REGIONE DEL VENETO
ULSS7 PEDEMONTANA
Via dei Lotti, n. 40
36061 Bassano del Grappa (VI)
Codice fiscale e partita IVA 00913430245

N. 190 DEL 03/02/2023

DELIBERAZIONE
del

DIRETTORE GENERALE

Nominato con D.P.G.R. n. 26 del 26/02/2021

Assume le funzioni di Direttore Generale dell'Azienda Sanitaria U.L.S.S. n. 7 Pedemontana il Direttore Amministrativo dott.ssa Michela Conte, delegato dal Direttore Generale dott. Carlo Bramezza come da delibera n. 408 del 12/3/2021

Coadiuvato dai sigg.:

DIRETTORE AMMINISTRATIVO	dott.ssa MICHELA CONTE
DIRETTORE SANITARIO	dr. ANTONIO DI CAPRIO
DIRETTORE DEI SERVIZI SOCIO – SANITARI	dott.ssa ALESSANDRA CORO'

OGGETTO: AUTORIZZAZIONE ALL'ESECUZIONE DELLO STUDIO CLINICO FOR PROFIT "UNO STUDIO DI FASE 3, MULTICENTRICO, RANDOMIZZATO, IN DOPPIO CIECO PER VALUTARE LA SICUREZZA E L'EFFICACIA DI CONTEZOLID ACEFOSAMIL E CONTEZOLID RISPETTO AL LINEZOLID SOMMINISTRATO PER VIA ENDOVENOSA E ORALE AD ADULTI CON INFEZIONI DEL PIEDE DIABETICO MODERATE O GRAVI" (MRXC -302) E APPROVAZIONE CONTRATTO.

per IL DIRETTORE GENERALE
DELL'AZIENDA ULSS 7 PEDEMONTANA
dott.ssa Michela Conte

Documento informatico firmato digitalmente ai sensi del D. Lgs n. 82/2005, del T.U. n. 445/2000 e norme collegate, il quale sostituisce il documento cartaceo e la firma autografa; il documento informatico è conservato digitalmente negli archivi informatici dell'Azienda.

Proponente: UOC AFFARI GENERALI
Anno Proposta: 2023 Numero Proposta: 107/23

Il Dirigente, Direttore dell'UOC Affari Generali, nonché Responsabile del procedimento, attesta che la presente proposta di deliberazione è stata regolarmente istruita nel rispetto della vigente normativa nazionale, regionale e regolamentare: f.to Cristiano Galizian

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Il Direttore dell'U.O.C. Affari Generali relaziona quanto segue.

Premesso che:

- con deliberazione n. 316 del 31.03.2017 si è provveduto ad istituire, ai sensi della deliberazione della Giunta Regionale del Veneto n. 2174 del 23.12.2016, recante "Disposizioni in materia sanitaria connesse alla riforma del sistema sanitario regionale approvata con L.R. 25 ottobre 2016 n. 19", il Nucleo per la Ricerca Clinica (N.R.C.) dell'Azienda ULSS 7 Pedemontana;
- la citata DGRV n. 2174/2016, Allegato L, richiama l'applicazione della disciplina regionale in materia di sperimentazione clinica (DGR n. 1066/2013 e DGR n. 925/2016), che prevede l'istituzione di un N.R.C. per ciascuna Azienda ULSS della Regione;
- la DGR n. 1066/2013 (Allegato B) prevede che il N.R.C. sia istituito preferibilmente "presso il Servizio di Farmacia Ospedaliera ovvero Servizio Farmaceutico territoriale ovvero Servizio di Farmacologia delle istituzioni sanitarie, fermo restando i criteri di indipendenza e di assenza di conflitti di interesse" e sia composto "da professionalità multidisciplinari appartenenti all'ambito sanitario, epidemiologico –statistico, etico-giuridico e organizzativo –gestionale";
- con deliberazione n. 1477 del 05.08.2022 è stato approvato, in aggiornamento della disciplina aziendale regolata con la deliberazione n. 453 del 28/5/2014, il Regolamento aziendale sulla gestione delle sperimentazioni cliniche profit e no-profit, comprensivo anche della regolamentazione dei fondi per la gestione della ricerca con determinazione delle quote dei fondi stessi e fissazione dei criteri per l'attribuzione dei compensi;
- con deliberazione n. 1684 del 09.09.2022 sono stati aggiornati i componenti del Nucleo per la Ricerca Clinica Aziendale (N.R.C.) ai sensi della DGRV n. 2174 del 23.12.2016;
- con l'entrata in vigore del regolamento sulla sperimentazione clinica, Regolamento (UE) n. 536/2014, in data 31 gennaio 2022, la modalità di conduzione delle sperimentazioni cliniche nell'Unione europea (UE) subisce un cambiamento importante;
- con l'applicazione del Regolamento (UE) n.536/2014, l'Unione Europea persegue la finalità di promuovere l'efficienza delle sperimentazioni cliniche, soprattutto nel caso di sperimentazioni svolte in più Stati Membri, stimolando nel contempo l'innovazione e la ricerca e limitando duplicazioni di valutazione e ripetizioni di sperimentazioni senza valore aggiunto.
- il Regolamento Europeo nasce quindi con lo scopo di creare un ambiente favorevole allo svolgimento delle sperimentazioni cliniche in Europa, mediante l'armonizzazione delle regole e dei processi di valutazione e supervisione delle stesse, garantendone al tempo stesso gli standard più elevati per la sicurezza dei partecipanti e la trasparenza delle informazioni, grazie alla relativa pubblicazione di tutte quelle riguardanti l'autorizzazione, lo svolgimento e i risultati di ciascuna sperimentazione condotta in Europa;
- riguardo a quest'ultimo punto e al fine di migliorare la trasparenza delle informazioni sugli studi clinici, è stato sviluppato un portale dedicato per la gestione di tutte le sperimentazioni in Europa, uno strumento fondamentale per la trasparenza e per consentire di rafforzare la collaborazione, lo scambio di informazioni e i processi decisionali tra gli Stati Membri e all'interno degli stessi.

Rilevato che:

- con nota del 20 aprile 2022, agli atti, la società Medpace Clinical Research ("CRO"), per conto di Micurx Pharmaceuticals Inc, ha comunicato a questa A.ULSS 7, che l'U.O.S. Diabetologia il cui responsabile è il dr Alberto Marangoni, era stata scelta quale centro di sperimentazione per il

seguente studio: “Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi”*;*

- trattasi di uno studio presentato e caricato sul portale europeo ai sensi del suddetto Regolamento (UE) n. 536/2014:

SCHEDA STUDIO CLINICO

Titolo	Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi”
Protocollo	MRXC - 302
Strutture interessate	U.O.S. Diabetologia Ospedale di Bassano UOC Farmacia UOC Laboratorio Analisi UOC Radiologia
Sperimentatore Principale	Dr Alberto Marangoni
Co-sperimentatore	Dr.ssa Sara Balzano
Promotore	Micurx Pharmaceuticals Inc,
CRO	Medpace Clinical Research
Centro Coordinatore	Policlinico Universitario A. Gemelli IRCCS

- è stato individuato, quale Responsabile della sperimentazione clinica presso questa Azienda, lo Sperimentatore Principale, il dr. Alberto Marangoni Responsabile dell’U.O.S. Diabetologia dell’Ospedale di Bassano;

Tenuto conto che:

- il N.R.C. Aziendale, nella seduta del 30.11.2022, ha espresso parere favorevole rispetto alla valutazione dello studio, vista la documentazione agli atti, in attesa del provvedimento di autorizzazione nazionale dell’AIFA, come da nota trasmessa allo Sperimentatore Principale, dr Alberto Marangoni, al prot. 105473 dell’1.12.2022;
- tale sperimentazione è stata infatti poi autorizzata, a norma del Capo II del Regolamento, con il provvedimento di autorizzazione nazionale AIFA, regolarmente caricato sul portale UE, di cui all’art. 80 del Regolamento UE stesso, e rilasciato in data 5.12.2022, con anche l’acquisizione del parere favorevole del Comitato Etico Unico - Fondazione Policlinico Universitario A.Gemelli, che si era espresso nella seduta del 20.10.2022;
- entrambi i pareri (di AIFA e del Comitato Etico Unico - Fondazione Policlinico Universitario A.Gemelli) sono stati trasmessi dalla società Medpace Clinical Research (“CRO”) e pervenuti al ns prot. 110982 del 20.12.2022;
- trattasi di uno studio for-profit, sperimentale con farmaco, e in particolare di studio fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi”*;*
- lo studio prevede l’arruolamento di circa n. 845 pazienti, 44 in Italia e n. 4 pazienti presso l’A.ULSS 7;
- trattandosi di studio interventistico è prevista una copertura assicurativa per RCT derivante da sperimentazioni cliniche, a carico della società Medpace Clinical Research (“CRO”) come da contratto e come anche previsto dall’art.76 del Regolamento UE , in particolare è stata stipulata con la Compagnia HDI Global SE la polizza n. 390-76574325-30011;
- l’introito totale per paziente arruolato, completato e valutabile, corrisponde ad € 8.093,00, e i

pazienti arruolati saranno 4 (per ulteriori dettagli si rinvia all'accordo allegato alla presente proposta e in particolare all'allegato A dello stesso relativo al budget);

- il Contratto, allegato alla presente proposta, per la gestione degli aspetti economici inerenti la sperimentazione clinica, è redatto secondo la normativa vigente in materia ed è stato visionato e approvato dallo Sperimentatore Principale;
- l'attività inerente lo studio in argomento sarà svolta, ai sensi dell'art.15 del Regolamento aziendale per lo svolgimento delle sperimentazioni (deliberazione del Direttore Generale n. 1477/2022), dal Dr. Alberto Marangoni e dalla Dr.ssa Sara Balzano, in orario aggiuntivo oltre a quello istituzionalmente dovuto. La stessa verrà remunerata con i proventi derivanti dalla sperimentazione secondo le indicazioni contenute nella deliberazione sopra citata, che regolamenta anche la gestione dei fondi per l'attribuzione dei compensi.

Per quanto sopra, il Direttore dell'U.O.C. Affari Generali, propone di autorizzare l'effettuazione dello studio clinico for-profit "Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi", presso l'U.O.S. Diabetologia – Ospedale di Bassano il cui sperimentatore principale è il dr Alberto Marangoni e di approvare il contratto con la Società Medpace Clinical Research LLC – CRO, che agisce nell'interesse di Micurx Pharmaceuticals Inc., Promotore dello studio in questione

IL DIRETTORE GENERALE

Vista la relazione e la proposta del Responsabile del procedimento;

Dato atto che il responsabile del Servizio competente ha attestato l'avvenuta regolare istruttoria della pratica, in ordine alla compatibilità con la vigente legislazione statale, regionale e regolamentare;

Visti:

- il decreto ministeriale 15/07/1997;
- la circolare del Ministero della Salute 02/09/2002 n. 6;
- il D.lgs 24/06/2003, n. 211;
- il decreto ministeriale 17/12/2004;
- la DGRV 28/12/2006, n. 4430;
- il decreto ministeriale 12/05/2006;
- il D.lgs 6/11/2007, n. 200;
- il decreto ministeriale 21/12/2007;
- la determinazione AIFA 20/03/2008;
- la DRGV 07/10/2008, n. 2855;
- la Legge 08/11/2012, n. 189 – Decreto Balduzzi;
- il decreto del Ministero della Salute 08/02/2013;
- la DRGV 28/06/2013 n. 1066;
- il D.M. 30/11/2021
- il Regolamento (UE) n. 536/2014;

Acquisito il parere favorevole del Direttore Amministrativo, Sanitario e dei Servizi Socio-Sanitari, per quanto di rispettiva competenza

DELIBERA

1. di autorizzare lo studio clinico for profit "Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico

moderate o gravi", in conformità al provvedimento AIFA rilasciato in data 5.12.2022, e al parere favorevole del Comitato Etico Unico - Fondazione Policlinico Universitario A.Gemelli, espresso nella seduta del 20.10.2022, agli atti (ns prot. n 110982 del 20.12.2022);

2. di autorizzare, per quanto in premessa illustrato, lo svolgimento dello studio sotto la diretta Responsabilità del dr. Alberto Marangoni, Responsabile dell'U.O.S. Diabetologia – Ospedale di Bassano;

3. di dare atto che il Dr. Alberto Marangoni e la Dr.ssa Sara Balzano sono autorizzati a svolgere l'attività di ricerca in orario aggiuntivo oltre a quello istituzionalmente dovuto, così come previsto dall'art. 15 del Regolamento aziendale sulle sperimentazioni cliniche, adottato con deliberazione n. 1477 del 5.08.2022;

4. di stabilire che lo studio clinico dovrà essere eseguito secondo quanto previsto dal Protocollo di studio, allegato alla presente deliberazione di cui è parte integrante e sostanziale, nonché dalla normativa vigente in ambito di sperimentazioni e dalle norme di buona pratica clinica (GCP),

5. di approvare il contratto tra l'Azienda ULSS 7 Pedemontana e la Società Medpace Clinical Research LLC – CRO, che agisce nell'interesse di Micurx Pharmaceuticals Inc., Promotore dello studio in questione, allegato alla presente deliberazione di cui è parte integrante e sostanziale, assieme ai propri allegati;

6. di precisare che l'introito totale per paziente arruolato, completato e valutabile è pari ad € 8.093,00 per n. 4 pazienti per un totale di € 32.372,00;

7. di precisare che, dall'esecuzione del predetto studio, non deriverà nessun onere aggiuntivo di spesa in capo all'Azienda ULSS7 Pedemontana;

8. di dare atto che ai sensi dell'art.8 del Regolamento aziendale sulla gestione delle sperimentazioni cliniche (deliberazione n. 1477/2022):
   a) il Responsabile della Sperimentazione durante il corso dello studio è tenuto a comunicare al CESC, per il tramite del NRC, le informazioni necessarie a consentire il periodico aggiornamento sull'andamento della ricerca, ogni evento o reazione avversa, l'interruzione anticipata di uno studio, con l'indicazione dettagliata dei motivi e degli eventuali risultati parziali ottenuti;
   b) lo Sperimentatore si impegna a fornire annualmente al CESC un rapporto scritto sullo stato di avanzamento dello studio (monitoraggio periodico) e una relazione analitica alla conclusione dello studio e pubblicazione se prevista;

9. di incaricare l'U.O. proponente di pubblicare la presente deliberazione nella sezione Amministrazione Trasparente del sito istituzionale, ai sensi dell'art. 23, lettera d) del D.L.vo 14 marzo 2013 n. 33;

10. di dare atto che la presente deliberazione viene pubblicata all'albo del sito istituzionale dell'Azienda per 10 gg. continuativi, inviata contestualmente al Collegio Sindacale e diventa esecutiva il giorno stesso della sua pubblicazione come da norma regolamentare approvata con deliberazione n. 1386 del 22/07/2022.

CLINICAL PROTOCOL

Protocol No.	MRXC-302
Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections
Study Phase:	3
Product Name:	Contezolid acefosamil/contezolid
IND	131668
EU CT	2022-500257-16
Indication:	Treatment of patients with diabetic foot infections
Investigators:	Multicenter Study
Sponsor:	MicuRx Pharmaceuticals, Inc. 950 Tower Lane, Suite 390 Foster City, CA 94404 Phone: 1-510-782-2022
Sponsor Contact:	Edward Fang, MD Chief Medical Officer MicuRx Pharmaceuticals, Inc Phone: 415-710-5481 Email: efang@micurx.com
Original	30 November 2021
Current Version	Amendment 1.0
Date	Final, 28 February 2022

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This document contains proprietary and confidential information of MicuRx Pharmaceuticals, Inc. Acceptance of this document constitutes agreement by the recipient that no previously unpublished information contained herein will be published or disclosed without the prior written approval of MicuRx Pharmaceuticals, Inc. with the exception that this document may be disclosed to study personnel under your supervision who need to know the contents for conducting the study and to appropriate Institutional Review Boards/Independent Ethics Committees under the condition that the personnel have agreed to keep this information confidential. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, MicuRx Pharmaceuticals, Inc. shall be promptly notified of any such disclosure.

PROTOCOL APPROVAL PAGE

Protocol No.	MRXC-302
Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections
Version	Amendment 1.0
Date:	Final, 28 February 2022

Personnel Approving Protocol	**Signature**
Edward Fang, MD Chief Medical Officer MicuRx Pharmaceuticals, Inc.	

INVESTIGATOR AGREEMENT PAGE

Protocol No.	MRXC-302
Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections
Version:	Amendment 1.0
Date:	Final, 28 February 2022

I have read and I understand protocol MRXC-302 and the Investigator's Brochure. I agree to the following:

1. To conduct the clinical study in compliance with Good Clinical Practices and with all applicable regulatory requirement(s), according to the latest version of the protocol agreed to by the Sponsor and given approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee

2. To comply with procedures for data recording and reporting

3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities

4. To retain the essential documents in the Investigator and Institution files until the Sponsor informs me or the Institution that these documents are no longer needed

5. To provide copies of the protocol, any subsequent protocol amendments, and all information provided by the Sponsor to the study personnel under my supervision. I will review and discuss these materials with them in the detail required to ensure that they are fully informed about the investigational drug and the study protocol as appropriate for their study-related responsibilities.

Investigator Signature _____ Date _____

1.0 STUDY SYNOPSIS

Sponsor: MicuRx Pharmaceuticals, Inc.	**Protocol Number:** MRXC-302
Study Drugs: Contezolid acefosamil for intravenous administration and contezolid for oral administration	
Title: A Phase 3, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections	
Phase of Development: 3	
Study Site: Approximately 75 sites	
Indication: Diabetic Foot Infections (DFI)	
Rationale: There is an unmet need for additional antibiotic choices to treat Gram-positive bacterial infections caused by organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Treatment for moderate and severe DFI requires up to 4 weeks of antimicrobial therapy (Lipsky 2019). An antibacterial that can be started during the earlier stages of an acute serious infection (in which intravenous [IV] administration is preferred), can be administered orally (PO) in the outpatient setting, and is safe for prolonged use is optimal for successfully treating DFI. In the United States (US), the prevalence of diabetes has been increasing, with 10.5% of the population (34.2 million people) affected in 2018. The incidence of diabetes increases with age, affecting 26.8% of those ≥65 years of age (CDC 2020). DFI causes considerable morbidity with pain, reduced mobility, and the need for medical visits, diagnostic studies, dressing changes, and antibiotic treatment. Of more concern is that DFI is the most frequent diabetic complication requiring hospitalization, as well as the most common cause of lower extremity amputation (Favila 2019; Uckay 2015). DFIs involve skin, soft tissue, and/or bone (with or without diabetic foot ulcers) and can include cellulitis, paronychia abscesses, myositis tendonitis, necrotizing fasciitis, osteomyelitis, and septic arthritis (NIH 2019 DFI: antimicrobial prescribing; Selva Olid 2015; Lipsky 2004). Clinical signs of DFI, which may occur with or without an open wound (usually an ulcer) include classic findings of inflammation (ie, redness, warmth, pain or tenderness, and tissue hardening) and purulent secretions (Selva Olid 2015; Lipsky 2004). In most countries, Gram-positive aerobic cocci are the predominant causes of acute DFI, and *S. aureus* is the most commonly isolated pathogen. There is an increasing rate of antibiotic resistance with DFI pathogens, particularly with MRSA, but also with vancomycin-intermediate *S. aureus*, and vancomycin-resistant *Enterococci* (Spichler 2015). Only 3 antibiotics have US FDA-approved labeling for DFI: linezolid, ertapenem, and piperacillin/tazobactam; and of those agents, only linezolid has a PO formulation. In spite of available treatments, DFIs have a suboptimal rate of resolution (often <85%), a poor rate of healing (approximately 50% after 1 year), a high rate of recurrence (15%-30%), and a high mortality risk (15% within 1 year) (Lipsky 2019). The oxazolidinone class of antimicrobials has provided an important therapeutic option in the treatment of DFI. Linezolid, the first oxazolidinone, was approved in 2000 and is highly efficacious for the treatment of both community-acquired and hospital acquired infections (Wilcox 2005). In the US, linezolid is indicated for the treatment of VRE infections (including cases with concurrent bacteremia), nosocomial pneumonia (caused by methicillin-sensitive *Staphylococcus aureus* [MSSA], MRSA, or *Streptococcus pneumoniae*, including multidrug-resistant [MDR] strains), uncomplicated and complicated skin and skin structure infections including DFIs without concomitant osteomyelitis (caused by MSSA, MRSA, *Streptococcus pyogenes*, or *Streptococcus agalactiae*), and community-acquired pneumonia caused by *S. pneumoniae*, including MDR strains and cases with concurrent bacteremia, or MSSA (Zyvox® Prescribing Information 2021). There is an extremely low propensity for developing bacterial resistance to linezolid in all target pathogens, even after 20 years of clinical use. Despite these benefits, linezolid is subject to serious safety limitations, primarily due to myelosuppression and monoamine oxidase inhibition with associated drug-drug interactions, and central nervous system and blood pressure effects that limit the duration of treatment. Myelosuppression is reversible and more commonly occurs with linezolid treatment regimens >14 days, and extended treatment may also be associated with mitochondrial toxicity resulting in peripheral and optic neuropathy (Zyvox® Prescribing Information 2021).	

The main objective of the contezolid acefosamil (IV)/contezolid (PO) clinical program is to develop oxazolidinone antibiotics with improved tolerability and reduced toxicity compared to the currently available oxazolidinones (linezolid and tedizolid) while maintaining efficacy in treating serious Gram-positive bacterial infections.

