collected either by fresh venipuncture or via a cannula used SOLELY for that purpose.

The dates and times for all doses of test article and PK sample collections will be recorded. The identification of the subject, sample number and the time of the sample collection to the nearest minute should be immediately recorded on the tube. The tube will be centrifuged at $1500 \times g$ for 10 minutes; the separated plasma transferred in 2 equal aliquots into pre-labeled tubes; and the tubes frozen at -20°C or colder within 60 minutes of collection. The time the sample is frozen should be recorded to the nearest minute.

19.3 Storing and Shipping of PK Samples

After all of the PK samples from a single subject have been collected and frozen at -20°C or colder, 1 sample from each time point can be batched together with corresponding complete sample sets from other subjects and be carefully packaged and shipped frozen at -20°C or colder to the Central Laboratory. Samples are to be shipped with sufficient dry ice to remain frozen during transit (up to a possible 4 day period). The Central Laboratory will process these samples and forward them at -20°C or colder to the Analytical Laboratory designated by the sponsor. For each subject and time point, the remaining stored aliquots will be retained on-site at -20°C or colder until released or requested by the sponsor.

19.4 Analysis of PK samples

The Analytical Laboratory will assay the samples for omadacycline using a specific, sensitive and validated Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) method approved by the sponsor.

20 OTHER BIOMARKERS

None.

21 SAFETY MONITORING

21.1 Definitions

21.1.1 Adverse Events

An AE is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or in a clinical study. The event does not need to be causally related to the test article or clinical study. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose of a test article, whether accidental or intentional. Overdose is a dose greater than that specified in the protocol.
- An AE occurring from abuse (eg, use for nonclinical reasons) of a test article
- An AE that has been associated with the discontinuation of the use of a test article

21.1.2 Serious Adverse Events

A SAE is an AE that:

- Results in death
- Is life-threatening (see below)
- Requires hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any one (1) of the outcomes listed above in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

21.1.3 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Pregnancy exposure to a test article: If a pregnancy is confirmed, use of the test article must be discontinued immediately. Information about pregnancy exposure includes the entire course of pregnancy and delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered other reportable information. For exposure involving the female partner of a male subject, the necessary information must be collected from the subject, while respecting the confidentiality of the partner.
- Lactation exposure to a test article with or without an AE
- Overdose of a test article as specified in this protocol with or without an AE
- Inadvertent or accidental exposure to a test article with or without an AE

21.1.4 Overdose

Any administration of omadacycline of greater than 900 mg within a 24 hour period will be an overdose, regardless of whether the overdose is intentional or accidental, it is a reportable event and the sponsor must be notified within 1 business day. Any administration of greater than 3000 mg of linezolid within a 24 hour period will be an overdose. In the event that a study subject takes an overdose of test article, the investigator may obtain the subject's treatment assignment by contacting the IxRS. IxRS will also provide a confirmation report of the drug assignment to site personnel. The site personnel will retain this confirmation report.

The physician managing the overdose may order any test he/she thinks is necessary to manage the subject properly.

21.1.5 Medication Errors

Medication errors are the result of administration or consumption of the wrong product, by the wrong subject, at the wrong time, and/or by the wrong administration route, due to human error.

Medication errors include, but are not limited to, the following:

- The administration and/or consumption of test article that has not been assigned to the subject
- Administration of expired test article

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE Report Form. All other medication errors will be reported by faxing or e-mailing the Clinical Test Article Error Incident Report Form as indicated in the Emergency Contacts (see [Section 2](#)).

21.2 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the ICF to the time of the Final Follow-up assessment. The investigator must instruct the subject to report AEs and SAEs during this time period. Reports of death within 30 days after the last contact with the subject will be reported to the sponsor and additional information relative to the cause of death will be sought and documented.

All AEs and SAEs must be recorded on source documents. All AEs and SAEs for subjects who receive a treatment assignment will be recorded in the eCRFs.

The investigator must follow-up as medically necessary on all AEs and SAEs until the events have subsided, the condition has returned to Baseline, or in case of permanent impairment, until the condition stabilizes.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the subject. In addition to the information obtained from those sources, the subject should be asked the following nonspecific question: "How have you been feeling since your last visit?" Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded using standard medical terminology.

If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.

Death should be recorded in the eCRF as an outcome of an AE. Any unanticipated risks to the subjects must be reported promptly to the IRB/IEC/REB.

21.2.1 Serious Adverse Event Reporting

All SAEs and follow-up information must be reported within 1 business day or 24 hours as required by local regulations by faxing a completed SAE Report Form to the fax number below or e-mailing a completed SAE Report Form to the email address below.

Serious Adverse Event (SAE) contact information:

E-Mail: [REDACTED]

Fax: [REDACTED]

21.2.2 Assessment of Relatedness

The investigator will assess causality (ie, whether there is a reasonable possibility that test article caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Not related: This relationship suggests that there is no association between test article and the reported event. The event can be explained by other factors such as an underlying medical

condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between test article and the event.

- Related: This relationship suggests that a definite causal relationship exists between test article administration and the AE, or there is a reasonable possibility that the event was caused by the study medication, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

AEs and SAEs also will be assessed for their potential relationship to the protocol. A protocol-related adverse event is one that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol.

21.2.3 Assessment of Severity

The severity (or intensity) of an AE will be classified using the following criteria:

- Mild: These events are usually transient, require minimal or no treatment, and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning but pose no significant or permanent risk of harm.
- Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented as a new event to allow an assessment of the duration of the event at each level of intensity to be performed.

21.2.4 Laboratory Findings

Protocol-defined safety laboratory test results will be analyzed as part of specific laboratory safety analyses. Additional laboratory test results at other time points may be available to the investigator as part of standard clinical practice. Throughout the study, laboratory-related abnormalities should be recorded as AEs only if considered clinically significant, outside the range of expected values given the subject's baseline assessments and clinical course, and not known to be part of another AE diagnosis.

21.2.5 Worsening or Progression of Qualifying ABSSSI

The skin infection that qualified the subject for entry in the study ("qualifying ABSSSI") is unique because data regarding the progress of this infection are being captured as part of efficacy analyses. Therefore, worsening or progression of the qualifying ABSSSI should be recorded as a clinical failure (as part of the efficacy assessment), rather than an AE, unless the worsening/progression also meets the criteria for a serious AE (in which case the event also should be reported as an SAE). In contrast, any new or secondary infections that the investigator

considers to be distinct from the qualifying ABSSEI (eg, a secondary skin abscesses in a different anatomical location) should be reported as AEs in all cases, whether non-serious or serious.

21.2.6 Pregnancies

To ensure subject safety, each pregnancy in a subject on test article must be reported to the sponsor within 1 business day of learning of its occurrence. Test article should be discontinued immediately and the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the test article of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

22 DATA ANALYSIS

All analyses of data for this study will comply with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-E9) and the sponsor's guidance documents and standards. Statistical analyses will be performed using Statistical Analysis Software (SAS).

A SAP incorporating the sections below and with mock table, figure and listing (TFL) shells will be prepared prior to the start of the study and approved and finalized by the sponsor prior to database lock. This plan will define populations for analysis, outline all data handling conventions and specify statistical methods to be used for analysis of safety and efficacy. As a consequence of differing regulatory requirements for the choice of the primary efficacy outcome and statistical analyses, 2 separate SAPs will be prepared (FDA and EMA). The sections below indicate the overall structure and approach of the analyses.

Inferential statistical analyses of the primary and secondary outcomes will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations (SD), medians, minimums, and maximums for continuous variables will be provided. All comparisons will be for omadacycline versus linezolid. Exploratory analyses may also be performed. Listings of individual subject's data will be produced.

22.1 Analysis Populations

A number of subject analysis populations have been defined for the various analyses of efficacy and safety, as follows:

- The intent-to-treat (ITT) population will consist of all randomized subjects.

- The modified intent-to-treat (mITT) population will consist of all randomized subjects without a sole Gram-negative causative pathogen(s) at Screening.
- The clinically evaluable (CE) population will consist of all mITT subjects who received test article, have a qualifying ABSSSI, an assessment of outcome, and meet all other evaluability criteria detailed in the SAP.
- The microbiological modified intent-to-treat (micro-mITT) population will consist of subjects in the mITT population who have at least 1 Gram-positive causative pathogen(s) at Screening.
- The microbiologically evaluable (ME) population will include subjects in the CE population who have at least 1 Gram-positive causative pathogen(s) at Screening.
- The safety population will consist of all randomized subjects who receive test article.

22.2 Subject Demographics and Other Baseline Characteristics

Descriptive statistics, by treatment arm, will be provided for the following:

- Subject disposition:
 - completed test article
 - discontinued test article by reason for discontinuation
 - completed study
 - discontinued study by reason for discontinuation
- Protocol deviations
- ABSSSI background information
 - Subject demographics: age (years), gender, race/ethnicity, height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2)
 - Description and location of the primary site of the ABSSSI
 - type of infection
 - site of infection
 - area (length \times width) of the lesion
 - presence of systemic signs of infection
 - severity of clinical signs and symptoms
 - culture source and type of specimen by specified Baseline pathogens isolated either from the ABSSSI site or from blood samples
 - Surgical procedures
- Medical histories and continuing medical conditions

Screening demographic and medical variables will be analyzed using a 2-sided Fisher's exact test (for categorical variables) or a 2-sided Wilcoxon Rank Sum test (for ordinal and continuous variables).

22.3 Treatments (Test Article, Rescue Medication, Other Concomitant Therapies, Compliance)

A listing will be provided that indicates the subject's date and time of randomization, randomized treatment assignment, randomized infection type and receipt of allowed antibacterial therapy in the 72 hours prior to randomization stratum.

The tablet count taken will be presented.

The total number of days on study therapy will also be provided by treatment group.

Prior medications, concomitant medications, separately for antibiotics and non-antibiotics will be summarized. For prior and concomitant antibiotics the reason for receipt will be provided.

22.4 Primary Efficacy Analysis

For all efficacy analyses, subject data will be analyzed in the group to which the subject was randomized. For the primary analyses for both the FDA and EMA, subjects will be analyzed in the stratum to which they were randomized (see [Section 25.1](#)).

22.4.1 Early Clinical Response Efficacy Variable

The Early Clinical Response can be Clinical Success, Clinical Failure and Indeterminate (defined in [Section 17.4.1](#)).

An Indeterminate Response is included in the denominator for the calculation of the percentage of subjects with a Clinical Success in the mITT population and thus, is essentially considered as a Clinical Failure for the purpose of the primary analysis for the FDA.