MicuRx Pharmaceuticals, Inc. pursued a research program to develop a novel oxazolidinone agent that maintains high antibacterial activity while potentially addressing key toxicity issues associated with linezolid and tedizolid therapy. Oral contezolid (previously referred to as MRX-I) is a novel synthetic antibiotic in the oxazolidinone class of antimicrobials that was well tolerated, safe, and shown to have efficacy comparable to linezolid in subjects with complicated skin infections in 2 previous Phase 2 studies and 1 previous Phase 3 study. A good safety profile was also demonstrated in multiple Phase 1 trials, including a study that administered PO contezolid 800 mg every 12 hours (q12h) for up to 28 days.

However, the poor solubility of contezolid made the production of an IV formulation impractical. Thus, contezolid acefosamil (a double prodrug of contezolid; previously referred to as MRX-4) was developed as an IV formulation. Intravenous and PO contezolid acefosamil were demonstrated to be well tolerated, safe, and to have efficacy comparable to linezolid in subjects with acute bacterial skin and skin structure infections (ABSSSI) in a Phase 2 study. Contezolid acefosamil (IV)/contezolid (PO) present the patient and physician the opportunity to utilize the same active molecular entity for both IV and PO therapy. Therefore, contezolid acefosamil/contezolid may provide an attractive option for ABSSSI and other serious Gram-positive infections in both hospital and community settings, particularly when long-term use is indicated, such as for DFI.

Both contezolid acefosamil and contezolid have proven to be highly efficacious in various models of animal infections caused by Gram-positive bacteria, including drug-resistant strains of *S. aureus, S. pneumoniae*, and enterococci. The animal models used for evaluation included murine sepsis and thigh infection.

This study is designed to evaluate the safety and efficacy of contezolid acefosamil (IV)/contezolid (PO) compared to linezolid (IV and PO) for 14 to 28 days (28 to 56 doses) in adults with moderate or severe DFI. The primary efficacy endpoint will be the Investigator's assessment of clinical response at the Day 35 (D35) visit in the Modified Intent-to-Treat (MITT) analysis set.

Study Objectives:

Primary

- The primary objective is to evaluate the Investigator's assessment of clinical response at the D35 visit in subjects receiving contezolid acefosamil/contezolid compared to subjects receiving linezolid in the MITT analysis set
- Evaluate safety and tolerability of contezolid acefosamil (IV)/contezolid (PO) compared with linezolid (IV and PO)

Secondary

- Evaluate the Investigator's assessment of clinical response at:
  - End-of-Therapy (EOT) visit in the MITT analysis set
  - D35 visit in the Clinically Evaluable (CE) at D35 (CE-D35) analysis set

Exploratory

- Evaluate the Investigator's assessment of clinical response at Day 10 (D10) and Late Follow-Up visits (LFU; 28-35 days after EOT) in the MITT analysis set
- Evaluate the Investigator's assessment of clinical response at D10, EOT, D35, and LFU in the Intent-to-Treat (ITT) analysis set
- Evaluate the Investigator's assessment of clinical response at LFU in the CE-D35 analysis set
- Evaluate the Investigator's assessment of clinical response at EOT in the CE at EOT (CE-EOT) analysis set
- Evaluate the Investigator's assessment of DFI signs and symptoms in the CE-EOT and CE-D35 analysis sets
- Evaluate the Investigator's assessment of clinical response stratified by the presence or absence of adjunctive therapies (eg, daily debridement) and by the receipt of prior antibacterial drug therapy in the CE-D35 analysis set
- Evaluate the Investigator's assessment of clinical response stratified by presence of ulceration/wound in the CE-D35 analysis set

- Evaluate the percent reduction in the surface area of redness, edema, and/or induration of the primary DFI site at Day 5, EOT, and D35 compared to Baseline, measured in patients who did not receive any rescue antibiotic therapy and are alive
- Evaluate per-subject microbiological response at:
  - D35 in the Microbiological-MITT (Micro-MITT) analysis set
  - D35 in Microbiologically Evaluable (ME) at Day 35 (ME-D35) analysis set
- Evaluate per-pathogen microbiological response at:
  - D35 in the Micro-MITT and ME-D35 analysis sets
  - EOT in the Micro-MITT and ME at EOT (ME-EOT) analysis sets
- Evaluate Investigator's assessment of clinical response at:
  - D35 (overall and by Baseline pathogen) in the Micro-MITT and ME-D35 analysis sets
  - LFU (overall and by Baseline pathogen) in the Micro-MITT and ME-D35 analysis sets
- Evaluate all-cause mortality at Day 28 in the ITT and MITT analysis sets
- Evaluate the composite endpoint of death, unplanned amputation, and infectious complications of the primary DFI in the CE-D35 and CE at LFU (CE-LFU) analysis sets
- Evaluate changes between Baseline and D10, EOT, D35, and LFU in subject reported outcomes and quality-of-life assessments
- Characterize the pharmacokinetic (PK) profile for the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320 using sparse PK sampling in adult subjects with moderate or severe DFI

Study Design:

This is a Phase 3, multicenter, randomized, double-blind, safety and efficacy study of contezolid acefosamil (IV)/contezolid (PO) compared with linezolid (IV and PO) administered for a total of 14 to 28 days in adult subjects with moderate or severe DFI.

Approximately 865 subjects (519 contezolid acefosamil/contezolid: 346 linezolid) will be enrolled at approximately 75 sites to achieve approximately 820 (492 contezolid acefosamil/contezolid: 328 linezolid) subjects with moderate or severe DFI that are confirmed or suspected to be due to a Gram-positive bacterial pathogen (MITT analysis set). Prompt enrollment procedures are encouraged to allow for prompt administration of study drug. Screening/Baseline assessments for study eligibility will be performed within 48 hours of randomization on Day 1 (D1).

Patients with concurrent suspected or proven osteomyelitis related to the primary DFI (specific DFI for which the subject was enrolled), or as a separate infection, will be excluded from the study. The presence of suspected osteomyelitis will be based on results from ≥1 of the following diagnostic studies: probe-to-bone test, erythrocyte sedimentation rate, or plain foot X-rays, which are all required at Screening/Baseline. If results from these diagnostic studies are compatible with osteomyelitis, or if the Investigator continues to suspect the possible presence of osteomyelitis, the subject will not be enrolled as a subject into the study. Plain foot X-rays will also be performed at the EOT visit to assess if any new changes compatible with osteomyelitis developed during the study period.

Non-surgeon Investigators should consider surgical consultation in more serious cases of moderate infections; all cases of severe infections; and in subjects with possible deep (below the fascia) infection, abscess, compartment syndrome, or severe lower limb ischemia. Lower limb arterial status should be assessed and categorized (using the 2019 International Working Group on the Diabetic Foot [IWGDF]) peripheral artery disease guideline; Hinchliffe 2020) with evaluations of pedal pulses, ankle brachial index, and/or toe brachial index.

Subjects who provide informed consent, are willing and able to collaborate and cooperate with study protocol requirements, and who meet all study eligibility criteria will be randomized in the study. Randomization will have a 3:2 (contezolid acefosamil/contezolid: linezolid) allocation ratio. Randomization will be stratified by geographic region and severity of infection.

Subjects will receive ≥1 dose of the IV study drug before being allowed to switch to PO study drug if the Investigator has determined that it is clinically appropriate to change the route of administration.

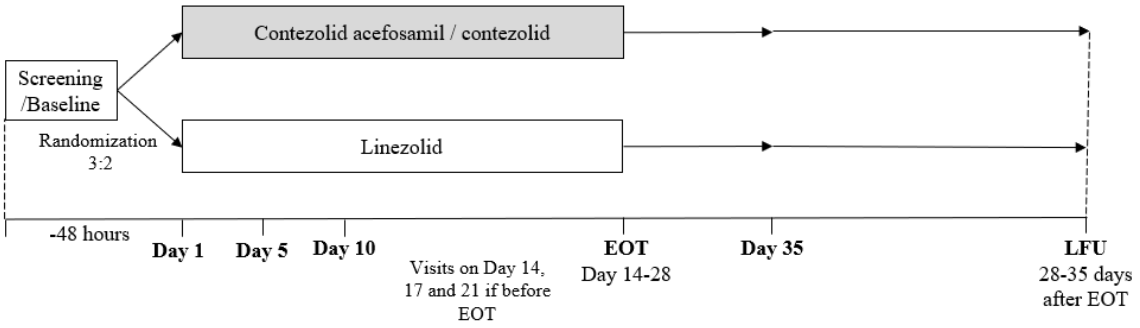
Subjects may receive adjunctive antimicrobial therapy with parenteral aztreonam (per standard-of-care dose regimen) if the Investigator suspects or has confirmed the presence of aerobic Gram-negative pathogens that, in addition to Gram-positive aerobic bacteria, are also associated with the pathogenic process. Similarly, subjects may also receive adjunctive antimicrobial therapy with parenteral or PO metronidazole (per standard-of-care dose regimen) if the Investigator suspects or has confirmed the presence of obligate anaerobic pathogens that, in addition to aerobic Gram-positive bacteria, are also associated with the pathogenic process.

Gram stain and culture specimens (aerobic and anaerobic) of the primary DFI lesion (specific DFI for which the subject was enrolled) must be obtained from all subjects for microbiologic evaluation at Screening/Baseline; the DFI site specimen must be obtained before administration of study antibacterial therapy. DFI site tissue specimens will be aseptically obtained by curettage or biopsy; specimens of purulent secretions obtained by sterile aspiration (but not by swab) are also acceptable. In addition, blood cultures (aerobic and anaerobic) from 2 separate venipuncture sites will be obtained from each subject before administration of antibacterial therapy, whenever possible. All DFI site specimens will be processed for Gram stain and aerobic and anaerobic culture at the local laboratory, and all blood cultures will be processed at the local laboratory. All bacterial isolates that are identified from a DFI site specimen or blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. Microbiological procedures will be detailed in the Laboratory Manual.

During the study, enrolled subjects should receive standard wound care (eg, pressure offloading, nonantimicrobial dressings). Preoperative topical antiseptics are permitted for surgical procedures or debridement but are not to be continued following the procedures. Investigators are encouraged to sharply debride ulcerated wounds to remove necrotic and infected material, as appropriate, at Screening/Baseline and as often as clinically indicated. Concomitant nonstudy systemic and topical antibacterial agents are prohibited during the study. Adjunctive therapies such as hyperbaric oxygen, wound-vacuum drainage systems, maggot or leech therapy, or granulocyte colony-stimulating factor are prohibited during the study.

D1 is the first day of study drug administration; subsequent study days are consecutive calendar days (Table 1). Assessments will be performed on D10 (±1 day), Day 14 (D14) (±1 day) if before EOT, Day 17 (D17) (±1 day) if before EOT, and Day 21 (D21) (±1 day) if before EOT. EOT (+1 day) will occur on the last day of study drug administration (D14 to Day 28 [D28], after 28 to 56 doses of study drug), D35 (+2 days) will occur on calendar Day 35, and LFU will occur 28 to 35 days after EOT. Subjects will undergo follow-up visits as described below to assess the safety, tolerability, and efficacy of the study drugs.

Study Design Schematic



EOT = End-of-Therapy; IV = intravenous; LFU = Late Follow-Up

Subjects must be evaluated directly by the Investigator from Screening/Baseline through D35 (+2 days). If the primary DFI site is associated with little or no pain, edema, redness or purulent/seropurulent drainage at the D35 (+2 days) visit, the LFU visit may be performed as a remote visit. DFI specimens (aerobic and anaerobic) for Gram stain and cultures may be obtained from the primary site of infection at each visit from Day 5 (D5) (±1 day) through LFU, only if clinically indicated (eg, the subject is deemed a clinical failure or relapse, or purulence and discharge from the DFI site continues after Screening/Baseline).

When conducting a clinical examination of the primary DFI site, the Investigator will perform and record the following:

- Extent of the infection as measured by redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for the length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at the Baseline assessment, if applicable.
- Color digital photograph of the DFI at Screening/Baseline
- Assessment of local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
- Record the following additional information (at Screening/Baseline only):
  - Primary DFI anatomical site
  - Predisposing cause of infection, if any (eg, ulcer, trauma [direct, penetrating, thermal, chemical], arthropod bite, fungal dermatosis, surgery, spontaneous)
  - Ankle brachial index of the primary DFI limb (if ankle blood pressure cannot be obtained, obtain the toe blood pressure and toe brachial index)

Efficacy assessments will include:

- Investigator's assessment of clinical response at D10, EOT, and D35. Clinical success is defined as the subject meeting ALL of the following:
  - Resolution or near resolution of Baseline DFI signs and symptoms with none worsening and thus not requiring further antibacterial or surgical therapy (only for EOT and D35)
    - Near resolution is defined as resolution of the signs and symptoms of DFI, except allowing one to persist but with continued improvement such that no further antibacterial therapy or surgical therapy are required to treat the primary DFI
  - No new signs, symptoms, or complications attributable to the primary DFI; no osteomyelitis at the primary DFI site diagnosed >7 days after start of study drug
  - Did not receive an intercurrent nonprotocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of DFI
  - Did not have a post-Baseline surgical procedure, major surgical debridement, or adjunctive intervention after 24 hours of start of study drug through D10, EOT, or D35, respectively, to treat the primary DFI that was not planned at Baseline
  - Did not die of any cause up to D10, EOT, or D35, respectively
- Investigator's assessment of sustained clinical success at LFU; sustained clinical success is defined as no new signs or symptoms of the primary DFI after D35, and no antimicrobial or surgical treatment aimed at presumed infection of the primary DFI. Subjects who were failures before LFU will be considered failures at LFU.

Subjects who prematurely discontinue study drug will undergo all EOT assessments on the day of study drug discontinuation (+1 day). Subjects who prematurely discontinue study drug will continue to be followed in the study. Before subjects withdraw from the study, efforts should be made to perform follow-up safety assessments per the study schedule. The duration of treatment within the specified window will be determined by the Investigator, based on the subject's clinical status (eg, therapy can be discontinued if the subject has improved, no more antibiotic treatment is medically necessary, and the risk of relapse is minimal).

Subjects will be monitored for the occurrence of adverse events (AEs) throughout the study, including AEs that are associated with the oxazolidinone class of antibiotics. Physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis) will be performed at Screening/Baseline and at various timepoints during and after study treatment (Table 1).

Estimated Study Duration:

The total duration of each subject's participation in the study will be at least 42 and up to 65 days, including the Screening period (≤48 hours before randomization). Subjects will receive study drug for 14 to 28 days. The duration of treatment within the specified window will be determined by the Investigator based on the subject's clinical status (eg, therapy can be discontinued if the subject has improved, no more antibiotic treatment is medically necessary, and the risk of relapse is minimal). Subjects will then be followed for at least 28 and up to 35 days after EOT.

Number of Subjects:

Approximately 865 (519 contezolid acefosamil/contezolid: 346 linezolid) adult subjects with moderate or severe DFI will be enrolled in this study. Randomization will have a 3:2 (contezolid acefosamil/contezolid:linezolid) allocation ratio with stratification for geographic region and severity of infection.

Study Drug, Dosage, and Route of Administration:

Study drugs are contezolid acefosamil (IV)/contezolid (PO) and linezolid (IV and PO), which will be administered for a total of 14 to 28 days (28 to 56 doses). All randomized subjects will start with 1 dose of IV study drug and may continue with IV therapy or be switched to PO study drug to complete study treatment.

Study treatment will be as follows:

- Subjects randomized to contezolid acefosamil/contezolid treatment will receive IV infusions of contezolid acefosamil q12h (±3 hours) with a minimum of 1 infusion followed by IV contezolid acefosamil or PO contezolid study drug q12h (±3 hours) for a total of 14 to 28 days. The first IV dose of contezolid acefosamil will be 2000 mg infused over 90 minutes (±5 minutes), and all other IV doses of contezolid acefosamil will be 1000 mg infused over 60 minutes (±5 minutes) q12h. Oral contezolid study drug will be contezolid 800 mg (2 tablets each of 400 mg of contezolid) and also a placebo tablet identical in appearance to linezolid (ie, subjects will take 3 tablets total for each PO administration). All PO study drug must be taken with food.
- Subjects randomized to linezolid treatment will receive IV infusions of linezolid q12h (±3 hours) with a minimum of 1 infusion followed by IV linezolid or PO linezolid study drug q12h (±3 hours) for a total of 14 to 28 days. The first IV dose of linezolid will be 600 mg infused over 90 minutes (±5 minutes), and all other IV doses of linezolid will be 600 mg infused over 60 minutes (±5 minutes) q12h. Oral linezolid study drug will be 1 linezolid 600 mg tablet and also 2 placebo tablets identical in appearance to contezolid (subjects will take 3 tablets total for each PO administration). All PO study drug must be taken with food.

To maintain blinding, each PO administration will utilize a double-dummy design with 3 tablets: subjects in the contezolid treatment arm will receive 2 contezolid tablets and 1 placebo tablet identical in appearance to a linezolid tablet, and subjects in the linezolid treatment arm will receive 1 linezolid tablet and 2 placebo tablets identical in appearance to contezolid tablets.

To maintain blinding, IV study drug will be prepared by an unblinded pharmacist or designee. IV bags will be used to administer IV study drug. Bags and IV tubing will be shrouded to blinded staff during transport and administration. An unblinded pharmacist or designee will confirm that the entire volume has been administered at the conclusion of the infusion.

It is expected that most subjects will remain in the hospital or clinic while receiving IV treatment with study drug; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions will not be administered at home.

After receiving at least 1 dose of IV study drug, subjects may switch to PO study drug to complete 14 to 28 days (28 to 56 doses) of therapy. The change from IV to PO study drug may take place after the Investigator has determined that the primary DFI lesion has not worsened (eg, has not increased in area of erythema or induration, tenderness has not increased) from the Screening/Baseline assessment, the subject feels better overall, the subject has adequate PO intake of food and fluids to safely support administration of PO doses of antibiotics, and that it is clinically appropriate to switch the subject to PO study drug. Subjects who are switched from IV to the PO study drug must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose. The subject may be discharged on PO study drug only after good tolerability has been demonstrated with the initial dose of PO treatment. All PO study drug must be taken with food. Subjects may switch from PO to IV study drug (eg, if nothing by mouth is allowed before a surgical procedure). However, switching from PO to IV study drug is not permitted due to treatment failure. Before switching from PO to IV study medication, discuss the case with the Medical Monitor.

During outpatient management, subjects will record study drug dosing details on subject-specific drug accountability logs.

Eligibility Criteria:

Inclusion Criteria:

1. Males or females ≥18 years of age
2. Willing and able to provide written informed consent
3. Have diabetes mellitus (type 1 or 2) per the American Diabetes Association criteria
4. Have a foot infection that started at or below the malleolus and does not extend above the knee. If the subject has multiple infections that meet all the criteria below, the one with the highest IWGDF classification and the largest size will be designated as the primary DFI
5. Foot infection that meets the IWGDF DFI criteria for classification 3 (moderate infection) or 4 (severe infection) (Appendix 8) that are confirmed or suspected to be due to a Gram-positive bacterial pathogen (Lipsky 2019)
6. Foot infection had acute onset or worsening of signs and symptoms within the past 14 days
7. Received <48 hours administration of a potentially effective antibiotic (ie, active against all pathogens known to be present) to treat the current target infection within 96 hours before the start of study drug administration
   a. EXCEPTION: Subjects who are considered to be therapeutic failures of prior antibiotic therapy with another agent may be enrolled if they have had worsening or no improvement in the clinical signs and symptoms of their DFI and have either:
      - Gram stain from the infection site showing both white blood cells and a potential Gram-positive pathogen

      OR

      - Culture and sensitivity results showing a Gram-positive pathogen resistant to prior antibiotics. Note: subjects must not have failed treatment with one of the study medications or any agent of the same class
8. Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative pregnancy test at Screening/Baseline and, if sexually active with male partners, be willing to use a highly effective method of contraception throughout the study, such as 1 of the following:
   a. Hormonal contraception (stable dose for 3 months)
   b. Intrauterine device/intrauterine hormone-releasing system
   c. Double barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)
9. Males, if nonsterile and sexually active with female partners of childbearing potential, must use a double-barrier method of contraception (eg, diaphragm, cervical cap, contraceptive sponge, condom) and be willing to continue to use such highly effective birth control measures while participating in the study and for 60 days following participation in the study. Males must also refrain from sperm donations during this time.

Exclusion Criteria:

1. Previous DFI known or suspected to be caused by Gram-positive pathogens that are resistant to oxazolidinone antibiotics
2. DFI with presumptive evidence or suspicion of osteomyelitis. EXCEPTION: if all infected bone was removed within 48 hours before the start of study drug administration but there remains infected soft tissue, the subject is acceptable for enrollment
3. DFI without presumptive evidence of osteomyelitis anticipated to require >28 days of antibiotic treatment
4. Necrotizing fasciitis, crepitant cellulitis, wet gangrene, gas gangrene, ecthyma gangrenosum, septic arthritis, or severely impaired arterial supply to any portion of the affected foot which may need revascularization before the end of the study
5. Infected prosthetic materials or devices that will not be removed before or at the time of enrollment
6. Anticipated requirement for complete resection or amputation (ie, removal of all infected tissue with clean margins) of the infected DFI anatomical site within 30 days
7. Known or suspected concurrent infection of any type that would require treatment with a systemic antibacterial agent with activity against Gram-positive bacteria

8. Life expectancy <3 months or evidence of immediately life-threatening disease, including, but not limited to, current or impending respiratory failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active gastrointestinal bleeding, profound metabolic, or acute cerebrovascular events
9. Evidence of significant hepatic, renal, hematologic, or immunologic disease as determined by the following:
    a. Total bilirubin >2× upper limit of normal (ULN)
    b. Alanine aminotransferase or aspartate aminotransferase >3×ULN
    c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    d. Current or anticipated absolute neutrophils <1500 neutrophils/mm^3
    e. Platelet count <75,000 cells/mm^3
    f. Known infection with human immunodeficiency virus (HIV) and a known CD4 count <200 cells/mm^3, or another acquired immune deficiency syndrome-defining illness
    g. Creatinine clearance <30 mL/min; creatinine clearance will be calculated from the serum creatinine concentration by the following equation:
        - Male: Creatinine clearance mL/min = (140-age) × weight (kg) / (72 × serum creatinine [mg/dL])
        - Female: Creatinine clearance mL/min = 0.85 × ([140-age] × weight [kg] / [72 × serum creatinine {mg/dl}])
10. Receipt of chemotherapy, radiotherapy, or potent, noncorticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids ≥10 mg of prednisone (or equivalent) per day for >14 days in the prior 30 days
11. Known or suspected pheochromocytoma or thyrotoxicosis or severe uncontrolled hypertension.
12. QT interval corrected for heart rate by Fridericia's formula (QTcF) duration >450 msec for males and >470 msec for females obtained as an average from the triplicate Screening/Baseline ECGs, history of QT prolongation, hypokalemia (serum potassium <3.0 mEq/L) at Screening/Baseline, or other proarrhythmic conditions
13. Concomitant condition that, in the opinion of the Investigator, would preclude an evaluation of a response or make it unlikely that the contemplated course of therapy could be completed
14. History of known or suspected serotonin syndrome, neuroleptic malignant syndrome, or carcinoid syndrome
15. History of known or suspected *Clostridioides difficile*-associated diarrhea
16. History of drug-related peripheral or optic neuropathy
17. History of a seizure disorder or known or suspected central nervous system condition that may predispose to seizures or lower the seizure threshold
18. Females who are pregnant or breastfeeding
19. Prior receipt of any formulation of contezolid acefosamil or contezolid
20. Prior (within the past 2 weeks) administration of, or expected or required concomitant (from the start of the study drug to EOT) administration of:
    a. Systemic adrenergic, dopaminergic, or serotonergic medications
    b. Monoamine oxidase inhibitors (eg, isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine)
21. Prior or expected concurrent systemic immunosuppressive therapy, defined as chronic treatment with known immunosuppressive medications
22. Expected concurrent hemodialysis, hemofiltration, peritoneal dialysis, or plasmapheresis
23. Inability to tolerate a PO study drug for duration of study treatment (eg, nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of PO study drug)
24. Poor venous access
25. History of any intolerance, hypersensitivity, or allergic reaction to any oxazolidinone antibiotic

26. History of any intolerance, hypersensitivity, or allergic reaction to aztreonam; note that while cross-reactivity of aztreonam with other β-lactams is rare, this drug should be administered with caution to any subject with a history of hypersensitivity to β-lactams (eg, penicillins, cephalosporins, carbapenems)
27. History of any intolerance, hypersensitivity, or allergic reaction to metronidazole
28. Taken any investigational drugs or used any investigational devices within 30 days before randomization
29. Inability to cooperate fully with the requirements of the study protocol, including the schedule of events, or likely to be noncompliant with any study requirements, or the Investigator determines that the subject should not participate in the study

Pharmacokinetic Assessments:

Pharmacokinetic assessments will be performed at selected clinical sites that have the appropriate equipment (including refrigerated centrifuges and -70ºC freezers) and experienced personnel to adequately obtain, handle, store, and ship PK samples for bioanalysis. At these selected clinical sites, PK samples will be obtained from as many subjects as possible. Drug exposure will be predicted using the population PK model developed from Phase 1 and Phase 2 studies based on demographic data (eg, body weight) for subjects from whom PK samples were not obtained.

- 3 PK samples after the first IV dose (to characterize the first dose):
  - Obtain 2 blood samples between 1.5 and 6 hours after the start of the first infusion, with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after the start of infusion)
  - Obtain 1 blood sample (trough level) within 2 hours before the start of the second dose (IV or PO) of study drug
- 3 PK samples on D5 (±1 day) (to characterize drug exposure after multiple doses):
  - Obtain 1 blood sample (trough level) within 2 hours before a designated D5 (±1 day) dose (IV or PO) of study drug
  - Obtain 2 blood samples between 1.5 and 6 hours after the designated D5 (±1 day) dose of study drug (when PO dose is taken or when IV dose is started), with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after PO dose taken or IV infusion started)
- 3 PK samples at EOT (to evaluate potential drug accumulation):
  - Obtain 1 blood sample (trough level) within 2 hours before the last dose (IV or PO) of study drug
  - Obtain 2 blood samples between 1.5 and 6 hours after the last dose of study drug (when last PO dose is taken or when last IV dose is started), with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after PO dose taken or IV infusion started)

The PK data acquisition and analysis strategy entails the use of a sparse PK sampling schedule for subjects randomized to contezolid acefosamil/contezolid. This PK sampling strategy is designed to characterize the drug exposure profiles of contezolid after the first dose on D1, a designated D5 (±1 day) dose, and the final dose. Exposures to the contezolid acefosamil metabolite MRX-1352 and the contezolid metabolite MRX-1320 will also be evaluated. Two (2) PK samples between 1.5 and 6 hours postdose, plus a trough concentration, will assure that informative individual drug exposures for the area under the curve (most important parameter associated with efficacy) will be obtained. Data analysis will be performed by population PK modeling. Additionally, given the range of demographic data in the expected subject population, these PK data will be used to perform exploratory analyses on the impact of demographic characteristics (eg, weight, body mass index, age, gender, race) upon the PK (including clearance) of the drug and its metabolites. Only those PK samples obtained from subjects randomized to contezolid acefosamil/contezolid will be analyzed. The bioanalytical laboratory will measure plasma concentrations for the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320 using validated and sensitive methods.

Efficacy Endpoints:

The primary endpoint is the Investigator's assessment of clinical response at D35 in the MITT analysis set, defined in the Efficacy Assessments section above.

Secondary and exploratory efficacy endpoints will be determined at D10, EOT, D35, and LFU according to the table below.

	Efficacy Analysis Sets						
Efficacy Endpoints	**ITT**	**MITT**	**Micro-MITT**	**CE-EOT**	**ME-EOT**	**CE-D35**	**ME-D35**
Secondary:							
Investigator's assessment of clinical response at EOT		√					
Investigator's assessment of clinical response at D35						√	
Exploratory:							
Investigator's assessment of clinical response at D10	√	√					
Investigator's assessment of clinical response at EOT	√			√			
Investigator's assessment of clinical response at D35	√						
Investigator's assessment of sustained clinical success at LFU	√	√				√	
Per-subject microbiological response at D35			√				√
Per-pathogen microbiological response at D35			√				√
Per-pathogen microbiological response at EOT			√		√		
Investigator's assessment of clinical response at D35 (overall and by Baseline pathogen)			√				√
Investigator's assessment of clinical response at LFU (overall and by Baseline pathogen)			√				√

Additional exploratory endpoints are outlined in detail in Section 5 and Section 12.1, Table 7.

CE = Clinically Evaluable; D = day; EOT = End-of-Therapy; ITT = Intent-to-Treat; LFU = Late Follow-Up; ME = Microbiologically Evaluable; MITT = Modified Intent-to-Treat; Micro-MITT = Microbiological Modified Intent-to-Treat

Safety and Tolerability Assessments:

Safety will be assessed through the determination and recording of the occurrence of AEs and AEs of special interest associated with the oxazolidinone class of antibiotics, as well as by adverse changes in physical examinations, vital signs, ECG parameters, and laboratory values. Adverse events will be evaluated by relationship to study drug and severity. Serious adverse events (SAEs) will be identified.

Statistical Methods:

Sample Size Considerations:

Approximately 865 subjects (3:2 randomization ratio with 519 subjects in the contezolid acefosamil/contezolid treatment arm and 346 subjects in the linezolid treatment arm) will be enrolled. The sample size determination is based on ensuring sufficient power for the primary endpoint of Investigator's assessment of clinical response at D35 in the MITT analysis set. For the primary efficacy endpoint, assuming an outcome rate of 75% for both treatment groups, a noninferiority (NI) margin of 10%, 90% power, and a 1-sided alpha of 0.025, using a Z-test with unpooled variance, a total of 820 subjects in the MITT analysis set are required. To account for an anticipated nonevaluable rate of 5%, an additional 45 subjects have been added for a total of 865 randomized subjects to achieve 820 subjects in the analysis set evaluated for the primary efficacy outcome (492 subjects in the contezolid acefosamil/contezolid and 328 in the linezolid groups).

Analysis Sets:

- ITT Analysis Set - All randomized subjects will be included in the ITT analysis set, regardless of whether study drug is administered.
- MITT (Modified-ITT) Analysis Set - All subjects in the ITT analysis set with a confirmed or suspected Gram-positive bacterial pathogen (ie, excluding subjects with only Gram-negative pathogens).
- Safety Analysis Set - All subjects who receive any amount of study drug will constitute the safety analysis set. Subjects in the safety analysis set will be analyzed according to study drug received.
- Micro-MITT Analysis Set - All subjects in the MITT analysis set who have culture evidence of a Baseline Gram-positive bacterial pathogen known to cause DFI.
- CE Analysis Sets (CE-D35, CE-EOT) – All subjects in the MITT analysis set who meet the minimal clinical disease criteria for DFI; receive ≥80% of expected doses based on length of therapy; did not receive any potentially-effective systemic antibacterial therapies other than protocol specified study drug(s) between D1 and timepoint for assessment (except for adjunctive aztreonam and/or metronidazole, or in cases of treatment failure).
  - To be included in the CE-EOT analysis set, the following conditions must be met:
    - Have an Investigator's assessment of clinical response at EOT (ie, response cannot be indeterminate)
    - Had the EOT visit on D14 to D28 (+1 day), or if study drug was prematurely discontinued, within 1 day of discontinuation
  - To be included in the CE-D35 analysis set, the following conditions must be met:
    - Have an Investigator's assessment of clinical response at D35 (ie, response cannot be indeterminate unless the subject is deemed a clinical failure at EOT)
    - Had the D35 (+2 days) visit
- In addition to meeting the above criteria, subjects must meet the following specific conditions to be included in the CE analysis sets:
  - Received ≥5 doses of study drug therapy to be considered an evaluable failure
  - Received ≥7 doses of study drug therapy to be considered an evaluable success
  - Did not have any major protocol violations that affected efficacy
  - Not diagnosed with osteomyelitis within 7 days after randomization
- ME Analysis Sets (ME-D35, ME-EOT,): All subjects in the Micro-MITT analysis set who also are in the CE-D35 or CE-EOT analysis set, respectively.
- PK Analysis Set: All subjects who received ≥1 dose of contezolid acefosamil/contezolid and had ≥1 blood sample obtained for analysis of contezolid and 2 metabolites (MRX-1352 and MRX-1320).

Statistical Analysis:

All data will be summarized separately by study drug (contezolid acefosamil/contezolid or linezolid). Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study drug. Frequency distributions (counts and percentages) will be presented for categorical variables. Listings will be provided for individual subject study data. All Baseline data will be summarized by treatment group.

The primary efficacy outcome is the Investigator's assessment of clinical response at D35 in the MITT analysis set. The number and percentage of subjects in each treatment group classified as clinical successes, clinical failures, and indeterminates will be summarized. Ninety-five percent confidence intervals (CIs) will be provided for each clinical success rate. The difference between the clinical success rates will be calculated and a 2-sided 95% CI for the difference in clinical success rates (contezolid acefosamil/contezolid minus linezolid groups) will be calculated using a Z-test. Contezolid acefosamil/contezolid will be considered noninferior to linezolid if the lower bound of the 95% CI is greater than -10%.

All secondary and exploratory efficacy endpoints will be summarized by treatment group as detailed in the Statistical Analysis Plan (SAP), which will be prepared and finalized before database lock.

Safety will be evaluated by presenting summaries of treatment-emergent adverse events (TEAEs) and SAEs, vital signs, laboratory evaluations (hematology, chemistry, and coagulation), and ECG parameters. Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT), and by SOC, PT, and relationship to study drug, and by SOC, PT, and severity. Serious AEs and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT. Descriptive statistics for clinical laboratory results, vital signs, and ECG parameters, including change from Baseline, will be presented by timepoint and for the overall most abnormal post-Baseline value (clinical laboratory results and vital signs only). Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by timepoint and the overall most abnormal post-Baseline value (clinical laboratory results and vital signs only).

Pharmacokinetic data will be summarized using descriptive statistics and graphically displayed, and population PK modeling analyses will be performed.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will review safety data at 2 timepoints (approximately when 33% and 67% of subjects have been randomized) while the clinical trial is ongoing. Additional details will be provided in the DMC Charter.

Interim Analysis:

An interim analysis is not planned.

Table 1: Schedule of Events

Procedure or Assessment	Screening/ Baseline[a] (≤48 hours of randomization)	Study Treatment Period							D35 (+2 days)	LFU[f] 28-35 days after EOT
		D1[b]	D5 (±1 day)	D10 (±1 day)	D14[c] (±1 day)	D17[c] (±1 day)	D21[c] (±1 day)	EOT[d] D14-28[e] (+1 day) (28-56 doses of study drug)		
Informed consent [g]	X									
Medical/surgical history	X									
Estimate CrCl [h]	X									
Serology tests [i]	X									
Pregnancy test [j]	X							X		
Foot X-ray and probe-to-bone test	X [k]							X[k]		
Examination, measurement, signs/symptoms of DFI [l]	X	X	X	X	X	X	X	X	X	X
DFI specimen Gram stain and culture [m]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Blood cultures [o]	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	
Complete physical examination [p]	X							X	X	
Focused physical examination [q]			X	X	X		X			
Height and weight	X									
Vital signs [r]	X	X	X	X	X	X	X	X	X	
12-Lead ECG [s]	X	X[t]	X		X		X	X		
Laboratory tests [u]	X		X	X	X	X	X	X	X	
Short Form-36 (SF-36) Health Survey	X								X	
Randomization [v]		X								
Administration of study drug (14 to 28 days) [w]		X	X	X	X	X	X	X		
Prior and concomitant therapy [x]	X	X	X	X	X	X	X	X	X	X
PK samples [y]		X	X					X		
Adverse events [z]	X	X	X	X	X	X	X	X	X	X

Procedure or Assessment	Screening/ Baseline[a] (≤48 hours of randomization)	Study Treatment Period							D35 (+2 days)	LFU[f] 28-35 days after EOT
		D1[b]	D5 (±1 day)	D10 (±1 day)	D14[c] (±1 day)	D17[c] (±1 day)	D21[c] (±1 day)	EOT[d] D14-28[e] (+1 day) (28-56 doses of study drug)		
Investigator's assessment of clinical response				X				X	X	X

Footnotes to Table 1

β–HCG = beta-human chorionic gonadotropin; CrCl = creatinine clearance; CRP = C-reactive protein; D = day; DFI = diabetic foot infections; ECG = electrocardiogram; EOT = end of therapy; ESR = erythrocyte sedimentation rate; HBcAg = hepatitis B virus core antigen; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IV = intravenous; LFU = late follow-up; PK = pharmacokinetic; PO = oral; UA = urinalysis.

a. Screening/Baseline assessments must occur ≤48 hours before randomization.
b. D1 is the first day of study drug administration; subsequent study days are consecutive calendar days.
c. Study visits on D14 (±1 day), D17 (±1 day), and D21 (±1 day) are not conducted if they occur on or after the EOT Visit.
d. Perform EOT assessments on the last day of study drug administration (+1 day). Subjects who prematurely discontinue study drug should have all EOT assessments performed on the day of discontinuation of study drug (+1 day).
e. Dosing on D29 will only be required if a subject receives the maximum 56 doses of study drug and also receives only a single dose of study drug on D1.
f. If the primary DFI site has little or no pain, swelling, redness or purulent/seropurulent drainage at the D35 (+2 days) visit, the LFU visit may be performed remotely.
g. Written informed consent must be obtained prior to initiating any study assessment or procedure.
h. Calculate estimated CrCl using Screening/Baseline height (m), actual weight (kg), and serum creatinine.
i. Serology tests include anti-HBcAg anti-HBsAg, HBsAg, HCV antibody, HIV antibody.
j. Females of childbearing potential up to 2 years postmenopause must have a serum or urine β–HCG pregnancy test at Baseline and EOT.
k. Plain foot X-ray and probe-to-bone test will be used to evaluate for osteomyelitis in all subjects; if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, or if the Investigator suspects the possible presence of osteomyelitis, the subject will not be enrolled into the study. Only X-rays need to be repeated at the EOT visit.
l. Direct evaluation of signs and symptoms of DFI by the Investigator includes extent of the infection as by redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor.; for the length (cm) of redness extending from the wound margin, measure same direction from rim of wound as used at Baseline assessment, if applicable. A color digital photograph of the DFI is obtained at Screening/Baseline only. Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent). In addition, record the primary DFI anatomical site, predisposing cause of infection, if any (eg, ulcer, trauma, arthropod bite, fungal dermatosis, surgery, spontaneous), and ankle brachial index (or toe brachial index) at Screening/Baseline only.
m. Obtain appropriate DFI site specimen (aerobic and anaerobic) from all subjects at Screening/Baseline and perform Gram stain and culture at the local laboratory. DFI site specimens will be aseptically obtained by curettage or biopsy; specimens of purulent secretions obtained by sterile aspiration (but not by swab) are also acceptable. The DFI site specimen must be obtained before administration of antibacterial therapy. All bacterial isolates that are identified from a DFI site specimen at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing.
n. Collect if clinically indicated.

o. Blood cultures from 2 separate venipuncture sites will be obtained from all subjects before administration of antibacterial therapy, whenever possible. Blood cultures must be repeated every 3 days (±1 day) if the previous blood culture was positive, or at any time after Screening/Baseline if clinically indicated. All bacterial isolates that are identified from a blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.
p. Perform a complete physical examination (ie, general appearance, head, ears, eyes [including basic Snellen visual acuity and visual field testing], nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes). Note that the physical examination does not include assessment of the primary DFI, as it is assessed separately.
q. Perform a focused (limited, symptom directed) physical examination as clinically indicated. Note that the physical examination does not include assessment of the primary DFI, as it is assessed separately.
r. Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs are not repeated on D1 if Screening/Baseline occurs on D1. Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the electronic case report form; the same method of temperature collection for each subject should be used throughout the study.
s. Obtain triplicate ECGs within a 15-minute period, each separated by ≥1 minute, at Screening/Baseline, D1 (predose and postdose), D5 (±1 day), D14 (±1 day), D21 (±1 day), and EOT. ECGs will be obtained before collection of blood laboratory (including PK) samples.
t. Within 1 hour before start of IV infusion (unless Screening/Baseline ECG is performed in triplicate and is within 1 hour before start of IV infusion) and another within 2 hours after completion of IV infusion.
u. Perform safety laboratory tests, including hematology, chemistry, and coagulation tests, UA, ESR, and CRP. Note that CRP and ESR will only be obtained at Screening/Baseline, D5 (±1 day), D10 (±1 day), and EOT. Note that UA is not obtained at D35. Include urine microscopy if UA is positive for red blood cells, white blood cells, or protein. Samples for Screening/Baseline tests will be drawn and sent to local laboratory (to confirm eligibility) and central laboratory. All subsequent laboratory tests will be drawn and sent to the central laboratory.
v. Verify that the subject meets all study inclusion and exclusion criteria before randomization on D1.
w. Subjects receive study drug q12h (±3 hours) for 14-28 days. On D1, the first dose of study drug should be administered as quickly as possible after eligibility criteria are met. Subjects will receive the first dose of study drug IV and then may switch to PO study drug. The switch from IV to PO study drug may take place after the Investigator has determined that the primary DFI lesion has not increased in area from the Screening/Baseline assessment, the subject has adequate PO intake of food and fluids to safely support administration of PO doses of antibiotics, and that it is clinically appropriate to change. Subjects who are switched from the IV to the PO formulation of study drug must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose. The subject may be discharged on PO medication only after good tolerability has been demonstrated with the initial dose of PO treatment.
x. Record all prior medications taken within 2 weeks before randomization; record all concomitant medications between D1 and LFU.
y. For selected sites, obtain PK samples (Section 14.0):
z. Adverse events are collected between written informed consent and LFU. During the LFU assessment, symptoms related to possible relapse of DFI will be evaluated as part of the safety assessment.