22.4.2 Investigator's Assessment of Clinical Response at PTE Efficacy Variable

This is defined as Investigator's Assessment of Clinical Response at the PTE visit with outcomes of Clinical Success, Clinical Failure and Indeterminate (defined in [Section 17.4.3](#)) in the mITT population and Clinical Success and Clinical Failure in the CE population. Subjects with a response of Clinical Failure at EOT will be defined as a Clinical Failure at PTE. An Indeterminate Response is included in the denominator for the calculation of the percentage of subjects with a Clinical Success in the mITT population and thus, is essentially considered a Clinical Failure for the purpose of the primary analysis for the EMA.

22.4.3 Statistical Model, Hypothesis, and Method of Analysis

To demonstrate the efficacy of omadacycline is non-inferior to linezolid in the treatment of adult subjects with ABSSSI, the following hypothesis will be evaluated by analysis of the Clinical Success rates.

The null hypothesis and alternate hypothesis for the Early Clinical Response endpoint will be assessed in the mITT population as follows:

$$H_0: \theta_T - \theta_C \leq -\Delta$$

$$H_{ai}: \theta_T - \theta_C > -\Delta$$

Where the clinical success rate for the omadacycline regimen is θ_T and for linezolid is θ_C

Δ is the non-inferiority (NI) margin and is 0.10.

Similar null and alternative hypotheses can be set up with Δ of 0.10 for the PTE endpoint. For the Early Clinical Response (FDA) endpoint, a 2-sided 95% confidence interval (CI) approach for the difference of clinical success rates (using the point estimate of the difference: omadacycline response proportion minus linezolid response proportion) will be used to test for the NI of the omadacycline arm compared to the linezolid arm in the mITT population. The 95% CI will be calculated using the unstratified method proposed by Miettinen and Nurminen.⁹ Omadacycline will be considered non-inferior to linezolid if the lower bound of the CI is greater than -0.10.

For Investigator's Assessment of Clinical Response at PTE (EMA) primary efficacy analyses in both the mITT and CE populations, a 2-sided 95% CI approach for the difference of clinical success rates (using the point estimate of the difference: omadacycline response proportion minus linezolid response proportion) will be used to test for the NI of the omadacycline arm compared to the linezolid arm. The 95% CI will be calculated using the stratified (for the randomization stratification factors) method proposed by Miettinen and Nurminen.⁹ Omadacycline will be considered non-inferior to linezolid if the lower bound of the CI is greater than -0.10.

Early Clinical Response and Investigator's Assessment of Clinical Response at PTE will be tested separately and are not co-primary endpoints. The probability for approving an ineffective drug based on PTE efficacy is 2.5%, regardless of the result for the Early Clinical Response endpoint and vice versa. An adjustment would only be required if winning on at least 1 endpoint would result in global approval which is not the case here. In addition, no alpha adjustment is needed for the co-primary efficacy endpoints for the EMA (mITT and CE populations) since NI must be shown in both populations to conclude NI. Hence there will be no adjustment for multiple endpoints.

22.4.4 Additional Analyses of the Primary Efficacy Outcomes

Additional and sensitivity analyses of the primary efficacy outcomes (Early Clinical Response and Investigator's Assessment of Clinical Response at PTE) will be performed. Analyses for the FDA primary efficacy outcome will be described here and in more detail in the SAP. Analyses for the EMA primary efficacy outcome will be described in the SAP.

If the null hypothesis of inferiority is rejected for the Early Clinical Response in the mITT population and the observed success response proportion for omadacycline is larger than the observed proportion for linezolid, a formal statistical analysis of superiority will be conducted. If the lower limit of the 2-sided 95% CI for the treatment difference is greater than 0%, omadacycline will be considered superior to linezolid.

The primary efficacy outcome will be assessed separately across the stratification factors of type of infection and receipt of allowed antibacterial therapy in the 72 hours prior to randomization stratum by treatment group. For each type of infection stratum and each prior antibacterial therapy stratum, a 2-sided 95% CI for the observed difference in Early Clinical Response rates will be calculated for the mITT population. Additional subgroup analyses of the primary efficacy outcome may be conducted as descriptive analyses.

Sensitivity analyses include: conducting an adjusted analysis of the primary efficacy outcome based on the randomized stratum and separately, based on the stratum the subject actually belongs, and conducting an analysis where all subjects with an Indeterminate response are considered Clinical Successes.

22.5 Analysis of Secondary Variables

Analyses for the FDA secondary outcomes will be described here and in more detail in the SAP. Analyses for the EMA secondary outcomes will be described in the SAP. The number and percentage of subjects classified as a Clinical Success, Clinical Failure and Indeterminate by the Investigator's Assessment at PTE in the mITT and CE populations (by definition subjects with an Indeterminate response are excluded from the CE population) will be calculated for each treatment group. A 2-sided unadjusted 95% CI will be constructed for the observed difference in the clinical success rate using the method of Miettinen and Nurminen.⁹ For Investigator's Assessment of Clinical Response at PTE in the mITT and CE populations the 2-sided 95% CI is for descriptive purposes only and no conclusion of NI will be made.

The number and percentage of subjects in each treatment group in each response category for Early Clinical Response will be presented for the micro-mITT population. The number and percentage of subjects who are classified as a Clinical Success and Clinical Failure by the investigator at the PTE visit in the ME population will be calculated. Two-sided unadjusted 95% CI will be constructed for the observed difference in the clinical success rates using the method of Miettinen and Nurminen.⁹

The number and percentage of subjects with an Early Clinical Response of success and an Investigator's Assessment of Clinical Response at PTE of Clinical Success by pathogen (including Gram-negative causative pathogens and MRSA) will be provided in the micro-mITT and ME populations.

22.6 Analysis of Additional Efficacy Variables

Additional efficacy analyses will be conducted to support the efficacy findings of the primary and secondary outcomes. CIs will be determined for descriptive purposes, but no conclusions of NI will be made.

The number and percentage of subjects classified as an Early Clinical Success, Clinical Failure and Indeterminate at 48 to 72 hours after the first dose of test article in the ITT population will be calculated. A 2-sided unadjusted 95% CI will be constructed for the observed difference in the Clinical Success rate using the method of Miettinen and Nurminen.⁹

The number and percentage of subjects classified as a Clinical Success, Clinical Failure and Indeterminate by the Investigator's Assessment at EOT in the mITT and CE populations (by definition subjects with an Indeterminate response are excluded from the CE population) will be calculated for each treatment group. A 2-sided unadjusted 95% CI will be constructed for the observed difference in the clinical success rate using the method of Miettinen and Nurminen.⁹

Descriptive summaries, including change from baseline where appropriate, of the clinical signs and symptoms (tenderness, edema, erythema, induration and drainage), complete resolution of the clinical signs and symptoms, temperature, ABSSSI lesion measurements (including absolute and percentage reduction in lesion area, eg, 0 to < 5%, 5 to < 10%, 10 to < 20%, ≥ 20%, etc., as detailed in the SAP), and systemic signs by study visit will be presented.

All-cause mortality (ACM) at 15 and 30 days after the first dose of test article will be summarized in the ITT population. Subjects who are lost to follow-up will be considered deceased for this analysis. A 2-sided unadjusted 95% CI for the observed difference in mortality rates will be calculated for ACM.

The per-subject and per-pathogen microbiologic outcomes will be provided for the micro-mITT and ME populations at the EOT and PTE visits. Two-sided unadjusted 95% CIs will be provided for the difference in per-subject microbiological favorable outcome rates.

A concordance analysis of Early Clinical Response and Investigator's Assessment of Clinical Response at PTE in the mITT analysis set will also be presented.

22.7 Safety Outcome Measures

Safety variables include the incidence rate of AEs, change in vital signs, ECG parameters and laboratory test results obtained during the course of the study. For safety analyses for both the FDA and EMA, subjects will be analyzed according to the treatment actually received.

22.7.1 Adverse Events

Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A TEAE is defined as an AE with a start date and time on or after the first dose of test article. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by presenting the number and percentage of subjects having each TEAE for each treatment group by system organ class (SOC) and preferred term (PT). Additional tabulations will provide summaries by SOC and PT of subjects experiencing SAEs, severe TEAEs, TEAEs judged to be related to test article, TEAEs leading to discontinuation of test article, and TEAEs of special interest.

22.7.2 Vital Signs

The following variables will be analyzed descriptively:

- Vital signs (systolic and diastolic BP, pulse rate, body temperature, respiratory rate), including change from Screening by visit

- Clinically notable vital signs (meeting predefined criteria as specified in the SAP) by visit

Subjects with notable vital signs data will be listed.

22.7.3 Electrocardiograms

ECG data (RR interval, PR interval, QRS interval, QTc, QTc Bazett's Correction Formula [QTcB], and QTc Fridericia's Correction Formula [QTcF]) will be summarized descriptively at each scheduled evaluation, as noted in [Section 8](#), and for the overall worst post-Screening value. Changes from Screening at each visit that a 12-lead ECG is obtained will also be provided. An outlier analysis will be conducted based on the worst post-Screening value.

22.7.4 Laboratory Tests

The following variables will be analyzed descriptively:

- Laboratory variables by visit
- Change from Screening of laboratory variables by visit
- Clinically notable laboratory values (meeting predefined criteria specified in the SAP) by visit

Listings of individual subject laboratory data will be generated. Values meeting predefined criteria for being clinically notable will be flagged within the listings.

22.8 Resource Utilization

The following are the variables relating to resource utilization. Data for resource utilization will be collected through the Final Follow-up visit.

- Hospitalizations including number of days hospitalized
- number of emergency room visits

Descriptive statistics for the resource utilization parameters will be provided by treatment group for the purpose of health economic evaluation.

22.9 Pharmacokinetics

Population PK analysis will be conducted to characterize PK parameters. A population PK data set including subjects with 1 or more quantified omadacycline concentration determinations will be constructed from the dates and times of the doses and blood samples along with all the bioanalytical determinations and subject background information. If the actual date or time for a blood sample or dose is missing, the related bioanalytical determination of the PK concentration will be excluded from all analyses. Omadacycline concentrations below the limit of quantification will be treated as missing data in summary statistics and for the calculation of PK parameters.

Variables including age (years), body weight (kg), gender, and race/ethnicity along with other covariates previously determined to be important will be incorporated into the population PK database. Based on the subjects in the population analysis data set, descriptive summaries at Screening for these variables will be reported. Outliers may be excluded from the analysis. These will be determined by a scatter plot of the observed concentration versus time post dose reported. The distribution of the number of samples contributed per subject to the model-based analysis will be tabulated. Also, simple summary descriptive statistics for the concentration of samples by study day or week will be computed.