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3.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Definition
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
CDAD	*Clostridium difficile* associated diarrhea
CE	Clinically Evaluable
CI	confidence interval
Contezolid	investigational medicinal product in this study; active metabolite of contezolid acefosamil moiety (formerly known as MRX-I)
Contezolid acefosamil	investigational medicinal product in this study (formerly known as MRX-4); a prodrug that undergoes a 2-step conversion process to contezolid (active moiety) by means of MRX-1352 (an intermediate metabolite)
CrCl	creatinine clearance
CRP	C-reactive protein
cSSSI	complicated skin and skin structure infections
D	day
DEHP	diethylhexyl phthalate
DFI	diabetic foot infections
DMC	Data Monitoring Committee
DMID	Division of Microbiology and Infectious Diseases
EA	Early Assessment (48 to 72 hours after the start of the first dose of study drug)
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Therapy (last day of study drug)
ESR	erythrocyte sedimentation rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IND	Investigational New Drug application
IRB	Institutional Review Board
IRT	Interactive Response System
ITT	Intent-to-Treat
IV	intravenous(ly)

Abbreviation	Definition
IWGDF	International Working Group on the Diabetic Foot
Km	substrate concentration that yields a half-maximal velocity
LFU	Late Follow-Up (21-28 days after EOT)
MAOI	monoamine oxidase inhibitor
MDR	multidrug-resistant
ME	Microbiologically Evaluable
MIC_{90}	minimum inhibitory concentration for 90% of microbial strains
MITT	Modified Intent-to-Treat
Micro-MITT	Microbiological Modified Intent-to-Treat
MRSA	methicillin-resistant *Staphylococcus aureus*
MRX-1320	primary metabolite of contezolid; MRX-1320 is also known as “M2” in other documents
MRX-1352	intermediate metabolite in the 2-step process by which prodrug (contezolid acefosamil) is converted into contezolid (active moiety)
MSSA	methicillin-sensitive *Staphylococcus aureus*
NMPA	National Medical Products Administration
NOAEL	no-observed adverse-effect level
PK	pharmacokinetic
PO	oral
PT	Preferred Term
PTE	Post-Therapy Evaluation
q12h	every 12 hours
QTcF	QT interval corrected for heart rate using Fridericia’s formula
RBC	red blood cell
SAE	serious adverse event
SAER	serious adverse event report
SAP	Statistical Analysis Plan
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
SOP	standard operating procedure
SSRI	serotonin reuptake inhibitor
Subject	individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TOC	Test-of-Cure
UA	urinalysis
ULN	upper limit of normal
US	United States
Vmax	maximum rate of an enzyme catalyzed reaction
VRE	vancomycin-resistant enterococci

Abbreviation	Definition
WBC	white blood cell

4.0 BACKGROUND AND RATIONALE

4.1 Diabetic Foot Infections

In the United States (US), the prevalence of diabetes has been increasing, with 10.5% of the population (34.2 million people) affected in 2018. The incidence of diabetes increases with age, affecting 26.8% of those ≥65 years of age (CDC 2020). Diabetic foot infections (DFI) cause considerable morbidity with pain, reduced mobility, and the need for medical visits, diagnostic studies, dressing changes, and antibiotic treatment. Of more concern is that DFI is the most frequent diabetic complication requiring hospitalization, as well as the most common cause of lower extremity amputation (Favila 2019; Uckay 2015). DFIs involve skin, soft tissue, and/or bone (with or without diabetic foot ulcers) and can include cellulitis, paronychia abscesses, myositis tendonitis, necrotizing fasciitis, osteomyelitis, and septic arthritis (NIH 2019 DFI: antimicrobial prescribing; Selva Olid 2015; Lipsky 2004). Clinical signs of DFI, which may occur with or without an open wound (usually an ulcer) include classic findings of inflammation (ie, redness, warmth, pain or tenderness, and tissue hardening) and purulent secretions (Selva Olid 2015; Lipsky 2004). In most countries, Gram-positive aerobic cocci are the predominant causes of acute DFI, and S. aureus is the most commonly isolated pathogen. There is an increasing rate of antibiotic resistance with DFI pathogens, particularly with methicillin-resistant *Staphylococcus aureus* (MRSA), but also with vancomycin-intermediate S. aureus, and vancomycin-resistant Enterococci (Spichler 2015).

4.2 Available Treatments for Diabetic Foot Infections

Only 3 antibiotics have US FDA-approved labeling for DFI: linezolid, ertapenem, and piperacillin/tazobactam; and of those agents, only linezolid has an oral (PO) formulation. In spite of available treatments, DFIs have a suboptimal rate of resolution (often <85%), a poor rate of healing (approximately 50% after 1 year), a high rate of recurrence (15%-30%), and a high mortality risk (15% within 1 year) (Lipsky 2019).

The oxazolidinone class of antimicrobials has provided an important therapeutic option in the treatment of DFI. Linezolid, the first oxazolidinone, was approved in 2000 and is highly efficacious for the treatment of both community-acquired and hospital acquired infections (Wilcox 2005). In the US, linezolid is indicated for the treatment of vancomycin-resistant enterococci (VRE) infections (including cases with concurrent bacteremia), nosocomial pneumonia (caused by methicillin-sensitive *Staphylococcus aureus* [MSSA], MRSA, or *Streptococcus pneumoniae*, including multidrug-resistant [MDR] strains), uncomplicated and complicated skin and skin structure infections (cSSSI) including DFIs without concomitant osteomyelitis (caused by MSSA, MRSA, *Streptococcus pyogenes*, or *Streptococcus agalactiae*), and community-acquired pneumonia caused by S. pneumoniae, including MDR strains and cases with concurrent bacteremia, or MSSA (Zyvox® Prescribing Information 2021). There is an extremely low propensity for developing bacterial resistance to linezolid in all target pathogens, even after 20 years of clinical use. Despite these benefits, linezolid is subject to serious safety limitations, primarily due to myelosuppression and monoamine oxidase inhibition with associated drug-drug interactions, and central nervous system and blood pressure effects that limit the duration of treatment. Myelosuppression is reversible and more commonly occurs with linezolid

treatment regimens >14 days, and extended treatment may also be associated with mitochondrial toxicity resulting in peripheral and optic neuropathy (Zyvox® Prescribing Information 2021).

4.2.1 Unmet Need

There is an unmet need for additional antibiotic choices to treat Gram-positive bacterial infections caused by organisms such as MRSA and VRE. Treatment for moderate and severe DFI requires up to 4 weeks of antimicrobial therapy (Lipsky 2019). An antibacterial that can be started during the earlier stages of an acute serious infection (in which intravenous [IV] administration is preferred), can be administered PO in the outpatient setting, and is safe for prolonged use is optimal for successfully treating DFI.

4.3 Contezolid Acefosamil and Contezolid

Contezolid is a novel synthetic antibiotic in the oxazolidinone class of antimicrobials.

MicuRx Pharmaceuticals, Inc. pursued a research program to develop a novel oxazolidinone agent that maintains high antibacterial activity while potentially addressing key toxicity issues associated with linezolid therapy. Oral contezolid (previously referred to as MRX-I) is a novel synthetic antibiotic in the oxazolidinone class of antimicrobials that was demonstrated to be well tolerated, safe, and to have efficacy comparable to linezolid in subjects with complicated skin infections in 2 previous Phase 2 studies and 1 previous Phase 3 study. A good safety profile was also demonstrated in multiple Phase 1 trials including a study that administered PO contezolid 800 mg every 12 hours (q12h) for up to 28 days.

However, the poor solubility of contezolid made the production of an IV formulation impractical. Thus, contezolid acefosamil (a double prodrug of contezolid, previously referred to as MRX-4) was developed for the IV formulation. Intravenous and PO contezolid acefosamil were demonstrated to be well tolerated, safe, and to have efficacy comparable to linezolid in subjects with acute bacterial skin and skin structure infections (ABSSSI) in a Phase 2 study.

Contezolid acefosamil/contezolid present the patient and physician the opportunity to utilize the same active molecular entity for both IV and PO therapy. Therefore, contezolid acefosamil/contezolid may provide an attractive option for DFI and other significant Gram-positive infections in both hospital and community settings, particularly when long-term use is indicated. Contezolid acefosamil and contezolid possess potent Gram-positive activity (including resistant *S. aureus* and *Enterococcal* species [spp.]) and have the potential for improved tolerability, especially with regards to hematological toxicity. Contezolid acefosamil/contezolid may provide an attractive option to overcome some of the limitations of the available oxazolidinones in both community and hospital settings, particularly when long-term use is indicated.

4.3.1 Relevant Nonclinical Experience

The active pharmaceutical ingredient, contezolid, has demonstrated excellent in vitro antibacterial activity against both nosocomial and community Gram-positive pathogens. The minimum inhibitory concentration for 90% of microbial strains (MIC_{90}) is <2 µg/mL against recent US-surveillance, Gram-positive isolates (Li 2014). Contezolid acefosamil and contezolid have proven to be highly efficacious in various models of animal infections caused by Gram-positive bacteria, including drug-resistant strains. Both contezolid acefosamil (IV or PO administration) and contezolid (PO administration) were highly efficacious agents in in vivo animal models of systemic (including murine sepsis) and local (including murine thigh) infections caused by MRSA, penicillin-resistant *S. pneumoniae*, and VRE. The mean effective protective dose was similar to linezolid in these clinically relevant infection models.

The pharmacokinetic (PK) profile of IV and PO contezolid acefosamil were evaluated in animals. Oral contezolid acefosamil was well absorbed in animals, when dosed with and without food. Oral absorption of contezolid in the mouse, rat, and dog was rapid with time to maximum concentration (absorption) (T_{max}) of 0.5 to 1 hour and a half-life ($t_{1/2}$) of 1 to 2 hours. Studies with radiolabeled ^{14}C-contezolid indicated primarily fecal excretion within the first 24 hours after PO administration. After IV administration in rats, contezolid acefosamil is rapidly metabolized into contezolid after 30 minutes; the prodrug (contezolid acefosamil) was not detectable in rat blood specimens (whole blood supernatant specimens). Peak concentrations of contezolid were demonstrated at 0.7 hours. After multiple IV doses of 40 mg/kg contezolid acefosamil in rats, no accumulation of the active molecule or its metabolites were noted over a 7-day period of consecutive administrations.

Contezolid acefosamil has good tolerability and safety, whether given PO or IV. In dog, the 28-day no-observed adverse-effect levels (NOAELs) for IV and PO contezolid acefosamil were 25 mg/kg twice daily (BID) for both sexes. In rat, the 28-day NOAELs for PO contezolid acefosamil was 80 mg/kg BID and for IV contezolid acefosamil was 160/120 mg/kg (ie, 160 mg/kg initial dose reduced to 120 mg/kg due to toxicity) BID in both sexes.

Contezolid (the pharmaceutically active moiety) was generally well tolerated in a panel of standard animal toxicology and safety pharmacology studies. In toxicology studies, contezolid was generally well tolerated after 13-week PO dosing in rats (NOAEL = 50 mg/kg/day in both sexes) and dogs (NOAEL = 60 mg/kg/day in both sexes).

A full battery of IND-enabling studies was performed with contezolid acefosamil (prodrug) and contezolid (active moiety). Contezolid acefosamil and contezolid were not phototoxic, genotoxic, clastogenic, or cytotoxic in in vitro Ames, in vitro chromosomal aberration tests, or in vivo bone marrow micronucleus tests. The NOAEL of contezolid acefosamil for potential reproductive and/or developmental toxicity was 120 mg/kg/dose BID in male and female rats. The NOAEL of contezolid acefosamil for embryo-fetal development retardation was 40 mg/kg/dose BID.

Further details regarding the microbiology and animal toxicology of contezolid and contezolid acefosamil are available in the contezolid acefosamil Investigator's Brochures (IBs).

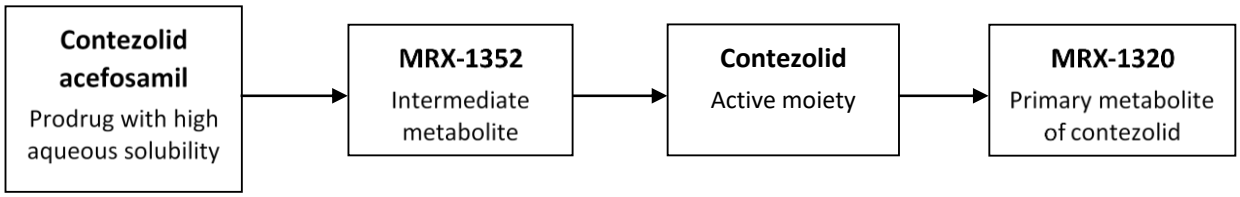
4.3.2 Relevant Clinical Experience

The main objective of the contezolid acefosamil/contezolid clinical program is to develop oxazolidinone antibiotics with improved tolerability and reduced toxicity compared to the currently available oxazolidinones (linezolid and tedizolid) while maintaining efficacy in treating serious Gram-positive bacterial infections.

4.3.2.1 Pharmacokinetics

Contezolid acefosamil (the sodium salt, prodrug of contezolid) has high aqueous solubility and degrades into bioactive contezolid in aqueous environments in a 2-step process (Figure 1). In the first degradation step, contezolid acefosamil quickly degrades into an intermediate metabolite, MRX-1352, and the second degradation step results in the active moiety, contezolid. Additionally, the primary metabolite of contezolid is MRX-1320. Neither contezolid acefosamil nor MRX-1352 have direct antibacterial activity and must be converted to contezolid to become active. Neither contezolid acefosamil, nor MRX-1352, nor the side chain fragments cleaved during biotransformation, are associated with unique toxicities in animal models.

Figure 1: Contezolid Acefosamil Metabolites



Further descriptions of the physical and chemical characteristics and PK profile of contezolid acefosamil and contezolid are found in the IBs.

4.3.2.2 Studies with Contezolid acefosamil

Contezolid acefosamil (previously referred to as MRX-4) is a novel synthetic antibiotic in the oxazolidinone class of antimicrobials and is a sodium salt prodrug of contezolid (previously referred to as MRX-1). Contezolid acefosamil has the physical and chemical characteristics needed for an IV formulation.

Across the pooled contezolid acefosamil clinical studies, 331 subjects were enrolled and received contezolid acefosamil (200 in clinical pharmacology studies and 131 in the Phase 2 ABSSSI study).

The overall safety profile of IV and PO contezolid acefosamil is consistent with known oxazolidinone class effects. No deaths or serious adverse events (SAEs) related to study drug, or dose-related or dose-limiting toxicities have been observed in the clinical development program. The treatment-emergent adverse events (TEAEs) considered related to contezolid were generally Grade 1 (mild) in severity, sporadic, and not related to a particular organ system. The most common TEAEs associated with dosing of contezolid for up to 28 days were gastrointestinal (GI) in nature; however, the GI TEAEs were generally Grade 1 (mild) in severity and did not result in study drug interruption. Laboratory abnormalities were generally Grade 1 (mild) in severity and asymptomatic.

For details on the safety, PK, and efficacy of IV and PO contezolid acefosamil, see the IB.

4.3.2.2.1 Phase 2 Study with Contezolid Acefosamil (MRX4-201)

Contezolid acefosamil, when administered IV as a single dose of 1500 mg followed by 1000 mg q12h for at least 3 total IV doses, followed by 1300 mg PO q12h, for a total of 10 to 14 days, was well tolerated and effective in treating subjects with ABSSSI, with efficacy and safety similar to that of linezolid.

Study MRX4-201 was a Phase 2, multicenter, randomized, double-blind study to evaluate the safety and efficacy of contezolid acefosamil compared with linezolid in 196 adult subjects with ABSSSI. Efforts were made to enroll a mixture of ABSSSI types (cellulitis/erysipelas, wound infection, and major cutaneous abscess, with a 30% cap on abscesses). Randomization was stratified by ABSSSI type.

Randomization had a 2:1 (contezolid acefosamil: linezolid) allocation ratio.

- Subjects randomized to the contezolid acefosamil group received a single dose of 1500 mg IV contezolid acefosamil followed by 1000 mg IV contezolid acefosamil q12h for ≥3 total IV doses, followed by 1300 mg PO contezolid acefosamil q12h, for a total of 10 to 14 days
- Subjects randomized to the linezolid group received 600 mg IV linezolid q12h for ≥3 total IV doses, followed by 600 mg PO linezolid q12h, for a total of 10 to 14 days

4.3.2.2.1.1 Disposition

The study randomized 196 male and female adult subjects with ABSSSI; 131 subjects to receive IV contezolid acefosamil and 65 subjects to receive linezolid.

Of the 196 subjects enrolled, 161 subjects completed the study (106 [80.9%] subjects in the contezolid acefosamil group and 55 [84.6%] subjects in the linezolid group). Most of the subjects in the contezolid acefosamil and linezolid groups who terminated the study early were lost to follow up or withdrew consent.

A total of 17 (13.0%) subjects in the contezolid acefosamil group and 10 (15.4%) subjects in the linezolid group prematurely discontinued study drug. The main reason for premature discontinuation of study drug was due to "other" reasons (13.0% and 3.8% subjects, respectively), most of which were related to subjects being lost to follow up.

4.3.2.2.1.2 Analysis Sets for Study MRX4-201

The number of subjects included in each analysis set by treatment group is presented in Table 2. Descriptions of the analysis sets and the relationship between analysis sets in Study MRX4-201 and the current Phase 3 study are displayed in Figure 3 and Table 12.

Table 2. Analysis Sets for Study MRX4-201

Analysis Sets	Contezolid acefosamil (N=131) n (%)	Linezolid (N=65) n (%)
ITT analysis set	131 (100)	65 (100)
MITT analysis set	122 (93.1)	64 (98.5)
Micro-ITT analysis set	91 (69.5)	46 (70.8)
Safety analysis set [a]	123 (93.9)	64 (98.5)
CE-EOT analysis set	96 (73.3)	47 (72.3)
CE-PTE analysis set	94 (71.8)	50 (76.9)
ME analysis set	62 (47.3)	33 (50.8)

CE = Clinically Evaluable; EOT = End-of-Therapy; ITT = Intent-to-Treat; ME = Microbiologically Evaluable; Micro-MITT = Microbiological Modified Intent-to-Treat; MITT = Modified Intent-to-Treat; PTE = Post-Therapy Evaluation

a. Safety analysis set is presented by treatment actually received (all subjects received correct study drug).

Note: Percentages are calculated as 100 × (n/N).

Source: MRX4-201 CSR Table 14.1.1.1

4.3.2.2.1.3 Demographics

Overall, the subjects enrolled in this study were in the younger age range (median ages of 46.0 and 47.0 years, respectively), and with normal weights and BMIs. Most subjects (>83%) had normal renal function as assessed by creatinine clearance (CrCl), and none had severe renal failure. A high proportion of subjects had a history of skin infection, injection drug use, overall drug and substance use, alcohol use, and hepatitis C.

The distribution of infection types at Baseline in the contezolid acefosamil and linezolid groups was cellulitis/erysipelas (17.6% and 18.5%), wound infection (70.2% and 67.7%), and major cutaneous abscess (12.2% and 13.8%), respectively. The predominance of wound infections reflected the types of subjects enrolled by the 7 sites that participated in the study, many of whom had infections precipitated by penetrating trauma through the skin. The most commonly reported anatomical sites of infection in both treatment groups were upper and lower extremities.

In the Microbiological Intent-to-Treat (Micro-ITT) analysis set, the most frequently cultured ABSSSI pathogen at Baseline in both the contezolid acefosamil and linezolid groups were MRSA (45.1% and 60.9%) and MSSA (25.3% and 28.3%), respectively. Additionally, *Streptococcus intermedius* and *Streptococcus pyogenes* were cultured from subjects in the contezolid acefosamil group (11% for both pathogens) and linezolid group (8.7% and 6.5%, respectively).

4.3.2.2.1.4 Safety

Safety analyses were conducted in the Safety analysis set. There were no unexpected safety signals. There was no clear trend in either treatment group in mean change from Baseline at any post-Baseline visit or across visits for any of the measured clinical laboratory parameters (hematology, chemistry, urinalysis [UA]), vital signs, or electrocardiograms (ECGs).

4.3.2.2.1.4.1 Adverse Events

The incidences of TEAEs were similar in the contezolid acefosamil (44.7%) and linezolid (42.2%) groups. The most common TEAEs (>5% of subjects in any group) were nausea, vomiting, and cellulitis in both the contezolid acefosamil and linezolid groups.

The System Organ Classes (SOC) with the highest incidence of TEAEs in the contezolid acefosamil and linezolid groups were Gastrointestinal Disorders (22.8% and 15.6%) and Infections and Infestations (21.1% and 20.3%), respectively.

- The incidence of TEAEs in the Gastrointestinal Disorders SOC was higher for the contezolid acefosamil group compared with the linezolid group
  - In the contezolid acefosamil group, the incidence of GI TEAEs was similar during the IV (9.8%) and PO (12.3%) administration periods, whereas in the linezolid group, the incidence was lower during the IV administration (3.1%) than PO administration (13.6%)
  - Most GI TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity
  - No GI TEAEs resulted in study drug discontinuation in either group
  - No TEAEs of *C. difficile* were reported
- The incidence and distribution of TEAEs in the Infections and infestations SOC was comparable for both study drugs

The only TEAE differing in incidence by >5.0% between treatment groups was nausea, experienced by 18 (14.6%) subjects in the contezolid acefosamil group and 5 (7.8%) subjects in the linezolid group. The incidence of TEAEs of nausea in the contezolid acefosamil group was similar during the IV (7.3%) and PO (7.9%) administration periods, whereas the incidence of nausea in the linezolid group was lower during the IV (1.6%) than PO (6.8%) administration periods.

The incidences of study drug-related TEAEs were similar in the contezolid acefosamil (16.3%) and linezolid (14.1%) groups. Nausea and vomiting were the most commonly reported study drug-related TEAEs, and none were serious or resulted in study drug discontinuation.

Most TEAEs, including GI TEAEs, were Grade 1 (mild) or Grade 2 (moderate) in severity in both groups. The incidence of Grade 2 (moderate) and Grade 3 (severe) GI TEAEs was similar between the 2 groups, and none resulted in premature discontinuation of either study drug. Grade 3 (severe) TEAEs were experienced by 4 (3.3%) subjects in the contezolid acefosamil group (abdominal pain, inguinal hernia, nausea, and fatal overdose [acute heroin, fentanyl, methamphetamine, and lorazepam intoxication] in 1 subject each). Grade 3 (severe) TEAEs were experienced by 2 (3.1%) subjects in the linezolid group (retinal detachment and eye infection, and fatal road traffic accident).