22.9.1 Population PK Modeling

Results from Phase 1 studies indicate that omadacycline PK is linear and that following intravenous infusion, plasma concentration-time profiles show a 3-compartmental disposition. Therefore, the probable structural PK model would be a 3-compartment model with zero order input for iv infusion and first order input for po administration. This PK model contains the parameters clearance, volume of distribution, bioavailability and absorption rate constant. The associated population models are nonlinear mixed-effects models. The population model adds random effects and covariates for the PK parameters in order to recognize differences among individuals and similarities across observations corresponding to the same subject. At the time of the population modeling, previously reported structural PK models will be considered first. A residual error model combining additive error and proportional error will also be initially considered. Simplifications (eg, fewer random affects or an alternative residual error model) may be appropriate if the diagnostics for the model suggest false convergence. Additional covariates will be investigated graphically (gender, race/ethnicity, age) as part of the model diagnostics and some may be retained in the final model and additional ones in a competing model to deliver estimates of arguably insignificant effects. Scatter plots of the observed concentrations versus population-estimated and individually estimated concentrations will be used as part of the overall assessment of the overall quality of the fit. During modeling, the broad principles outlined by the FDA¹⁰ will be followed.

The individual model-based exposure measures at steady state (area under the curve $[AUC]_{0-24,ss}$, time to maximum plasma concentration $[T_{max,ss}]$, maximum plasma concentration $[C_{max,ss}]$) will be computed and summarized.

22.10 Pharmacogenetics/Pharmacogenomics

Pharmacogenetics/pharmacogenomics studies are not planned as part of this protocol.

22.11 Biomarkers

Not applicable.

22.12 PK/PD

The relationship between omadacycline exposure and response (efficacy and safety) will be examined as appropriate for the data. A population PK model will be used to calculate individual subject AUCs and, subsequently, possible AUC/MIC breakpoints.

22.13 Sample Size Calculation

The study is designed to show NI in the primary efficacy outcome of Early Clinical Response at 48 to 72 hours following the first dose of test article in the mITT population. An NI margin of 10% will be used for the analysis in the mITT population. The NI margin was based on an analysis of the historical data regarding the treatment effect of antibiotics in ABSSSI.

In the po study of tedizolid versus linezolid, the rates of Early Clinical Response were 79% in both treatment arms in the ITT population.¹¹ Thus, an outcome rate of 79% in the mITT population was used for determination of the sample size. For the Early Clinical Response primary efficacy endpoint, assuming an outcome rate of 79% for both treatment groups, NI margin of 10%, 90% power and a 1-sided alpha of 0.025, using the sample size determination method of Farrington and Manning,¹² a total of 704 subjects are required.

The rates of clinical success based on the Investigator’s Assessment at PTE were 86% in the ITT population and 95% in the CE population for linezolid, in the recent po clinical study in ABSSSI subjects.¹¹ To be conservative, outcome rates of 85% in the mITT and 90% in the CE population are used for the sample size determination. Assuming an 85% outcome rate in both treatment groups, NI margin of 10%, and a 1-sided alpha of 0.025, with a total of 704 subjects, there is more than 90% power to show NI for Investigator’s Assessment of Clinical Response at PTE in the mITT population. With an evaluability rate of 80%, there will be 564 subjects in the CE population. Assuming a 90% outcome rate in both treatment groups, NI margin of 10% and a 1-sided alpha of 0.025, 564 subjects provides more than 90% power to show NI in the CE population.

Thus, a total of 704 subjects provide sufficient power for the primary efficacy analyses for both the FDA and EMA regulatory authorities. A summary of the sample size calculations and assumptions is provided in Table 6.

Table 6. Sample Size and Power Calculations

	Primary Efficacy Outcome FDA (Early Clinical Response)	Primary Efficacy Outcome EMA (Investigator’s Assessment of Clinical Response at PTE)	
Population	mITT	mITT	CE
N	704	704	564
Outcome Rate	79%	85%	90%
Evaluability Rate	N/A	N/A	80%
Power	90%	96%	97%

CE = clinically evaluable; EMA = European Medicines Agency; FDA = United States Food and Drug Administration; mITT = modified intent-to-treat; N = number; N/A = not applicable; PTE = post therapy evaluation.

22.14 Interim Analyses

No interim analyses of efficacy are planned.

22.15 Handling of Missing Values/Censoring/Discontinuations

Missing values will not be imputed for primary and secondary efficacy and safety analyses (except as detailed in the SAP for missing dates) and only observed values will be used in data analyses and presentations. For the primary efficacy outcome measure, if any data field needed to determine the response is missing the subject will be assigned an Indeterminate response. For analyses of the primary efficacy outcome, subjects with an Indeterminate response are included in the denominator, and thus, are considered Clinical Failures. A sensitivity analysis of the primary efficacy outcome will be conducted in which subjects with an Indeterminate response are considered Clinical Successes.

For the secondary outcome measure of Investigator's Assessment of Clinical Response at PTE in the mITT population (co-primary for the EMA analysis), subjects with missing data are assigned an Indeterminate response. Subjects with an Indeterminate response are included in the denominator, and thus, are considered failures. Table 7 provides a summary of the handling of missing/indeterminate outcomes for the Investigator's Assessment of Clinical Response at PTE.

Table 7. Investigator's Assessment of Clinical Response at PTE Determination Considering Missing Data

EOT Visit	PTE Visit	Overall Assessment of Clinical Response at PTE (Investigator's Assessment)
Missing/indeterminate	Success	Indeterminate
Missing/indeterminate	Failure	Failure
Missing/indeterminate	Missing/indeterminate	Indeterminate
Success	Missing/indeterminate	Indeterminate
Failure	Missing/indeterminate	Failure

EOT = end of treatment; mITT = modified intent-to-treat population; PTE = post therapy evaluation.