TEAEs leading to study drug discontinuation were reported in 1 subject in each group: an SAE of bacteremia in the contezolid acefosamil group and a Grade 1 (mild) TEAE of infusion site pain in the linezolid group. Both events were considered not related to study drug by the Investigator.

4.3.2.2.1.4.2 Serious Adverse Events

SAEs were experienced by 3 (2.4%) subjects in the contezolid acefosamil group and 1 subject (1.6%) in the linezolid group, all considered not related to study drug by the Investigator.

In the contezolid acefosamil group:

- One fatal SAE of overdose (verbatim term: acute heroin, fentanyl, methamphetamine, and lorazepam intoxication)
- One Grade 2 (moderate) SAE of bacteremia (*Acinetobacter johnsonii, Acinetobacter lwoffii, E. coli, Pseudomonas putida,* and *Aerococcus viridans* were cultured from the blood) that resulted in hospitalization
- One Grade 2 (moderate) SAE of secondary wound infection that resulted in hospitalization, and which occurred 3 days after completing study drug treatment

In the linezolid group:

- One fatal SAE of road traffic accident (subject struck by car while walking)

4.3.2.2.1.4.3 Visual Acuity Test Scores

No clinically significant changes were observed in either group as assessed by the Snellen visual acuity test scores. Two (2) subjects in the contezolid acefosamil group reported Grade 1 (mild) in severity, nonserious TEAEs of vision blurred considered possibly related to study drug by the Investigator, that were not associated with clinically significant changes in visual acuity test scores. Both subjects recovered while continuing to receive study drug. Visual blurring has been reported in subjects treated with linezolid for <28 days and does not constitute a new safety signal (Zyvox® Prescribing Information 2021).

4.3.2.2.1.4.4 Hematology Abnormalities

No hematological abnormalities were associated with TEAEs in this study, although hematological and liver laboratory abnormalities are known oxazolidinone class effects (Zyvox® Prescribing Information 2021; Sivextro® Prescribing Information 2019; Section 4.1.1).

The incidence of shifts for neutrophils of ≥2 Division of Microbiology and Infectious Diseases (DMID) toxicity grades (Appendix 1 in Section 18.1) from Baseline to lowest post-Baseline value was lower in the contezolid acefosamil group (0 subjects) compared with the linezolid group (2 [3.7%] subjects). The incidence of shifts for hemoglobin and platelets were comparable between treatment groups.

Hematology values below the lower limit of normal in the contezolid acefosamil group, compared with the linezolid group, were less frequent for neutrophils (3.7% vs 7.4%) and platelets (7.6% vs 12.1%) and comparable for hemoglobin (73.9% vs 74.1%), respectively.

Hematology values considered substantially abnormal in the contezolid acefosamil group compared with the linezolid group were less frequent for neutrophils (0% vs 3.7%) and platelets (2.5% vs 5.2%) and comparable for hemoglobin (0% in both groups), respectively.

4.3.2.2.1.4.5 Chemistry Abnormalities

No chemistry abnormalities in the contezolid acefosamil group were associated with TEAEs; 1 subject in the linezolid group had a Grade 1 (mild) TEAE of hepatic enzyme increased. No subject in either treatment group met Hy's law criteria.

A higher incidence of shifts of ≥2 DMID toxicity grades (Appendix 1 in Section 18.1) from Baseline to highest values were observed in the contezolid acefosamil group compared to the linezolid group for alanine aminotransferase (ALT) (4.2% vs 0%), aspartate aminotransferase (AST) (4.1% vs 0%), gamma-glutamyl transpeptidase (5.2% vs 0%), and uric acid (1.7% vs 0%).

Most chemistry laboratory abnormalities were not considered substantially abnormal. Substantially abnormal values of ALT and/or AST were reported in 7 subjects in the contezolid acefosamil group and 1 subject in the linezolid group. However, the frequency of all other chemistry values that were above the upper limit of normal (ULN) was comparable between the 2 groups or lower in the contezolid acefosamil group. In the contezolid acefosamil group, most elevations peaked at End-of-Therapy (EOT) or later and all resolved, or were resolving, at Late Follow-Up (LFU) (10 to 14 days after EOT). Three (3) of the 7 subjects in the contezolid acefosamil group who had substantially abnormal post-Baseline ALT and/or AST elevations also had viral hepatitis at Baseline and the other 4 subjects had a history of alcohol and heroin use.

4.3.2.2.1.4.6 Vital Signs and Electrocardiograms

No subjects in the contezolid acefosamil group had a vital sign measurement reported as a TEAE; 1 subject in the linezolid group experienced a TEAE of hypertension. In general, changes in vital signs were comparable between groups.

There were no TEAEs associated with any post-Baseline ECG evaluations. In general, ECG evaluations were comparable between treatment groups.

4.3.2.2.1.5 Efficacy

Although this exploratory study was not powered for noninferiority (NI), the study incorporated recommendations from the US FDA Guidance for Industry on developing antibacterial treatment for ABSSSI (2013). Secondary endpoints align with the European Medicines Agency (EMA) Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections, Rev. 3 (2018).

4.3.2.2.1.5.1 Primary Efficacy Endpoint

The percentages of subjects in the Intent-to-Treat (ITT) analysis set who had early clinical responses at Early Assessment (EA) were similar between the contezolid acefosamil (77.9%) and linezolid (78.5%) groups (Table 3).

The rate of nonresponders was lower in the contezolid acefosamil group (2.3%) compared with the linezolid group (9.3%). Of note, the rate of indeterminate responses in the contezolid acefosamil group was higher than in the linezolid group, in large part due to the number of subjects in the contezolid acefosamil group who were randomized but never dosed (8/26 vs 1/8); similar results were seen for the secondary endpoints in the ITT, Modified Intent-to-Treat (MITT), and Micro-ITT analysis sets (Section 4.2.2.1.1.5.2).

Table 3. MRX4-201 Early Clinical Response at the Early Assessment Visit (ITT Analysis Set)

Response Category	Treatment Group				Difference
	Contezolid acefosamil (N=131)		Linezolid (N=65)		95% CI[b]
	n (%)	95% CI[a]	n (%)	95% CI[a]	
Responder	102 (77.9)	(69.8,84.6)	51 (78.5)	(66.5,87.7)	-0.6 (-14.0,12.8)
Nonresponder	3 (2.3)	--	6 (9.2)	--	--
Indeterminate	26 (19.8)	--	8 (12.3)	--	--

CI = confidence interval; ITT = Intent-to-Treat
a. 95% CI for responder rate using the Exact (Clopper-Pearson) Confidence Limits.
b. Difference in responder rates for contezolid acefosamil minus the responder rate for linezolid and the CI for this difference is based on Wald Method with Continuity Correction.
Note: Percentages are calculated as 100 × (n/N).
Source: MRX4-201 CSR Table 14.2.1.1

4.3.2.2.1.5.2 Secondary Efficacy Endpoints

Clinical responses for secondary endpoints (Table 4) were consistent with and supportive of the primary endpoint results (Table 3). The percentage of subjects who were early clinical responders or a clinical success, as assessed by the Investigator, were similar between the contezolid acefosamil and linezolid groups for all study analysis sets (ITT, MITT, Clinically Evaluable [CE]-EOT, CE-Post-Therapy Evaluation [PTE], CE at LFU [CE-LFU]) and at all analysis timepoints (EA, EOT, PTE, LFU).

Table 4. MRX4-201 Early Clinical Responder and Investigator Assessed Clinical Success Rates

Analysis Set	Time point	Treatment Group				Difference 95% CI[b]
		Contezolid acefosamil (N=131)		Linezolid (N=65)		
		n (%)	95% CI[a]	n (%)	95% CI[a]	
MITT	EA	95 (77.9)	(69.5,84.9)	50 (78.1)	(66.0,87.5)	-0.3 (-14.0,13.5)
ITT by ABSSSI type						
Cellulitis/ erysipelas	EA	19 (82.6)	(61.2,95.0)	12 (100)	(73.5,100.0)	-17.4 (-39.2,4.4)
Wound infection		68 (73.9)	(63.7,82.5)	34 (77.3)	(62.2,88.5)	-3.4 (-20.3,13.6)
Major cutaneous abscess		15 (93.8)	(69.8,99.8)	5 (55.6)	(21.2,86.3)	38.2 (-5.0,81.4)
ITT	EOT	107 (81.7)	(74.0,87.9)	52 (80.0)	(68.2,88.9)	1.7 (-11.2,14.6)
MITT		98 (80.3)	(72.2,87.0)	52 (81.3)	(69.5,89.9)	-0.9 (-14.0,12.2)
CE-EOT		95 (99.0)	(94.3,100.0)	44 (93.6)	(82.5,98.7)	5.3 (-3.5,14.2)
ITT	PTE	100 (76.3)	(68.1,83.3)	48 (73.8)	(61.5,84.0)	2.5 (-11.6,16.6)
MITT		91 (74.6)	(65.9,82.0)	48 (75.0)	(62.6,85.0)	-0.4 (-14.7,13.9)
CE-PTE		91 (96.8)	(91.0,99.3)	45 (90.0)	(78.2,96.7)	6.8 (-3.8,17.4)
ITT by ABSSSI type						
Cellulitis/ erysipelas	PTE	18 (78.3)	(56.3,92.5)	9 (75.0)	(42.8,94.5)	3.3 (-32.8,39.3)
Wound infection		69 (75.0)	(64.9,83.4)	31 (70.5)	(54.8,83.2)	4.5 (-13.3,22.4)
Major cutaneous abscess		13 (81.3)	(54.4,96.0)	8 (88.9)	(51.8,99.7)	-7.6 (-44.4,29.1)
ITT	LFU	94 (71.8)	(63.2,79.3)	48 (73.8)	(61.5,84.0)	-2.1 (-16.4,12.2)
MITT		87 (71.3)	(62.4,79.1)	48 (75.0)	(62.6,85.0)	-3.7 (-18.2,10.8)
CE-LFU		86 (91.5)	(83.9,96.3)	45 (90.0)	(78.2,96.7)	1.5 (-10.1,13.1)

ABSSSI = acute bacterial skin and skin structure infections; CE = Clinically Evaluable; CI = confidence interval; EOT = End-of-Therapy; ITT = Intent-to-Treat; LFU = Late Follow-Up; ME = Microbiologically Evaluable; MITT = Modified Intent-to-Treat; PTE= Post-Therapy Evaluation

a. 95% CI for responder rate using the Exact (Clopper-Pearson) Confidence Limits.

b. Difference in responder rates for contezolid acefosamil minus the responder rate for linezolid and the CI for this difference is based on Wald Method with Continuity Correction.

Note: Percentages are calculated as 100 × (n/N).

Source: MRX4-201 CSR Table 14.2.2.1, Table 14.2.4.1, Table 14.2.8.1, Table 14.2.8.2, Table 14.2.8.3, and 14.2.8.4, Table 14.2.10.1

4.3.2.3 Studies with Contezolid

Before the start of the contezolid acefosamil studies, the clinical program initiated 6 Phase 1 (5 under China National Medical Products Administration [NMPA] IND, 1 under US FDA IND), two Phase 2 (1 under China NMPA IND, 1 under US FDA IND), and one Phase 3 study (under China NMPA IND) with PO contezolid (the active moiety of contezolid acefosamil).

For details on the safety, efficacy, and PK of PO contezolid, see the IB.

The overall safety profile of PO contezolid is consistent with known oxazolidinone class effects. No deaths or dose-related or dose-limiting toxicity was observed in the clinical development program. Only 1 subject (in the contezolid group) experienced a study-drug related SAE (severe gastrointestinal discomfort reported as an SAE because the subject was switched to an IV antibiotic that required hospitalization). The TEAEs considered related to contezolid were generally Grade 1 (mild) in severity, sporadic, and not related to a particular organ system. The most common TEAEs associated with dosing of contezolid for up to 28 days were GI in nature; however, the GI TEAEs were generally Grade 1 (mild) in severity and did not result in study drug interruption. Laboratory abnormalities were generally Grade 1 (mild) in severity and asymptomatic.

4.3.2.3.1 Phase 3 Efficacy, Pharmacokinetic, and Safety Study (MRX-I-06)

Study MRX-I-06 was a Phase 3, multicenter, randomized, double-blind, double-dummy study evaluating the safety and efficacy of PO contezolid vs linezolid in adult subjects with cSSSI. Chinese subjects with cSSSI (wound infection, post-traumatic infection, surgical wound infection, or infectious ulcer) caused by Gram-positive pathogens were randomized (1:1) to PO contezolid (800 mg q12h) or PO linezolid (600 mg q12h) for 7 to 14 days.

4.3.2.3.1.1 Subject Disposition

A total of 719 subjects were randomized: 360 subjects to the contezolid group and 359 subjects to the linezolid group. Most subjects completed the study in the contezolid (81.1%) and linezolid (83.3%) groups. The most common reasons for withdrawal in the contezolid and linezolid groups were withdrawal of informed consent (5.3% vs 3.3%) and loss to follow up (1.7% vs 4.5%), respectively. Most subjects in the contezolid and linezolid groups were included in the Full Analysis Set (FAS) (92.5% vs 93.6%) and CE-Test-of-Cure (TOC) analysis set (79.7% vs 84.1%) used for the co-primary efficacy endpoint.

4.3.2.3.1.2 Subject Demographics and Baseline Characteristics

A majority of subjects were male (65.0%) and Han Chinese (94.2%). The mean age was 41.5 years and the mean body mass index was 25.21 kg/m^2. Demographics were balanced and comparable between treatment groups. The major coexisting diseases or conditions in the contezolid and linezolid groups were hypertension (14.4% vs 13.7%), diabetes (8.7% vs 10.7%), and tinea (5.4% vs 7.7%), respectively.

Clinical signs and symptoms of cSSSI were balanced and comparable between treatment groups. The types of infections in the contezolid and linezolid groups were main cutaneous abscess (44.1% vs 42.0%), cellulitis (47.4% vs 50.6%), and wound infection/post-traumatic infection/surgical wound infection/infectious ulcer (8.1% vs 7.1%), respectively. The most common infection sites in the contezolid and linezolid groups were lower limbs (53.5% vs 51.2%) and buttocks (13.2% vs 12.5%), respectively. The mean infected area was 250.7 cm^2 in MRX-I group and 272.4 cm^2 in the linezolid group, respectively. The symptoms of most subjects in the infection sites included erythema (98.2% vs 99.1%), local fever (95.2% vs 97.3%), pain/tenderness (98.5% vs 98.5%), and swelling/induration (98.2% vs 97.0%), respectively. cSSSI clinical signs and symptoms were similar in the CE analysis set.

Baseline pathogen distribution was balanced and comparable between treatment groups. Most subjects in the contezolid and linezolid groups had a single bacterium (92.9% vs 93.8%) and only Gram-positive bacterial infection (70.2% vs 67.6%), respectively. The main Baseline pathogen was S. aureus (61.8% vs 54.2%), dominated by MSSA. The next most common pathogens in the contezolid and linezolid groups were coagulase negative staphylococci (16.4% vs 23.9%) and streptococci (6.6% vs 8.4%), respectively.

Most subjects in the contezolid and linezolid groups did not use any antibiotics within 72 hours before enrollment (67.9% vs 69.3%), respectively. Most of the subjects in the contezolid and linezolid groups who used antibiotics within 72 hours before enrollment had a duration of ≤24 hours (63.6% vs 57.3%), while a few had a duration >72 hours with no response (36.4% vs 42.7%), respectively.

4.3.2.3.1.3 Efficacy

4.3.2.3.1.3.1 Primary efficacy endpoint

At the TOC visit, contezolid was not inferior to linezolid in the FAS and CE-TOC analysis sets.

For the co-primary efficacy endpoint, the clinical cure rate in the FAS at the TOC visit was 92.8% in the contezolid group and 93.4% in the linezolid group (Table 5). The difference of clinical cure rate between the treatment groups was -0.6%, and the lower bound of the 95% confidence interval (CI) of the difference (-4.7%, 3.5%) was greater than the preset noninferiority threshold of -10%.

For the co-primary efficacy endpoint, the clinical cure rate in the CE analysis set at the TOC visit was 93.0% in the contezolid group and 93.4% in the linezolid group (Table 5). The difference of clinical cure rate between the treatment groups was -0.3%, and the lower bound of the 95% CI of the difference (-4.4%, 3.7%) was greater than the preset noninferiority threshold of -10%.

Table 5. MRX-I-06 Primary Efficacy Endpoint

	FAS		CE Analysis Set	
	Contezolid (N=292)	**Linezolid (N=304)**	**Contezolid (N=287)**	**Linezolid (N=302)**
Clinical efficacy at TOC, n (%)				
Cured	271 (92.8%)	284 (93.4%)	267 (93.0%)	282 (93.4%)
Invalid	21 (7.2%)	20 (6.6%)	20 (7.0%)	20 (6.6%)
95% CI	(89.2%, 95.5%)	(90.0%, 95.9%)	(89.4%, 95.7%)	(90.0%, 95.9%)
Comparison between contezolid and linezolid groups				
Difference	-0.6%		-0.3%	
95% CI	(-4.7%, 3.5%)		(-4.4%, 3.7%)	
P value	0.595		0.704	

CE = Clinically Evaluable; CI = confidence interval; FAS = Full Analysis Set; TOC = Test-of-Cure

4.3.2.3.1.3.2 Sensitivity Analysis of Primary Efficacy Endpoint

Since 7 subjects (5 in the contezolid group and 2 in the linezolid group) used antibiotics between EOT and TOC visits, leading to impossible evaluation of the clinical efficacy at the TOC visit, the 7 subjects were excluded from the CE-TOC analysis set, and included as nonevaluable treatment failure cases for the sensitivity analysis of clinical efficacy, microbiological efficacy and overall efficacy of subjects at the TOC visit.

In the sensitivity analysis, the clinical cure rate was 91.4% (95% CI: 87.6%, 94.4%) in the contezolid group and 92.8% (95% CI: 89.2%, 95.4%) in the linezolid group. The difference of clinical cure rate between the treatment groups was -1.3%, and the lower bound of the 95% CI of the difference (-5.7%, 3.0%) was greater than the preset noninferiority threshold of -10%.

4.3.2.3.1.3.3 Secondary Efficacy Endpoints

For all secondary efficacy endpoints, clinical and microbiological efficacy results in the contezolid group were similar to those in the linezolid group and supported the results for the primary efficacy endpoint.

Clincial cure at EOT was similar in the contezolid and linezolid groups (Table 6). The clinical cure rates of contezolid and linezolid for different infection types of (main cutaneous abscess; cellulitis; wound infection, post-traumatic infection, surgical wound infection, infectious ulcer) were high (>80%) and similar at the TOC visit in the FAS. Similar results were also obtained at the EOT visit. In the CE analysis set, the clinical efficacy results at TOC and EOT visits for different infection types were similar to that in the FAS.

Table 6. MRX-I-06 Secondary Efficacy Endpoints at EOT

	FAS		CE Analysis Set	
	Contezolid (N=299)	**Linezolid (N=314)**	**Contezolid (N=293)**	**Linezolid (N=312)**
Clinical efficacy at EOT, n (%)				
Cured	281 (94.0%)	299 (95.2%)	276 (94.2%)	297 (95.2%)
Invalid	18 (6.0%)	15 (4.8%)	17 (5.8%)	15 (4.8%)
95% CI	(90.7%, 96.4%)	(92.2%, 97.3%)	(90.9%, 96.6%)	(92.2%, 97.3%)
Comparison between contezolid and linezolid groups				
Difference	-1.2%		-1.0%	
95% CI	(-4.8%, 2.3%)		(-4.6%, 2.6%)	
P value	0.392		0.488	

CE = Clinically Evaluable; CI = confidence interval; FAS = Full Analysis Set; EOT = End-of-Therapy

At the TOC visit in the modified FAS (all randomized subjects who received ≥1 dose of study drug, qualified for cSSSI diagnosis, and received ≥1 follow-up observation), the bacterial clearance rate was 93.5% in the contezolid group and 93.9% in the linezolid group (p>0.999).

The infections caused by different pathogens were dominated by those caused by *Staphylococcus aureus*. The cure rates of contezolid at the TOC visit in the treatment of MRSA and MSSA induced infections of the FAS were 93.8% and 92.4% respectively, which were similar to those of the linezolid group. The clinical cure rates of infections caused by streptococci, enterococci or anaerobic Gram-positive bacteria was 100%, which was also similar to those in the linezolid group. Results were similar in the CE-TOC analysis set.

Single bacterium and multiple bacteria showed similar clearance rates in both groups. In the FAS, the clinical cure rate of subjects in the contezolid group and linezolid group with single aerobic Gram-positive bacteria infections were 93.6% (103/110) and 92.3% (108/117); and that with single anaerobic Gram-positive bacteria infections were 100% (5/5) and 100% (7/7). The clinical cure rates for multiple bacteria infections in the contezolid group and linezolid group were both 100%. The clinical cure rate of subjects with MRSA infection was 93.8% (15/16) in the contezolid group and 92.3% (12/13) in the linezolid group. Results were similar in the CE-TOC analysis set.