For the analysis in the mITT analysis set of Investigator's Assessment of Clinical Response at PTE, indeterminate responses are included in the denominator and are thus considered clinical failures.

Missing data are handled in a similar manner for the outcome of microbiological response at PTE.

23 SUBJECT IDENTIFICATION

Each subject in the study is assigned a unique subject number and must keep that number throughout the study even if he/she transfers to another site. A subject who discontinues participation or is withdrawn before receiving a treatment assignment code, and who re-enrolls at a later time will be assigned a new subject number and recorded as rescreened. The investigator must maintain a subject master log of all subjects.

24 TEST ARTICLE ACCOUNTABILITY, RECONCILIATION, AND RETURN

The investigator must maintain a complete and current dispensing and inventory record that has been supplied by the sponsor.

All unused test articles must be returned in the original containers or destroyed at the site with approval of the sponsor. Test articles can only be returned or destroyed after the sponsor has performed accountability. Test article return/destruction must be documented.

24.1 Supply, Storage and Tracking of Test Article

Test article must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Upon receipt, the test article should be stored according to the instructions specified on the drug labels. Storage conditions must be adequately monitored and appropriate temperature logs maintained as source data.

The designated study personnel must maintain an accurate record of the shipment and dispensing of test articles in the study specific medication accountability ledger. Test article supplies are completely blinded. Monitoring of oral medication accountability will be performed by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused test article and packaging at each visit and at the end of the study, last study visit or at the time of test article discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, with instruction from the sponsor, the designated study personnel will destroy on site or return all unused test articles, packaging, drug labels, and send a copy of the completed medication accountability ledger to the monitor or to the address provided to the investigator.

25 RANDOMIZATION AND BLINDING

25.1 Treatment Assignment

All eligible subjects will be randomized via an IxRS that assigns them to 1 of the treatment arms (in a 1:1 ratio). The site delegate will contact the IxRS (via phone or web) after confirming that the subject fulfills all the inclusion criteria and none of the exclusion criteria. The IxRS will assign a test article to the subject based on a computer-generated randomization schedule. The randomization will be a blocked randomization sequence stratified by type of infection (wound infection, cellulitis/erysipelas or major abscess) and receipt of an allowed antibacterial therapy (see [Appendix 1](#)) in the 72 hours prior to randomization as defined in the IxRS specifications and SAP. Subjects randomized into the study will be assigned the treatment corresponding to the next available number in the respective stratum of the computer-generated randomization schedule. The subject is considered randomized when the IxRS provides the test article assignment, regardless of whether the subject actually receives any medication. Enrollment of subjects with major abscess will be capped at 30% of the subjects randomized. Enrollment of subjects who have received an allowed antibacterial therapy in the 72 hours prior to randomization will be capped at 25% of the subjects randomized.

25.2 Dispensing the Test Article

Each study site will be supplied by the sponsor with the investigational product and comparator. Test articles will be supplied to the sites in kits that contain active omadacycline tablets or matched placebo tablets, and active linezolid over-encapsulated tablets or matched placebo over-encapsulated tablets. Oral test article supplies are completely blinded and blinded study personnel can conduct storage, dispensation, and reconciliation. The IxRS will instruct the designated study personnel as to the appropriate test article kit to be administered. The study coordinator/staff will instruct the subject on the use of po test article.

25.3 Treatment Blinding

The investigator and sponsor will be blinded to treatment arm assignments throughout the study. The sponsor designee (eg, study statistical team, IxRS vendor, etc.) will have a designated randomization administrator who will maintain the randomization codes in accordance with standard operating procedures to ensure the blind is properly maintained, and that only sponsor personnel who require knowledge of treatment assignments will be unblinded (eg, staff involved in maintaining the randomization codes or SAE reporting).

The study will follow a double-dummy design. Subjects assigned to omadacycline will receive active omadacycline tablets and over-encapsulated linezolid placebo tablets. Subjects assigned to the linezolid arm will receive omadacycline placebo tablets and over-encapsulated active linezolid tablets.

Randomization data are kept strictly confidential until the time of database lock and unblinding at the end of the study.

All eCRFs must be completed, entered and checked; all safety laboratory results must have been reported; all AEs must have been fully characterized (eg, relationship to test article determined) and coded; and all queries must have been resolved prior to database lock and unblinding. Determination of inclusion in the analysis populations, characterization of protocol deviations as major/minor and final approval of the SAP will also be completed prior to database lock.

Plasma samples for subjects receiving omadacycline may be analyzed during the course of the study. To permit the sponsor to review the drug concentration data prior to locking the dataset and without unblinding, any PK data provided prior to unblinding will be re-coded by the bioanalytic laboratory to avoid revealing the individual subject numbers.

Unblinding is only to occur in the case of subject emergencies (see Section 25.4) and at the conclusion of the study.

25.4 Emergency Unblinding of Treatment Assignment

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, test article discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. It is encouraged for the investigator, when contemplating unblinding, to contact the

sponsor or sponsor's designated Medical Monitor or designee to confirm the need to unblind, prior to unblinding. However, if required, the investigator can unblind without consulting the Medical Monitor.