4.3.2.3.1.4 Safety

The incidences of TEAEs were similar in the contezolid (47.5%) and linezolid (48.4%) groups. The most common clincial TEAEs in the contezolid and linezolid groups were upper respiratory tract infection (7.3% vs 5.4%); nausea in GI diseases (4.5% vs 2.8%), vomiting (3.4% vs 0.9%); fever in various reactions of systemic diseases and administration sites (3.1% vs 2.3%), respectively. The most common laboratory abnormalities in the contezolid and linezolid groups were elevation of ALT (10.7% vs 1.1%), elevation of AST (7.3% vs 6.8%), elevation of blood uric acid (2.3% vs 2.3%), decreased white blood-cell count (0.6% vs 3.7%) and decreased platelet count (0% vs 2.3%), respectively.

The incidences of drug-related TEAEs were similar in the contezolid (23.4%) and linezolid (26.8%) groups. Most study-drug realted TEAEs in the contezolid and linezolid groups were mild in severity. Severe study-drug related TEAEs occurred in 4 (4.8%) subjects in the contezolid group and no subjects in the linezolid group. Hematological abnormalities related to study drug were less in the contezolid group than in the linezolid group; neutrophile granulocyte count decrease (0.3% and 1.7%, respectively), reticulocyte count decrease (0.3% and 1.4%, respectively), and platelet count decrease (0% and 2.3%, respectively).

The incidences of SAEs were similar in the contezolid (3.7%) and linezolid (2.6%) groups. Only 1 subject (in the contezolid group) experienced a study-drug related SAE (severe gastrointestinal discomfort reported as an SAE because the subject was switched to an IV antibiotic that required hospitalization).

The incidences of advere events (AEs) leading to early withdrawal from the study were similar in the contezolid (4.0%) and linezolid (1.1%) groups.

4.3.2.3.1.5 Pharmacokinetics

In a contezolid population PK analysis, the type of subjects (healthy subjects in Study MRX-I-04 vs cSSSI subjects in study MRX-I-06) had an impact on the distribution volume, but no significant impact on clearance or exposure. Weight had an impact on clearance and distribution volume, but little impact on exposure. Thus, contezolid dose adjustment by weight is not necessary.

4.4 Summary of Benefits and Risks

Further information is provided in the contezolid acefosamil and contezolid IBs and can also be obtained from the prescribing information for linezolid (Zyvox® Prescribing Information 2021).

4.4.1 Potential Benefits

Based on a recently completed Phase 2 study of contezolid acefosamil (Section 4.3.2.2.1) and completed Phase 3 study of contezolid (Section 4.3.2.3.1), as well as in vivo and in vitro data, it is anticipated that subjects participating in this study who are randomized to the contezolid acefosamil/contezolid treatment group should experience at least similar therapeutic benefits as subjects randomized to the linezolid group. Approximately 60% of the subjects enrolled in this study will be randomized to receive contezolid acefosamil/contezolid for treatment of their DFI.

The therapeutic benefit of linezolid (comparator) for the treatment of DFI has been established (Zyvox® Prescribing Information 2021). Approximately 40% of the subjects enrolled in this study will be randomized to receive linezolid for treatment of their DFI.

4.4.2 Known Risks

Overall, IV contezolid acefosamil was well tolerated in Phase 1 and Phase 2 studies (Section 4.3.2.2) and PO contezolid was well tolerated in Phase 1, Phase 2, and Phase 3 studies (Section 4.3.2.3.).

Overall, linezolid was well tolerated in clinical registration trials. Warnings and precautions in the linezolid label include the risks for myelosuppression, peripheral and optic neuropathy, serotonin syndrome, *Clostridium difficile*-associated diarrhea (CDAD), and potential drug interactions producing hypertension and hypoglycemia.

Based on linezolid (Zyvox® Prescribing Information 2021) prescribing information, linezolid and contezolid acefosamil and contezolid (as oxazolidinones) are contraindicated in subjects with known hypersensitivity to oxazolidinones and in subjects taking any monoamine oxidase inhibitors (MAOIs) or within 2 weeks of taking an MAOI.

4.4.3 Potential Risks

CDAD has been reported with the use of nearly all systemic antibacterial agents, including linezolid, and may range in severity from Grade 1 (mild) diarrhea to fatal colitis (Zyvox® Prescribing Information 2021). In all subjects who present with diarrhea following antibiotic use, including contezolid acefosamil/contezolid use, CDAD must be considered. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

4.5 Justification for the Study Design and Dosing Regimen

4.5.1 Study Design

The primary and secondary efficacy endpoints were developed with input from clinical experts for DFI, as well as in collaboration with regulatory authorities. The primary endpoint (Investigator's assessment of clinical response at Day 35 (D35) was selected as a clinically relevant and meaningful endpoint. The study design incorporates feedback from the FDA and EMA.

The safety parameters monitored during the study are well-accepted measures of safety in clinical study subjects.

Blood specimens will be obtained at selected clinical sites to understand the PK performance of contezolid tablets used in this study population. Contezolid acefosamil PK concentrations will not be assessed in this study based on Phase 1 study results indicating rapid conversion (within 0.25 hours) of contezolid acefosamil to MRX-1352, an intermediate metabolite of the prodrug, and subsequent conversion to active contezolid. The levels of the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320 will be assessed.

A COVID-19 risk mitigation approach for this study has been developed to provide guidance on study conduct and oversight in the setting of the COVID-19 global pandemic. The plan has been developed to ensure the safety of study subjects and minimize risk to trial integrity while maintaining compliance with Good Clinical Practices (GCP).

4.5.2 Dosing Regimen

The IV contezolid acefosamil doses chosen for this study (Section 8.0) were evaluated in two Phase 1 studies (MRX4-002 and MRX4-003) and a Phase 2 ABSSSI study (MRX-201; Section 4.3.2.2.1), in which IV contezolid acefosamil was well tolerated. In addition, clinical PK results of contezolid acefosamil trials are supportive of the IV dose in subjects with DFI.

The PO contezolid dose regimen chosen for this study (Section 8.0) was evaluated in two Phase 2 studies (MRX-I-03 and MRX-I-04) and a Phase 3 study (MRX-I-06) in cSSSI and ABSSSI studies (Section 4.3.2.3), in which PO contezolid was well tolerated and noninferior to linezolid. This same contezolid dose regimen was approved by the China National Medical Products Administration in June 2021 for the treatment of complicated skin and soft tissue infections (Hoy 2021). In addition, clinical PK results of contezolid are supportive of PO dosing in subjects with DFI.

The linezolid dose regimen is based on the current prescribing information (Zyvox® Prescribing Information 2021).

4.5.2.1 Population Pharmacokinetic Modeling

Population PK modeling supports the dosing regimen in this Phase 3 study. The population PK analysis comprised data on IV contezolid acefosamil and PO contezolid in healthy volunteers from Phase 1 studies and subjects from Phase 2 ABSSSI and cSSSI studies. Due to the rapid conversion and the limited stability of contezolid acefosamil, the final population PK modeling analysis contained data on contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320. This combined dataset was used for simultaneous estimation of all model parameters.

Monte Carlo simulations were performed for subjects receiving possible IV contezolid acefosamil and PO contezolid dosage regimens in this Phase 3 study (1000 subjects simulated for each dosage regimen). All dosage regimens started with 2000 mg contezolid acefosamil as a 90-minute infusion at 0 hour and then included different numbers of additional contezolid acefosamil IV infusions of 1000 mg over 60 minutes q12h starting at 12 hours. Twelve hours after the last IV dose, contezolid was dosed PO at 800 mg q12h with food for the remainder of the simulations. These simulations used the larger variability in clearance estimated in Phase 2 subjects. All simulations were performed in the Berkeley Madonna software package and included the covariance between the maximum rate of an enzyme catalyzed reaction (V_{max}) and substrate concentration that yield a half-maximal velocity (K_m) of MRX-1320. The adaptive step-size differential equation solver was used for simulations and percentiles of individual plasma concentration time-profiles calculated via Perl scripts.

The Phase 3 dose regimen simulation yielded efficacious contezolid exposures as early as Day 1 (D1) due to the 2000 mg contezolid acefosamil IV loading dose. Thus, steady-state contezolid exposures were attained by Day 1 to Day 2, and these exposures were maintained throughout the 14 days of therapy. Both the average contezolid exposures (area under the time-concentration curve) and their between-subject variability were reasonably well matched between the IV and PO dosing phase. Neither contezolid nor the contezolid acefosamil metabolite MRX-1352 showed accumulation on later days of therapy. However, a small fraction of subjects was predicted to have a comparatively large contezolid metabolite MRX-1320 exposure. At present, this simulation is an extrapolation and that increase may be caused by the large between-subject variability in Phase 2 subjects. Such accumulation of MRX-1320 was not seen in the US Phase 2 study in ABSSSI (MRX4-201). By obtaining plasma concentrations in this Phase 3 study, we will evaluate whether a small fraction of subjects shows higher MRX-1320 concentrations during the later days of therapy.

Detailed information is provided in the contezolid acefosamil Investigator's Brochure.

4.6 Study Population

Adult males and females, 18 years of age or older, with DFI.

5.0 STUDY OBJECTIVES

The objectives of this study are to compare contezolid acefosamil/contezolid to linezolid in treating DFI that are confirmed or suspected to be caused by Gram-positive pathogens.

Primary:

- The primary objective is to evaluate the Investigator's assessment of clinical response at D35 in subjects receiving contezolid acefosamil/contezolid compared to subjects receiving linezolid in the MITT analysis set
- Evaluate the safety and tolerability of contezolid acefosamil (IV)/contezolid (PO) compared with linezolid (IV and PO)

Secondary:

- Evaluate the Investigator's assessment of clinical response at:
  - EOT visit in the MITT analysis set
  - D35 in the CE at D35 (CE-D35) analysis set

Exploratory

- Evaluate the Investigator's assessment of clinical response at Day 10 (D10) and LFU (28-35 days after EOT) in the MITT analysis set
- Evaluate the Investigator's assessment of clinical response at D10, EOT, D35, LFU in the ITT analysis set
- Evaluate the Investigator's assessment of clinical response at LFU in the CE-D35 analysis set
- Evaluate the Investigator's assessment of clinical response at EOT in the CE at EOT (CE-EOT) analysis set
- Evaluate the Investigator's assessment of DFI signs and symptoms in the CE-EOT and CE-D35 analysis sets (an infection scoring system will be described in the SAP)
- Evaluate the Investigator's assessment of clinical response stratified by the presence or absence of adjunctive therapies (eg, daily debridement) and by the receipt of prior antibacterial drug therapy in the CE-D35 analysis set
- Evaluate the Investigator's assessment of clinical response stratified by presence of ulceration/wound in the CE-D35 analysis set
- Evaluate the percent reduction in the surface area of redness, edema, and/or induration of the primary DFI site at Day 5, EOT, and D35 compared to Baseline, measured in subjects who did not receive any rescue antibiotic therapy and are alive
- Evaluate per-subject microbiological response at:
  - D35 in the Microbiological-MITT (Micro-MITT) analysis set
  - D35 in Microbiologically Evaluable (ME) at D35 (ME-D35) analysis set

- Evaluate per-pathogen microbiological response at:
  - D35 in the Micro-MITT and ME-D35 analysis sets
  - EOT in the Micro-MITT and ME at EOT (ME-EOT) analysis sets
- Evaluate Investigator's assessment of clinical response at:
  - D35 (overall and by Baseline pathogen) in the Micro-MITT and ME-D35 analysis sets
  - LFU (overall and by Baseline pathogen) in the Micro-MITT and ME-D35 analysis sets
- Evaluate all-cause mortality at Day 28 in the ITT and MITT analysis sets
- Evaluate the composite endpoint of death, unplanned amputation, and infectious complications of the primary DFI in the CE-D35 and CE-LFU analysis sets
- Evaluate changes between Baseline and D35 in subject quality-of-life assessments (Short Form-36 [SF-36] Health Survey) (Ware 1992).
- Characterize the PK profile for the contezolid acefosamil metabolite (MRX-1352), contezolid, and the contezolid metabolite (MRX-1320) using sparse PK sampling in adult subjects with moderate or severe DFI

Additional exploratory analyses may be conducted and described in the SAP.

6.0 STUDY DESIGN

6.1 Type of Study

This is a Phase 3, multicenter, randomized, double-blind, safety and efficacy study of contezolid acefosamil (IV)/contezolid (PO) compared with linezolid (IV and PO) administered for a total of 14 to 28 days in adult subjects with moderate or severe DFI.

Approximately 865 subjects (519 contezolid acefosamil/contezolid:346 linezolid) will be enrolled at approximately 75 sites to achieve approximately 820 (492 contezolid acefosamil/contezolid: 328 linezolid) subjects with moderate or severe DFI that are confirmed or suspected to be due to a Gram-positive bacterial pathogen (MITT analysis set). Prompt enrollment procedures are encouraged to allow for prompt administration of study drug. Screening/Baseline assessments for study eligibility will be performed within 48 hours of randomization on D1.

Patients with concurrent suspected or proven osteomyelitis related to the primary DFI (specific DFI for which the subject was enrolled), or as a separate infection, will be excluded from the study. The presence of suspected osteomyelitis will be based on results from ≥1 of the following diagnostic studies: probe-to-bone test, erythrocyte sedimentation rate (ESR), or plain foot X-rays, which are all required at Screening/Baseline. If results from these diagnostic studies are compatible with osteomyelitis, or if the Investigator continues to suspect the possible presence of osteomyelitis, the subject will not be enrolled into the study. Plain foot X-rays will also be performed at the EOT visit to assess if any new changes compatible with osteomyelitis developed during the study period.

Non-surgeon Investigators should consider surgical consultation in more serious cases of moderate infections; all cases of severe infections; and in subjects with possible deep (below the fascia) infection, abscess, compartment syndrome, or severe lower limb ischemia. Lower limb arterial status should be assessed and categorized (using the 2019 International Working Group on the Diabetic Foot [IWGDF]) peripheral artery disease guideline; Hinchliffe 2020) with evaluations of pedal pulses, ankle brachial index, and/or toe brachial index.

Subjects who provide informed consent, are willing and able to collaborate and cooperate with study protocol requirements and who meet all study eligibility criteria will be randomized in the study. Randomization will have a 3:2 (contezolid acefosamil/contezolid: linezolid) allocation ratio. Randomization will be stratified by geographic region and severity of infection.

Subjects will receive ≥1 dose of the IV study drug before being allowed to switch to PO study drug if the Investigator has determined that it is clinically appropriate to change the route of administration.

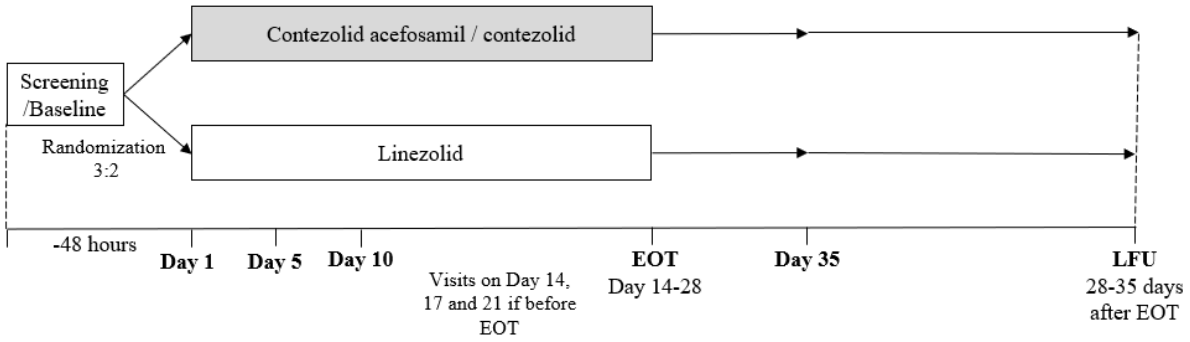
Subjects may receive adjunctive antimicrobial therapy with parenteral aztreonam (per standard-of-care dose regimen) if the Investigator suspects or has confirmed the presence of aerobic Gram-negative pathogens that, in addition to Gram-positive aerobic bacteria, are also associated with the pathogenic process. Similarly, subjects may also receive adjunctive antimicrobial therapy with parenteral or PO metronidazole (per standard-of-care dose regimen) if the Investigator suspects or has confirmed the presence of obligate anaerobic pathogens that, in addition to aerobic Gram-positive bacteria, are also associated with the pathogenic process.

Gram stain and culture specimens (aerobic and anaerobic) of the primary DFI lesion (specific DFI for which the subject was enrolled) must be obtained from each subject for microbiologic evaluation at Screening/Baseline; the DFI site specimen must be obtained before administration of study antibacterial therapy. DFI site tissue specimens will be aseptically obtained by curettage or biopsy; specimens of purulent secretions obtained by sterile aspiration (but not by swab) are also acceptable. In addition, blood cultures (aerobic and anaerobic) from 2 separate venipuncture sites will be obtained from each subject before administration of antibacterial therapy whenever possible. All DFI site specimens will be processed for Gram stain and aerobic and anaerobic culture at the local laboratory, and all blood cultures will be processed at the local laboratory. All bacterial isolates that are identified from a DFI site specimen or blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. Microbiological procedures will be detailed in the Laboratory Manual.

During the study, enrolled subjects should receive standard wound care (eg, pressure offloading, nonantimicrobial dressings). Preoperative topical antiseptics are permitted for surgical procedures or debridement but are not to be continued following the procedures. Investigators are encouraged to sharply debride ulcerated wounds to remove necrotic and infected material, as appropriate, at Screening/Baseline and as often as clinically indicated. Concomitant nonstudy systemic and topical antibacterial agents are prohibited during the study. Adjunctive therapies such as hyperbaric oxygen, wound-vacuum drainage systems, maggot or leech therapy, or granulocyte colony-stimulating factor are prohibited during the study.

Day 1 is the first day of study drug administration; subsequent study days are consecutive calendar days (Figure 2). Assessments will be performed on D10 (±1 day), Day 14 (D14) (±1 day) if before EOT, Day17 (±1 day) if before EOT, and Day 21 (D21) (±1 day) if before EOT. EOT (+1 day) will occur on the last day of study drug administration (D14 to Day 28 [D28], after 28 to 56 doses of study drug), D35 (+2 days) will occur on calendar Day 35, and LFU will occur 28 to 35 days after EOT. Subjects will undergo follow-up visits to assess the safety, tolerability, and efficacy of the study drugs.

Figure 2: Study Design Schematic



EOT = End-of-Therapy; IV = intravenous; LFU = Late Follow-Up

6.2 Outcome Measures

Subjects must be evaluated directly by the Investigator from Screening/Baseline through D35 (+2 days). If the primary DFI site is associated with little or no pain, edema, redness or purulent/seropurulent drainage at the D35 (+2 days) visit, the LFU visit may be performed as a remote visit. DFI specimens (aerobic and anaerobic) for Gram stain and cultures may be obtained from the primary site of infection at each visit from Day 5 (D5) (±1 day) through LFU, only if clinically indicated (eg, the subject is deemed a clinical failure or relapse or purulence and discharge from the DFI site continues after Screening/Baseline).

When conducting a clinical examination of the primary DFI site, the Investigator will perform and record the following:

- Extent of the infection as measured by redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for the length (cm) of redness extending from the wound margin, measure same direction from rim of wound as used at the Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Color digital photograph of the DFI at Screening/Baseline
- Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent)

- Record the following additional information (at Screening/Baseline only):
  - Primary DFI anatomical site
  - Predisposing cause of infection, if any (eg, ulcer, trauma [direct, penetrating, thermal, chemical], arthropod bite, fungal dermatosis, surgery, spontaneous)
  - Ankle brachial index of the primary DFI limb (if ankle blood pressure cannot be obtained, obtain the toe blood pressure and toe brachial index)

Efficacy assessments will include (see Section 12.0 for additional information):

- Investigator's assessment of clinical response at D10, EOT, and D35. Clinical success is defined as the subject meeting ALL of the following:
  - Resolution or near resolution of Baseline DFI signs and symptoms with none worsening and thus not requiring further antibacterial or surgical therapy (only for EOT and D35)
    - Near resolution is defined as resolution of the signs and symptoms of DFI, except allowing one to persist with continued improvement such that no further antibacterial or surgical therapy are required to treat the primary DFI
  - No new signs, symptoms, or complications attributable to the primary DFI; no osteomyelitis at the primary DFI site diagnosed >7 days after starting study drug
  - Did not receive an intercurrent nonprotocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of DFI
  - Did not have a post-Baseline surgical procedure, major surgical debridement, or adjunctive intervention after 24 hours of start of study drug through D10, EOT or D35, respectively, that was not planned at Baseline
  - Did not die of any cause up to D10, EOT, or D35, respectively
- Investigator's assessment of sustained clinical success at LFU; sustained clinical success is defined as no new signs or symptoms of the primary DFI after D35, and no antimicrobial or surgical treatment aimed at presumed infection of the primary DFI.

Subjects who prematurely discontinue study drug will undergo all EOT assessments on the day of study drug discontinuation (+1 day). Subjects who prematurely discontinue study drug will continue to be followed in the study. Before subjects withdraw from the study, efforts should be made to perform follow-up safety assessments per the study schedule. The duration of treatment within the specified window will be determined by the Investigator based on the subject's clinical status (eg, therapy can be discontinued if the subject has improved, no more antibiotic treatment is medically necessary, and the risk of relapse is minimal).

Subjects will be monitored for the occurrence of adverse events (AEs) throughout the study, including AEs that are associated with the oxazolidinone class of antibiotics. Physical examinations, vital signs, ECGs, and clinical laboratory tests (hematology, chemistry, coagulation, and UA) will be performed at Screening/Baseline and at various timepoints during and after study treatment (Table 1).

6.3 Number of Subjects

Approximately 865 (519 contezolid acefosamil/contezolid: 346 linezolid) adult subjects with moderate or severe DFI will be enrolled in this study. Randomization will have a 3:2 (contezolid acefosamil/contezolid:linezolid) allocation ratio with stratification for geographic region and severity of infection.

6.4 Measures Taken to Minimize or Avoid Bias

Bias is minimized by subject randomization and blinding (Section 6.5).

6.5 Randomization and Blinding

Subjects will be randomized to treatment provided they meet all inclusion and no exclusion criteria (see Section 7.1 and Section 7.2, respectively). Subjects will be randomized using an Interactive Response Technology (IRT) system to contezolid acefosamil/contezolid or linezolid with a 3:2 ratio. Randomization will be stratified by geographic region and severity of infection.

After informed consent has been obtained and study eligibility established, the study site's unblinded Pharmacist or unblinded Pharmacist's designee will randomize the subject in the IRT and obtain the study drug assignment from the IRT system. The IRT system will assign study drug for dispensation based on treatment assignment. A subject is considered randomized when the unblinded Pharmacist or unblinded Pharmacist's designee receives the randomization number or study drug assignment.

This is a double-blind study. Those blinded to study drug assignment include the Sponsor, Investigator, study statistician, clinical study personnel participating in direct subject care, and those involved in clinical evaluations.

- For subjects randomized to contezolid acefosamil/contezolid, PO contezolid study drug will be contezolid 800 mg (2 tablets each with 400 mg of contezolid) and also a placebo tablet identical in appearance to linezolid (ie, subjects will take 3 tablets total for each PO administration).

- For subjects randomized to linezolid, PO linezolid study drug will be linezolid 600 mg (1 tablet) and also 2 placebo tablets identical in appearance to contezolid acefosamil/contezolid (ie, subjects will take 3 tablets total for each PO administration).

To maintain blinding, each PO administration will utilize a double-dummy design with all subjects receiving 3 tablets: subjects in the contezolid treatment arm will receive 2 contezolid tablets and 1 placebo tablet identical in appearance to a linezolid tablet, and subjects in the linezolid treatment arm will receive 1 linezolid tablet and 2 placebo tablets identical in appearance to contezolid tablets.

To maintain blinding, IV administrations will be prepared by an unblinded pharmacist or designee. IV bags will be used to administer IV study drug. Bags and IV tubing will be shrouded to blinded staff during transport and administration. An unblinded pharmacist or designee will confirm that the entire volume has been administered at the conclusion of the infusion.

Blinded personnel will remain blinded to study drug assignment until all subjects have completed the study and the database is locked. Blinded personnel must not make any effort to determine which study drug therapy is being administered. Procedures to ensure that the blind is maintained are detailed in the Pharmacy Manual and Study Reference Manual.

Those unblinded to study drug assignment include the pharmacy personnel, unblinded study monitor, unblinded clinical project manager, unblinded statistician, unblinded clinical supply manager, and the bioanalytical laboratory.

If study drug is determined not to be safe and/or not tolerated for a subject, the study drug assignment for that subject with a significant safety concern may be unblinded.

The blind may also be broken in the case of a medical emergency requiring the Investigator to know the identity of the study drug to appropriately guide the subject's medical management. Emergency unblinding should take place through the IRT for both IV and PO doses, and both the Clinical Research Organization and the Sponsor should be notified. Prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. If the blind is broken for any reason and the Investigator is unable to contact the Medical Monitor and/or Sponsor before unblinding the subject, the Investigator must notify the Medical Monitor and Sponsor as soon as possible, without revealing the subject's study drug treatment assignment (unless important to the safety of subjects remaining in the study). All instances of unblinding will be thoroughly investigated and documented by the unblinded study monitor.

6.6 Expected Duration of Subject Participation

The total duration of each subject's participation in the study will be at least 42 and up to 65 days, including the Screening period (≤48 hours before randomization on D1. Subjects will receive study drug for 14 to 28 days. The duration of treatment within the specified window will be determined by the Investigator based on the subject's clinical status (eg, therapy can be discontinued if the subject has improved, no more antibiotic treatment is medically necessary, and the risk of relapse is minimal). Subjects will then be followed for at least 28 and up to 35 days after EOT.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Males or females ≥18 years of age

2. Willing and able to provide written informed consent

3. Have diabetes mellitus (type 1 or 2) per the American Diabetes Association criteria (Appendix 3 in Section 18.3)

4. Have a foot infection that started at or below the malleolus and does not extend above the knee. If the subject has multiple infections that meet all the criteria below, the one with the highest IWGDF classification and the largest size will be designated as the primary DFI

5. Foot infection that meets the IWGDF DFI criteria for classification 3 (moderate infection) or 4 (severe infection) (Appendix 8, Section 18.8) that are confirmed or suspected to be due to a Gram-positive bacterial pathogen (Lipsky 2019)

6. Foot infection had acute onset or worsening of signs and symptoms within the past 14 days

7. Received <48 hours administration of a potentially effective antibiotic (ie, active against all pathogens known to be present) to treat the current target infection within 96 hours before the start of study drug administration

   EXCEPTION: Subjects who are considered to be therapeutic failures of prior antibiotic therapy with another agent may be enrolled if they have had worsening or no improvement in the clinical signs and symptoms of their DFI and have either:

   a. Gram stain from the infection site showing both white blood cells (WBC) and a potential Gram-positive pathogen

      OR

   b. Culture and sensitivity results showing a Gram-positive pathogen resistant to prior antibiotics. Note: subjects must not have failed treatment with one of the study medications or any agent of the same class

8. Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative pregnancy test at Screening/Baseline and, if heterosexually active with male partners, be willing to use a highly effective method of contraception throughout the study, such as 1 of the following:

    a. Hormonal contraception (stable dose for 3 months)

    b. Intrauterine device/intrauterine hormone-releasing system

    c. Double barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

9. Males, if nonsterile and sexually active with female partners of childbearing potential, must use a double-barrier method of contraception (eg, diaphragm, cervical cap, contraceptive sponge, condom) and be willing to continue to use such highly effective birth control measures while participating in the study and for 60 days following participation in the study. Males must also refrain from sperm donations during this time.

7.2 Exclusion Criteria

Subjects must NOT meet any of the following exclusion criteria:

1. Previous DFI known or suspected to be caused by Gram-positive pathogens that are resistant to oxazolidinone antibiotics
2. DFI with presumptive evidence or suspicion of osteomyelitis. EXCEPTION: if all infected bone was removed within 48 hours before the start of study drug administration but there remains infected soft tissue, the subject is acceptable for enrollment
3. DFI without presumptive evidence of osteomyelitis anticipated to require >28 days of antibiotic treatment
4. Necrotizing fasciitis, crepitant cellulitis, wet gangrene, gas gangrene, ecthyma gangrenosum, septic arthritis, or severely impaired arterial supply to any portion of the affected foot which may need revascularization before the end of the study
5. Infected prosthetic materials or devices that will not be removed before or at the time of enrollment
6. Anticipated requirement for complete resection or amputation (ie, removal of all infected tissue with clean margins) of the infected DFI anatomical site within 30 days
7. Known or suspected concurrent infection of any type that would require treatment with a systemic antibacterial agent with activity against Gram-positive bacteria
8. Life expectancy <3 months or evidence of immediately life-threatening disease, including, but not limited to, current or impending respiratory failure, shock, acute coronary syndrome, unstable arrhythmias, hypertensive emergency, acute hepatic failure, active GI bleeding, profound metabolic, or acute cerebrovascular events

9. Evidence of significant hepatic, renal, hematologic, or immunologic disease as determined by the following:
    a. Total bilirubin >2×ULN
    b. Alanine aminotransferase or aspartate aminotransferase >3×ULN
    c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    d. Current or anticipated absolute neutrophils <1500 neutrophils/mm^3
    e. Platelet count <75,000 cells/mm^3
    f. Known infection with human immunodeficiency virus (HIV) and a known CD4 count <200 cells/mm^3, or another acquired immune deficiency syndrome-defining illness
    g. CrCl <30 mL/min; CrCl will be calculated from the serum creatinine concentration by the following equation:
        - Male: CrCl mL/min = (140-age) × weight (kg) / (72 × serum creatinine [mg/dL])
        - Female: CrCl mL/min = 0.85 × ([140-age] × weight [kg] / [72 × serum creatinine {mg/dL}])
10. Receipt of chemotherapy, radiotherapy, or potent, noncorticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy) within the past 3 months, or the receipt of corticosteroids ≥10 mg of prednisone (or equivalent) per day for >14 days in the prior 30 days
11. Known or suspected pheochromocytoma or thyrotoxicosis or severe uncontrolled hypertension.
12. QT interval corrected for heart rate by Fridericia's formula (QTcF) duration >450 msec for males or >470 msec for females obtained as an average from the triplicate Screening/Baseline ECGs, history of QT prolongation, hypokalemia (serum potassium <3.0 mEq/L) at Screening/Baseline, or other proarrhythmic conditions
13. Concomitant condition that, in the opinion of the Investigator, would preclude an evaluation of a response or make it unlikely that the contemplated course of therapy could be completed
14. History of known or suspected serotonin syndrome, neuroleptic malignant syndrome, or carcinoid syndrome
15. History of known or suspected CDAD
16. History of drug-related peripheral or optic neuropathy
17. History of a seizure disorder or known or suspected central nervous system condition that may predispose to seizures or lower the seizure threshold
18. Females who are pregnant or breastfeeding
19. Prior receipt of any formulation of contezolid acefosamil or contezolid

20. Prior (within the past 2 weeks) administration of, or expected or required concomitant (from the start of the study drug to EOT) administration of:
    a. Systemic adrenergic, dopaminergic, or serotonergic medications
    b. Monoamine oxidase inhibitors (eg, isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine)
21. Prior or expected concurrent systemic immunosuppressive therapy, defined as chronic treatment with known immunosuppressive medications
22. Expected concurrent hemodialysis, hemofiltration, peritoneal dialysis, or plasmapheresis
23. Inability to tolerate a PO study drug for duration of study treatment (eg, nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of PO study drug)
24. Poor venous access
25. History of any intolerance, hypersensitivity, or allergic reaction to any oxazolidinone antibiotic
26. History of any intolerance, hypersensitivity, or allergic reaction to aztreonam; note that while cross-reactivity of aztreonam with other β-lactams is rare, this drug should be administered with caution to any subject with a history of hypersensitivity to β-lactams (eg, penicillins, cephalosporins, carbapenems)
27. History of any intolerance, hypersensitivity, or allergic reaction to metronidazole
28. Taken any investigational drugs or used any investigational devices within 30 days before randomization
29. Inability to cooperate fully with the requirements of the study protocol, including the schedule of events, or likely to be noncompliant with any study requirements, or the Investigator determines that the subject should not participate in the study

7.3 Criteria for Premature Discontinuation of Study Drug or Subject Withdrawal from Study

Subjects should be encouraged to complete all study assessments. Each subject has the right to prematurely discontinue study drug administration or withdraw from the study at any time during the study without prejudice. Subjects who prematurely discontinue study drug should remain in the study. If a subject prematurely discontinues study drug before EOT, the EOT visit should be completed, and the subject will continue to be followed in the study. If a subject prematurely withdrawals from the study (eg, withdrawal of consent) before EOT, all efforts should be made to have the subject complete the EOT visit. If the subject prematurely withdrawals from the study after the EOT visit, the subject should complete the LFU visit.

Criteria for premature discontinuation of study drug include:

- AE or SAE (warranting study drug discontinuation)
- Confirmed to have only Gram-negative or anaerobic pathogens
- Clinical failure per judgement of the Investigator
- Pregnancy

Criteria for subject withdrawal from study include:

- Withdrawal of consent
- Lost to follow up
- Death
- Study terminated by Sponsor

7.4 Replacement of Subjects

None of the subjects will be replaced once they have been randomized.

7.5 Study Termination by Sponsor and Termination Criteria

The Sponsor reserves the right to terminate any investigational site or the clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- Unacceptable safety and tolerability
- The incidence or severity of AEs or SAEs in this study indicates a potential health hazard to subjects
- Serious or persistent noncompliance by the Investigator with the protocol, clinical research agreement, GCP, or applicable regulatory guidelines in conducting the study
- Institutional Review Board/Independent Ethics Committee (IRB/IEC), or health authority decision to terminate or suspend approval for the Investigator
- Investigator request to withdraw from participation
- Subject enrollment is unsatisfactory

7.6 Follow-up of Subjects Prematurely Discontinued from Study Drug

For subjects who prematurely discontinue either study drug, efforts will be made to complete all protocol-specified assessments listed for the EOT visit at the time of premature study drug discontinuation (Section 10.6), and to perform follow-up safety and outcome assessments specified for the D35 (+2 days) visit (Section 10.7) and the LFU visit (Section 10.8) as scheduled. Safety assessments at the EOT visit should be performed before beginning rescue therapy, as appropriate. Any ongoing AEs should be followed to resolution or to a satisfactory outcome, as determined by the Investigator.

8.0 TREATMENT OF SUBJECTS

Study drugs are contezolid acefosamil (IV)/contezolid (PO) and linezolid (IV and PO), which will be administered for a total of 14 to 28 days (28 to 56 doses). All randomized subjects will start with 1 dose of IV study drug and may continue with IV therapy or be switched to PO study drug to complete study treatment.

Study treatment will be as follows:

- Subjects randomized to contezolid acefosamil/contezolid treatment will receive IV infusions of contezolid acefosamil q12h (±3 hours) with a minimum of 1 infusion followed by PO contezolid study drug q12h (±3 hours) for a total of 14 to 28 days. The first IV dose of contezolid acefosamil will be 2000 mg infused over 90 minutes (±5 minutes), and all other IV doses of contezolid acefosamil will be 1000 mg infused over 60 minutes (±5 minutes) q12h. Oral contezolid study drug will be contezolid 800 mg (2 tablets each of 400 mg of contezolid) and also 1 placebo PO tablet identical in appearance to linezolid (ie, subjects will take 3 tablets total for each PO administration). All PO study drug must be taken with food.

- Subjects randomized to linezolid treatment will receive IV infusions of linezolid q12h (±3 hours) with a minimum of 1 infusion followed by PO linezolid study drug q12h (±3 hours) for a total of 14 to 28 days. The first IV dose of linezolid will be 600 mg infused over 90 minutes (±5 minutes), and all other IV doses of contezolid acefosamil will be 600 mg infused over 60 minutes (±5 minutes) q12h. Oral linezolid study drug will be 1 linezolid 600 mg tablet and also 2 placebo PO tablets identical in appearance to contezolid (subjects will take 3 tablets total for each PO administration). All PO study drug must be taken with food.

To maintain blinding, PO administrations will utilize a double-dummy design with all subjects receiving 3 tablets total: subjects in the contezolid treatment arm will receive 2 contezolid tablets and 1 placebo tablet identical in appearance to a linezolid tablet, and subjects in the linezolid treatment arm will receive 1 linezolid tablet and 2 placebo tablets identical in appearance to contezolid tablets.

To maintain blinding, IV administrations will be prepared by an unblinded pharmacist or designee. Intravenous bags will be used to administer IV study drug. Bags and IV tubing will be shrouded to blind staff during transport and administration. An unblinded pharmacist or designee will confirm that the entire volume has been administered at the conclusion of the infusion.
It is expected that most subjects will remain in the hospital or clinic while receiving IV treatment with study drug; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions will not be administered at home.

After receiving at least 1 dose of IV study drug, subjects may switch to PO study drug to complete 14 to 28 days (28 to 56 doses) of therapy. The change from IV to PO study drug may take place after the Investigator has determined that the primary DFI lesion has not worsened (eg, has not increased in area of erythema or induration, tenderness has not increased) from the Screening/Baseline assessment, the subject feels better overall, the subject has adequate PO intake of food and fluids to safely support administration of PO doses of antibiotics, and that it is clinically appropriate to switch the subject to PO study drug. Subjects who are switched from IV to the PO study drug must be observed for ≥60 minutes after the first PO dose. The subject may be discharged on PO study drug only after good tolerability has been demonstrated with the initial dose of PO treatment. All PO study drug must be taken with food. Subjects may switch from PO to IV study drug (eg, if nothing by mouth is allowed before a surgical procedure). However, switching from PO to IV study drug is not permitted due to treatment failure. Before switching from PO to IV study medication, discuss the case with the Medical Monitor.

During outpatient management, subjects will record study drug dosing details.

8.1 Intravenous Contezolid Acefosamil/Oral Contezolid

Contezolid acefosamil will be supplied as lyophilized powder for reconstitution as an IV formulation and contezolid will be supplied as tablets in an immediate release PO formulation. The clinical label will identify the investigational products by name, lot number, Sponsor, and storage conditions. Administration of the study drug is limited to investigational use only. Refer to the Pharmacy Manual for additional information.

8.1.1 Intravenous Administration

Contezolid acefosamil drug product will be supplied in 20 mL vials containing 1000 mg of contezolid acefosamil (calculated on free acid basis), a suitable amount of sodium citrate dihydrate and citric acid produced by filter sterilization and lyophilization.

The drug product powder is to be reconstituted in 300 mL of 5% dextrose in water or normal saline for IV administration. The contezolid acefosamil solution in either a diethylhexyl phthalate (DEHP) containing or non-DEHP containing IV bag is stable for up to 16 hours at 25ºC (77ºF), and stable for up to 48 hours at 4ºC (39.2ºF). To ensure long term stability of the drug product, the lyophilized vials will be maintained at -20ºC at the investigative site until it is to be reconstituted for use in the clinic.

An unblinded pharmacist or designee will prepare and blind the contezolid acefosamil IV infusion and will be unblinded to the subject's assigned treatment; however, all other staff will be blinded to the subject's treatment. Please refer to the Pharmacy Manual for details on dose preparation and administration.

8.1.2 Oral Administration

Contezolid for PO administration is a conventional tablet containing 400 mg contezolid. To maintain the study blind, PO contezolid study drug will be contezolid 800 mg (2 tablets each with 400 mg of contezolid) and also a placebo PO tablet identical in appearance to linezolid (ie, subjects will take 3 tablets total for each PO administration). Placebo to match the linezolid tablet will be included as part of a blinded kit to ensure all study staff will be blinded to the subject's treatment. All PO study drug must be taken with food.

8.1.3 Contezolid and Contezolid Acefosamil Study Drug Storage

Unused study drug supplies should be stored according to the directions on the study drug labels.

Lyophilized contezolid acefosamil (for IV formulation) must be stored in a secure area (eg, a locked freezer), protected from moisture, and kept frozen between -25ºC and -15ºC until the time of preparation for study drug administration. The 5% dextrose in water or normal saline (0.9% NaCl) must be stored at room temperature, per manufacturer's requirements. Once reconstituted with 5% dextrose in water or normal saline, the solution is stable in either a DEHP containing or non-DEHP containing IV bag for up to 16 hours at 25ºC (77ºF), and stable for up to 48 hours at 4ºC (39.2ºF).

Contezolid for PO administration will be packaged as part of a blinded blister pack. All blister packs must be stored between 15ºC and 30ºC and can be stored at the study site for a duration governed by study drug expiry dating. Temperature of study drug storage that exceeds or falls below these ranges must be reported to the Sponsor or designee and captured as a deviation. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

Refer to the Pharmacy Manual for any additional storage, handling, or updated stability data of the study drug supplies.

8.2 Intravenous/Oral Linezolid

Linezolid is an FDA-approved commercially available product and will be supplied as IV and PO formulations. The clinical label will identify the product by name, lot number, Sponsor, storage conditions, and expiry date. Refer to the Pharmacy Manual for additional information.

8.2.1 Intravenous Administration

Linezolid for IV administration will be provided as 300 mL (600 mg linezolid) single-use, ready to use flexible plastic infusion bags in a foil laminate overwrap. Please refer to the Pharmacy Manual for details on dose preparation and administration. The unblinded pharmacist or unblinded pharmacist designee will prepare and blind the linezolid IV infusion and will be unblinded to the subject's assigned treatment; however, all other staff will be blinded to the subject's treatment.

8.2.2 Oral Administration

Linezolid for PO administration will be provided as 600 mg tablets. To maintain the study blind, PO linezolid study drug will be 1 linezolid 600 mg tablet and also 2 placebo PO tablets identical in appearance to contezolid (ie, subjects will take 3 tablets total for each PO administration). Placebo to match the contezolid tablet will be included as part of a blinded kit to ensure all study staff will be blinded to the subject's treatment. All PO study drug must be taken with food.

8.2.3 Linezolid Study Drug Storage

Unused study drug supplies should be stored according to the directions on the study drug labels.

Store linezolid infusion bags between 20ºC and 25ºC and protect from light. It is recommended that the infusion bags be kept in the overwrap until ready to use. Protect infusion bags from freezing (Zyvox® Prescribing Information 2021).

Linezolid PO tablets will be packaged as part of a blister pack. All blister packs must be stored between 15ºC and 30ºC and can be stored at the study site for a duration governed by study drug expiry dating. Temperature of study drug storage that exceeds or falls below these ranges must be reported to the Sponsor or designee and documented as a deviation. The Sponsor will notify the site if the study drug is to be quarantined or can be used.

Refer to the Pharmacy Manual for any additional storage, handling, or updated stability data of the study drug supplies.

8.3 Adjunctive Therapy

8.3.1 Aztreonam

Linezolid, contezolid acefosamil, and contezolid have no useful antimicrobial activity against Gram-negative pathogens and are not indicated for the treatment of Gram-negative infections; it is critical that specific Gram-negative therapy with aztreonam be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. The PK of linezolid and aztreonam are not altered when co-administered (Zyvox® Prescribing Information 2021).