Emergency code breaks are performed using the IxRS. When the investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax or e-mail confirming that the treatment assignment of the subject was unblinded. The system will automatically inform the sponsor's monitor for the site and the sponsor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IxRS code break information in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, test article name if available, subject number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case emergency unblinding is required at a time when the investigator and backup are unavailable.

In the event of a medical emergency in which the investigator judges that the subject cannot be managed safely without unblinding, the investigator may obtain the treatment allocation directly from the research pharmacist. All steps outlined above will be followed, including contacting the Medical Monitor as soon as possible and not more than 24 hours afterwards. It will be the responsibility of all study personnel to ensure that, except for the above procedure, investigator blinding is maintained until after study completion.

26 SUBJECT DISCONTINUATION OR WITHDRAWAL

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to, AE, subject request, protocol violation, subject noncompliance, and study termination by the sponsor. Subjects may voluntarily withdraw from the study for any reason at any time. Subjects are considered withdrawn from the study if they state an intention to withdraw, or fail to return for visits, or become lost to follow-up for any other reason. If premature withdrawal from the study occurs for any reason, the investigator should determine the primary reason for a subject's premature withdrawal from the study and record this information on the eCRF.

Subjects who discontinue study treatment (unless that subject withdraws informed consent) should NOT be considered withdrawn from the study. The date and primary reason for discontinuation of study treatment should be recorded in source documents. Subjects who discontinue the study treatment should have the EOT visit and the procedures listed for that visit in [Section 8](#), a PTE visit and a Final Follow-up Assessment, if possible. The site should also collect subject safety information through the Final Follow-up assessment.

Site personnel should also contact the IxRS to register the subject's discontinuation from test article.

For subjects who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

27 STUDY SUSPENSION, TERMINATION, AND COMPLETION

27.1 Study Completion and Post-Study Test Article

A subject will have successfully completed the study after the planned test article regimen has been administered, and all assessments and visits have been made. Visits include the final follow-up visit (Final Follow-up). The study will be completed when the last subject has either discontinued or completed the Final Follow-up visit.

No long-term follow-up of subjects is planned, with the exception of pregnancies, as described in [Section 21.2.6](#), and SAEs described in [Section 21.2](#).

Sites will be notified by either the Sponsor or IxRS to stop enrollment when the desired number of treated subjects have been enrolled. Subjects already consented will be allowed to continue in the study.

Upon study completion, the investigator will provide the sponsor, IRB/IEC/REB, and regulatory agency with final reports and summaries as required by regulations. The investigator must submit a written report to the sponsor and the IRB/IEC/REB within 3 months after the completion or termination of the study.

27.2 Study Suspension or Termination

The sponsor may suspend or terminate the study or part of the study at any time for any reason. Should this be necessary, subjects should be seen as soon as possible and treated as described in [Section 26](#) for prematurely withdrawn subjects. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) of the early termination of the study.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC/REB and provide them with a detailed written explanation. Subjects should be seen as soon as possible and treated as described in [Section 26](#) for prematurely withdrawn subjects. The investigator will also return all test articles, containers, and other study materials to the sponsor.

28 ETHICAL CONSIDERATIONS

28.1 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, United States [US] Code of Federal Regulations [CFR] Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

28.2 Informed Consent Procedures

The investigator will provide for the protection of the subjects by following all applicable regulations. These regulations are available upon request from the sponsor. The ICF must be reviewed by the sponsor and approved by the IRB/IEC/REB.

Before any procedures specified in the protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC/REB approved ICF

28.3 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and ICF have been approved by the IRB/IEC/REB must be given to the sponsor before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol, and to give access to all relevant data and records to the sponsor monitors, auditors, designated agents of the sponsor, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

29 PROTOCOL ADHERENCE

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact the sponsor or its agents to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the sponsor and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report (CSR).

29.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for subject safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

30 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the case report forms (CRFs) and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor monitors the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, information recorded in the CRFs is verified against source documents.

31 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

31.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the eCRFs.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

An updated form 1572 will be filed with the sponsor for any changes in the study personnel reported in the current form 1572.

31.2 Sponsor

The data is entered into an electronic database via eCRFs. The Sponsor Medical Monitor reviews the data for safety information. The data is reviewed for completeness and logical consistency. Automated validation checks identify missing data, out-of-range data, and other data inconsistencies. The central safety and microbiology data will be processed electronically. Requests for data clarification are forwarded to the investigative site for resolution.

32 SUBJECT INJURY

In general, subject to specific provisions in the clinical study agreement (CSA), if a subject is injured as a direct result of a test article, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

33 PRESTUDY DOCUMENTATION

The investigator must provide the sponsor with the following documents BEFORE enrolling any subjects:

- Completed and signed form 1572
- All applicable country-specific regulatory forms
- Current signed and dated curricula vitae for the investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the form 1572 or equivalent, or the clinical study information form
- Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC/REB. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor.
- Copy of the IRB/IEC/REB-approved informed consent document to be used
- Where applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure
- Copy of the protocol sign-off page signed by the investigator
- Fully executed CSA
- Where applicable, a financial disclosure form
- A written document containing the name, location, certification number, and date of certification of the laboratories to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor must be notified if normal values or units of measurement change.

34 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (a) 2 years after the last marketing authorization for the investigational test article has been approved or the sponsor has discontinued its research with respect to such investigational test article or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of its intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

35 PUBLICATION POLICY

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Upon completion of the study, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and Principal Investigator (PI) shall not publish or present data from an individual study center until the complete multi-center study has been presented in full or for 2 years after the termination of the multi-center study, whichever occurs first. Subsequent publications must refer to the multi-center findings. Thereafter, if the PI expects to participate in the publication of data generated from this site, the institution and PI shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including, without limitation, the deletion of confidential information. The PI shall act in good faith upon requested revisions, except that the PI shall delete any confidential information from such proposed publication. The PI shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

36 REFERENCES (AVAILABLE UPON REQUEST)

1. David MZ, Daum RS. 2010. Community-Acquired Methicillin-Resistant Staphylococcus aureus: Epidemiology and Clinical Consequences of an Emerging Epidemic. Clin. Microbiol. Rev. 23(3):616-87.
2. Paratek Pharmaceuticals, Inc. 2016 Omadacycline/PTK 0796 Investigator's Brochure, Edition 9.0.
3. FDA. 2013. Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. CDER.
4. EMA. 2011. Guideline on the evaluation of medical products indicated for treatment of bacterial infections. European Medicines Agency. CPMP/EWP/558/95 rev 2.
5. EMA. 2013. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2), European Medicines Agency. EMA/CHMP/351889/2013.]
6. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC. 2014. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. Clin. Infect. Dis. 59:10-52.
7. Talbot GH, Powers JH, Fleming TR, Siuciak JA, Bradley J, Boucher H on behalf of the CABP-ABSSSI Project Team. 2012. Progress on Developing Endpoints for Registrational Clinical Trials of Community-Acquired Bacterial Pneumonia and Acute Bacterial Skin and Skin Structure Infections: Update From the Biomarkers Consortium of the Foundation for the National Institutes of Health. Clin. Infect. Dis. 55:1114-21.
8. McCaffery, M, Beebe, A. 1993. Pain: Clinical Manual for Nursing Practice. Baltimore: V.V. Mosby Company.
9. Miettinen O, Nurminen M. 1985. Comparative Analysis of Two Rates. Statistics in Medicine 4:213-26.
10. FDA. 1999. Guidance for Industry, Population Pharmacokinetics. Center for Drug Evaluation and Research, U.S. Department of Health and Human Services February 1999.
11. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. 2013. Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections: The ESTABLISH-1 Randomized Trial. JAMA. 309:559-69.
12. Farrington CP, Manning G. 1990. Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-zero Risk Difference or Non-unity Relative Risk Statistics in Medicine 9:1447-54.

Appendix 1. Allowed and Disallowed Prior Antibiotics

Allowed Antibiotics (One dose within 72 hours prior to randomization*)	Disallowed Antibiotics
<u>Penicillins</u>	
Amoxicillin	Nafcillin
Amoxicillin-Clavulanate	Oxacillin
Amoxicillin-Sulbactam	Penicillin-G or -V
Ampicillin	Piperacillin
Ampicillin-Sulbactam	Piperacillin-Tazobactam
Dicloxacillin	Ticarcillin-Clavulanate
<u>Cephalosporins</u>	
Cefaclor	Cefpodoxime
Cefadroxil	Cefprozil
Cefazolin	Ceftaroline
Cefdinir	Ceftazidime
Cefepime	Ceftibuten
Cefixime (200 mg)	Cefuroxime
Cefditoren	Cephalexin
Cefotaxime	Loracarbef
<u>Carbapenems</u>	
Doripenem	Ertapenem
Imipenem	
Meropenem	
<u>Glycopeptides</u>	
Televancin	Dalbavancin
Vancomycin	Oritavancin
<u>Fluoroquinolones</u>	
Ciprofloxacin	Levofloxacin
	Moxifloxacin
<u>Macrolides</u>	
Clarithromycin	Azithromycin
Erythromycin	Clarithromycin XL
<u>Tetracyclines</u>	
Doxycycline (100 mg)	Doxycycline (200 mg)
Minocycline	Minocycline Extended Release
	Tigecycline
<u>Oxazolidinones</u>	
	Linezolid
	Tedizolid
<u>Miscellaneous</u>	
Clindamycin	
Metronidazole	
Trimethoprim-sulfamethoxazole/Co-trimoxazole	

*Prior (within 72 hours prior to randomization) administration of potentially effective systemic antibacterial therapy is an exclusion criterion; however, subjects may be eligible for the study despite prior antimicrobial therapy if they received a single dose of a short-acting systemic antibiotic within 72 hours prior to randomization. For the purposes of this protocol, short-acting is defined as having a dosage frequency of more than once a day. If a subject received a prior short-acting systemic antibiotic that is not listed here, the investigator must contact the Medical Monitor to ensure subject eligibility.

Appendix 2. Equations and Conversion Factors

1. Cockcroft-Gault equation to calculate creatinine clearance (CrCL) (relevant to Exclusion Criterion number 8):

$$\frac{(140 - \text{age}[\text{yrs}]) * \text{weight} [\text{kg}] * (Z)}{\text{Cr} [\text{mg/dL}] * 72}$$

Z = 1.0, if Male
Z = 0.85, if Female

2. $\text{mm}^3 = \mu\text{L}$
3. $\text{cc} = \text{mL}$
4. Conversion of immature neutrophils (band) forms in K/ μL or K/mL to % bands (relevant to Inclusion Criterion number 4 and Exclusion Criterion number 11):
[(bands K/ μL)/(total WBC K/ μL)] \times 100 = % bands
Or
[(bands K/mL)/(total WBC K/mL)] \times 100 = % bands