According to standard of care treatment guidelines, subjects will receive adjunctive antimicrobial therapy with parenteral aztreonam for confirmed or suspected aerobic Gram-negative pathogens as causes of the DFI, in addition to Gram-positive pathogens. Outpatients may receive either intramuscular or IV aztreonam at the Investigator's discretion (eg, IV aztreonam may be administered as outpatient parenteral antibiotic therapy in an infusion center). If no Gram-negative pathogen is isolated from the Screening/Baseline cultures by D3, aztreonam is to be discontinued.

Parenteral aztreonam will be provided by the study sites and should be prepared and administered in accordance with current label information (Azactam® Prescribing Information 2021).

8.3.2 Metronidazole

According to standard of care treatment guidelines, subjects will receive adjunctive antimicrobial therapy with parenteral metronidazole or PO metronidazole, as directed by the approved package labeling, for confirmed or suspected obligate anaerobic pathogens as causes of the DFI, in addition to Gram-positive pathogens. Outpatients may receive PO metronidazole at the Investigator's discretion. If no obligate anaerobic pathogens are isolated from the Screening/Baseline cultures by D3, metronidazole is to be discontinued.

Parenteral or PO metronidazole will be provided by the study sites and should be prepared and administered in accordance with current label information (Metronidazole Injection Package Insert 2013; Metronidazole Oral Package Insert 2021).

8.4 Dose Adjustment

No adjustments to study drug doses or frequencies are allowed.

8.5 Study Drug Compliance

Each dose of IV study drug will be administered by study staff, who are oriented to the details of the clinical protocol and under direct supervision of the Investigator.

The following study drug compliance information will be documented as study information and reported in the electronic case report form (eCRF):

- The dates and times of each PO administration will be recorded; subjects will record this information when PO dose administration occurs outside of the Investigative site.
- The dates and infusion start and stop times will be recorded for each infusion and will specify if the total volume of study drug solution was administered (if infusion is halted or interrupted for any reason, record the time of premature discontinuation and re-initiation of infusion). An unblinded member of the study staff will inspect the infusion line and bag at the end of infusion to confirm that the full dose has been infused, followed by a rapid IV push to clear any residual study drug in the line. If possible, infusion bags will be retained by the pharmacy for drug accountability purposes until reconciliation by the unblinded monitor.
- For any infusion that is incomplete or otherwise not administered over 90 minutes (±5 minutes) for the first IV dose or over 60 minutes (±5 minutes) for the second IV dose, the actual volume infused, infusion duration, and conditions or complications that prevented complete and/or timely administration must be documented. In any case, study site personnel should strive to administer the entire dose regardless of the inter-current problems of drug administration.

8.6 Breaking the Blind

This study is a double-blind design. The Investigator, study personnel, and subjects will not make any effort to determine which study drug therapy is being administered. Unblinded pharmacy personnel or unblinded study personnel will be utilized in this study to maintain the blind for blinded personnel. In addition, the PO blister packs will be blinded and IV bags and tubing will be shrouded.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific subject, may the Investigator unblind a subject's treatment assignment.

Prior to any unblinding the Investigator is strongly advised to discuss options with the regional Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the subject's study treatment assignment (unless important to the safety of subjects remaining in the study), the Investigator must notify the Medical Monitor if the blind is broken for any reason and the Investigator was unable to contact the Medical Monitor and/or Sponsor prior to unblinding. The Investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the source documentation.

8.7 Study Drug Accountability

All supplies of study drug (IV contezolid acefosamil, PO contezolid, IV linezolid, and PO linezolid) required for completion of this study will be provided by the Sponsor. Adjunctive therapy with aztreonam and/or metronidazole will be supplied by the study sites.

The unblinded pharmacy personnel are responsible for ensuring that a current record of inventory and drug accountability is maintained during study conduct. A specifically designated unblinded study monitor or unblinded designee will be responsible for drug accountability at the site. The Investigator is ultimately responsible for ensuring that a current record of inventory/drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the unblinded Sponsor or designee, or applicable regulatory authorities at any time.

Each shipment of study drug will contain a packing slip or equivalent to assist in maintaining current and accurate inventory records. Upon receipt of the study drug, the unblinded pharmacy personnel will visually inspect the shipment and verify the number and condition of study drug (vials, infusion bags, blister packs) received. Used vials of study drug will be retained by the pharmacy for drug accountability purposes until reconciliation by the unblinded monitor. Refer to the Pharmacy Manual for additional information.

Sites must maintain subject-specific drug accountability logs and subjects will be instructed to record their drug dosing during outpatient management throughout the treatment period.

At each subject visit, the study site will calculate compliance of the at-home administration of the PO drug. The dosing will be reviewed with the subject and returned pills will be counted to calculate compliance. Any discrepancies or omissions will be discussed and resolved. If compliance is <80%, the subject will be re-instructed on the importance of appropriate dose administration.

8.8 Study Drug Handling and Disposal

Only upon written authorization from MicuRx or its representative will partially used, used, unused, or expired study drug be destroyed at the investigative site or at another site designated by the Sponsor. Unopened drug kits will be destroyed at a site designated by the Sponsor or approval by the Sponsor. If drug is to be destroyed on-site, the Investigator MUST SUPPLY MicuRx, or its representative, with their drug-destruction standard operating procedures (SOPs) for review and approval and receive written authorization that their policy is appropriate before study drug destruction.

8.9 Prior and Concomitant Therapy

All prescription medications and over-the-counter medications, including herbal, nutritional, and dietary supplements (eg, any antacid, iron supplement, or multivitamin), and illicit medications administered within 2 weeks (14 days) before randomization and during the study between D1 and LFU will be documented in the eCRF. Any changes in prior or concomitant medications will also be recorded.

Note: Subjects who received ≥48 hours administration of a potentially effective antibiotic (ie, active against all pathogens known to be present) within 96 hours before the start of study drug administration will be excluded during Screening.

Concomitant topical or systemic antibacterial therapy, other than study drug and adjunctive parenteral therapy (aztreonam and/or metronidazole), is not allowed between Screening/Baseline and D35 (+2 days) (unless the subject is a clinical failure).

Concomitant nonstudy systemic and topical antibacterial agents are prohibited during the study. Adjunctive therapies such as hyperbaric oxygen, wound-vacuum drainage systems, maggot or leech therapy, or granulocyte colony-stimulating factor are prohibited during the study.

The following additional adjunctive therapies are allowed, as clinically indicated:

- Preoperative topical antiseptics are permitted for surgical procedures or debridement but are not to be continued following the procedures
- Standard wound care (eg, pressure offloading, nonantimicrobial dressings).
- Surgical procedure or surgical debridement within 24 hours of start of study drug to treat the primary DFI, or a surgical procedure/debridement more than 24 hours after start of study drug that is planned at Baseline.

9.0 SUBJECT RESTRICTIONS

Subjects are required to:

- Avoid taking any of the following concomitant medications between D1 (first administration of study drug) and EOT (last day of study drug administration).
  - Any adrenergic, dopaminergic, or serotonergic medication, including selective serotonin reuptake inhibitors or tricyclic antidepressants (Appendix 5 in Section 18.5).
  - Any MAOI (eg, isocarboxazid, isoniazid, nialamide, phenelzine, procarbazine, and hydracarbazine).
  - Any nonstudy systemic antibiotic or topical antimicrobial therapy with specific antibacterial activity (eg, topical mupirocin, retapamulin, or fusidic acid)
  - *Note*: While hypoglycemic medications are not contraindicated, such agents (eg, insulin or PO hypoglycemic) should be used with caution. Postmarketing cases of-symptomatic hypoglycemia have been reported in subjects with diabetes mellitus receiving hypoglycemic agents when treated with linezolid. While a causal relationship between linezolid (or other oxazolidinones) and hypoglycemia has not been established, diabetic subjects should be cautioned of potential hypoglycemic reactions when treated with study drug. If hypoglycemia occurs, a decrease in the dose of the hypoglycemic agent, or discontinuation of the hypoglycemic agent and/or study drug may be required.
- Avoid consumption of large amounts of foods or beverages with high-tyramine content, including those foods that have been processed by aging, fermentation, pickling, or smoking to improve flavor (eg, aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, tap beers) from D1 to EOT; see Appendix 6 in Section 18.6) for a detailed list.
- Females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative serum or urine pregnancy test (beta-human chorionic gonadotropin) at Screening/Baseline and, if sexually active with male partners, be willing to use a highly effective method of contraception throughout the study such as 1 of the following:
  - Hormonal contraception (stable dose for 3 months)
  - Intrauterine device/intrauterine hormone-releasing system
  - Double barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)
- Males, if nonsterile and sexually active with female partners of childbearing potential must use a method of double-barrier contraception (ie, diaphragm, cervical cap, contraceptive sponge, condom) and be willing to continue to use these same birth control measures while participating in the study (and for 60 days following participation in the study). Males must also refrain from sperm donations during this time.

10.0 STUDY PROCEDURES

The schedule of events is provided in Table 1.

- Written informed consent must be obtained prior to initiating any study assessment or procedure.
- It is expected that most subjects will remain in the hospital or clinic while receiving IV study drug; however, subjects who are clinically stable and have adequate home support with reliable transportation to/from the hospital or clinic may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions will not be administered at home.
- Subjects who are switched to the PO formulation of study drug must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose(s) of the PO formulation are clearly tolerated in the judgment of the Investigator.
- During outpatient management, subjects will record PO study drug dosing details.
- All assessments and procedures on dosing days are obtained predose, unless otherwise specified.
- Assessment of the DFI, wound measurements, and evaluation of the signs and symptoms of DFI should be performed by the same Investigator on the same subject throughout the study, whenever possible.
- The Investigator's assessment of clinical response should be performed by the same Investigator on the same subject throughout the study, whenever possible.
- After Screening/Baseline, microbiological assessments (DFI lesion and/or blood cultures) should be repeated only if clinically indicated (eg, if a subject is deemed a clinical failure or if purulence and discharge from the DFI lesion continues after Screening/Baseline).
- Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.1 Screening

Study eligibility must be confirmed before randomization. The following Screening/Baseline assessments and procedures will be performed up to 48 hours before randomization (see Table 1):

- Obtain written informed consent prior to initiating any study-related assessment or procedure
- Obtain complete medical and surgical history
- Record all prior medications taken within 2 weeks before randomization (Section 8.9).
- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
    - Record the primary DFI anatomical site, predisposing cause of infection, if any (eg, ulcer, trauma, arthropod bite, fungal dermatosis, surgery, spontaneous), and ankle brachial index (or toe brachial index)
    - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
    - Evaluate extent of the infection as measured by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
    - Obtain color digital photograph of the DFI at Screening/Baseline
- Perform microbiological assessments (see Section 11.2); additional microbiological specimen collection and processing details are available in the Laboratory Manual:
    - Obtain appropriate DFI site specimen (aerobic and anaerobic) from all subjects and perform Gram stain and culture at the local laboratory. DFI site specimens will be aseptically obtained by curettage or biopsy; specimens of purulent secretions obtained by sterile aspiration (but not by swab) are also acceptable. All bacterial isolates that are identified from a DFI site specimen at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing.
    - Obtain 2 sets of blood cultures (each consisting of 1 aerobic and 1 anaerobic blood culture bottle from 2 separate venipuncture sites) from all subjects. The blood cultures should be obtained before administration of antibacterial therapy, whenever possible.
- Plain foot X-rays, ESR, and probe-to-bone test will be used to evaluate for osteomyelitis in all subjects; if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, or if the Investigator suspects the possible presence of osteomyelitis, the subject will not be enrolled into the study.
- Perform a complete physical examination (ie, general appearance, head, ears, eyes [including basic Snellen visual acuity and visual field testing], nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes).

- Evaluate for peripheral arterial disease by obtaining ankle brachial blood pressures on the primary DFI limb to determine ankle:brachial index. If ankle blood pressure cannot be obtained, obtain toe blood pressure and toe:brachial index.
- Record height and weight.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by ≥1 minute. ECGs will be obtained before collection of blood laboratory samples.
- Complete SF-36 Health Survey (Ware 1992)
- Obtain samples for laboratory assessments (see Appendix 7 in Section 18.7 for specific tests). Laboratory samples for Screening/Baseline will be drawn and sent to both the local laboratory (for eligibility) and to the central laboratory.
    - Obtain blood samples for hematology, chemistry, hemoglobin A1c, C-reactive protein (CRP), ESR, serology (anti-hepatitis B core antigen, anti-hepatitis B surface antigen, hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody), and coagulation tests
    - Obtain urine sample for UA (includes urine microscopy if UA is positive for red blood cells (RBCs), WBCs, or protein)
    - Perform serum or urine beta-human chorionic gonadotropin pregnancy test for females of childbearing potential up to 2 years postmenopause (alternatively, females must be surgically sterile, ie, have had a tubal ligation, hysterectomy, or bilateral oophorectomy)
    - Obtain the subject's estimated CrCl. The subject's estimated CrCl will be calculated by the site or local laboratory (for eligibility purposes) using Screening/Baseline height (m), actual weight (kg), and serum creatinine:

Males:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

- Identify, assess, and record any AEs or SAEs from the time the informed consent is signed.
- Verify that the subject meets all inclusion criteria (Section 7.1) and none of the exclusion criteria (Section 7.2).

10.2 Day 1

D1 is the first day of study drug administration; subsequent study days are consecutive calendar days. Eligible subjects are randomized on D1. It is expected that most subjects will remain in the hospital or clinic while receiving the IV study drug; however, subjects who are clinically stable and have adequate home support may leave and return to the hospital or clinic for IV infusions. Study drug IV infusions will not be administered at home.

The following will be performed on D1:

- Verify the subject meets all inclusion criteria and exclusion criteria before randomization (Section 7.1 and Section 7.2, respectively)
- Record vital signs; vital signs are not repeated if Screening/Baseline occurs on D1.
- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
    - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
    - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2); additional microbiological specimen collection and processing details are available in the Laboratory Manual:
    - If clinically indicated, obtain appropriate DFI site specimen (aerobic and anaerobic) and perform Gram stain and culture at the local laboratory.
    - Blood cultures may be repeated at any time after Screening/Baseline if clinically indicated.
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by ≥1 minute, within 1 hour before the start of IV infusion and 2 hours after the completion of the IV infusion. The ECG recordings will be obtained before collection of any blood laboratory (including PK) samples.
- Unblinded personnel will randomize the subject to treatment

- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
  - The first dose of study drug should be administered as quickly as possible after eligibility criteria are met
  - Subjects must receive at least 1 dose of IV study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Obtain postdose (2 hours after completion of IV infusion) triplicate 12-lead ECG recordings within a 15-minute period, each separated by ≥1 minute.
- For selected sites, obtain 3 blood samples for PK analysis: 2 samples between 1.5 and 6 hours after the first dose (IV or PO) of study drug, and 1 sample before the second dose of study drug (Section 14.0)
- Record any new concomitant medications; verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.3 Day 2 to EOT

In-person evaluation by the Investigator is not required unless clinically indicated (eg, perform microbiological assessments, including DFI lesion specimen and blood cultures only if clinically indicated [eg, if study drug is prematurely discontinued for insufficient therapeutic effect]).

- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0).
  - Subjects may continue to receive the IV study drug or PO study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Clinically indicated microbiological assessments as described in Section 11.2, including DFI lesion specimen (only if clinically indicated).
- Blood cultures must be repeated every 3 days (±1 day) if the previous blood culture was positive, or at any time after Screening/Baseline if clinically indicated. All bacterial isolates that are identified from a blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.
- Record any new concomitant medications; verify the subject is not taking any restricted medications
- Record any AEs or SAEs if the subject is seen during an unscheduled visit

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.4 Day 5 (±1 day)

The following will be performed:

- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
  - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
  - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at the Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2); additional microbiological specimen collection and processing details are available in the Laboratory Manual:
  - If clinically indicated, obtain appropriate DFI site specimen (aerobic and anaerobic) and perform Gram stain and culture at the local laboratory.
  - Blood cultures must be repeated every 3 days (±1 day) if the previous blood culture was positive, or at any time after Screening/Baseline if clinically indicated. All bacterial isolates that are identified from a blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.
- Perform a focused physical examination (limited, symptom directed) as clinically indicated.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Obtain triplicate ECGs within a 15-minute period, each separated by ≥1 minute. ECGs will be obtained before collection of blood laboratory (including PK) samples.

- Obtain samples for laboratory assessments and send to central laboratory (see Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, CRP, ESR, and coagulation tests
  - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)
- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
  - Subjects may continue to receive the IV study drug or PO study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- For selected sites, obtain 3 blood samples for PK analysis: 1 sample within 2 hours before a designated D5 (±1 day) dose (IV or PO) of study drug, and 2 samples between 1.5 and 6 hours after the designated D5 (±1 day) dose of study drug (Section 14.0)
- Record any new concomitant medications; verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.5 Day 10 (±1 day)

The following will be performed:

- Perform Investigator's assessment of clinical response
- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
  - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
  - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at the Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Perform a focused physical examination (limited, symptom directed) as clinically indicated.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Obtain samples for laboratory assessments and send to central laboratory (see Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, CRP, ESR, and coagulation tests
  - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)
- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
  - Subjects may continue to receive the IV study drug or PO study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Record any new concomitant medications; verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.6 Day 14

The study visit on D14 (±1 day) is not conducted if it occurs after the EOT Visit.

The following will be performed:

- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
  - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
  - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Perform a focused physical examination (limited, symptom directed) as clinically indicated.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Obtain samples for laboratory assessments and send to central laboratory (Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, and coagulation tests
  - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by ≥1 minute.

- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
  - Subjects may continue to receive the IV study drug or PO study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Record any new concomitant medications or changes to medications (if prior to EOT); verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.7 Day 17

The study visit on Day 17 (D17) (±1 day) is not conducted if it occurs after the EOT Visit.

The following will be performed:

- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
    - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
    - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Obtain samples for laboratory assessments and send to central laboratory (Appendix 7 in Section 18.7 for specific tests).
    - Obtain blood samples for hematology, chemistry, and coagulation tests
    - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)

- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
    - Subjects may continue to receive the IV study drug or PO study drug
    - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Record any new concomitant medications or changes to medications (if prior to EOT); verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

10.8 Day 21

The study visit on D21 (±1 day) is not conducted if it occurs after the EOT Visit.

The following will be performed:

- Perform DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
  - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
  - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Perform a focused physical examination (limited, symptom directed) as clinically indicated.
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.

- Obtain samples for laboratory assessments and send to central laboratory (see Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, and coagulation tests
  - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)
- Obtain triplicate 12-lead ECG recordings within a 15-minute period, each separated by ≥1 minute.
- Administer study drug (IV or PO) q12h (±3 hours) (Section 8.0)
  - Subjects may continue to receive the IV study drug or PO study drug
  - If the Investigator has determined that it is clinically appropriate to switch the subject from the IV study drug to PO study drug, the subject must remain in the hospital or clinic for observation for ≥60 minutes after the first PO dose, and until the initial dose of the PO formulation is clearly tolerated in the judgment of the Investigator
- Record any new concomitant medications or changes to medications (if prior to EOT); verify the subject is not taking any restricted medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.9 End of Therapy (28-56 doses of study drug)

Perform EOT assessments on the last day of study drug administration (or the next day). Subjects who prematurely discontinue study drug should have all EOT assessments performed on the day of discontinuation of study drug (+ 1 day) (Section 7.6).

Subjects will receive study drug for 14 to 28 days as described in Section 8.0. Dosing on D29 will only be required if a subject receives the maximum 56 doses of study drug and also received only a single dose of study drug on D1. If a subject requires a longer course of therapy for any reason, the subject will be deemed a clinical failure and open-label antimicrobial(s) should be started at the discretion of the Investigator. Such cases must be discussed with the Medical Monitor.

The following will be performed:

- Plain foot X-rays
- Perform Investigator's assessment of clinical response
- DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
    - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
    - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at the Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform microbiological assessments only if clinically indicated (see Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Perform a complete physical examination (ie, general appearance, head, ears, eyes [including basic Snellen visual acuity and visual field testing], nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes).
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.

- Obtain samples for laboratory assessments and send to central laboratory (see Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, CRP, ESR, and coagulation tests
  - Obtain urine sample for UA (includes urine microscopy if UA is positive for RBCs, WBCs, or protein)
  - Perform serum or urine beta-human chorionic gonadotropin pregnancy test for females of childbearing potential up to 2 years postmenopause (alternatively, females must be surgically sterile, ie, have had a tubal ligation, hysterectomy, or bilateral oophorectomy)
- Obtain triplicate ECGs within a 15-minute period, each separated by ≥1 minute. ECGs will be obtained before collection of blood laboratory (including PK) samples.
- Administer last dose of study drug (IV or PO) q12h (±3 hours) (if applicable) (Section 8.0)
- For selected sites, obtain 3 blood samples for PK analysis: 1 sample within 2 hours before the last dose of study drug, and 2 samples between 1.5 and 6 hours after the last dose of study drug (Section 14.0)
- Record any new concomitant medications
- Identify, assess, and record any AEs or SAEs

Refer to Section 7.6 for follow-up of subjects who prematurely discontinue study drug or the study.

10.10 Day 35 (+2 days)

The following will be performed:

- DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
  - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
  - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Perform Investigator's assessment of clinical response
- Perform microbiological assessments only if clinically indicated (see Section 11.2), including DFI site specimen and blood culture (only if clinically indicated).
- Perform a complete physical examination (ie, general appearance, head, ears, eyes [including basic Snellen visual acuity and visual field testing], nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes).
- Record vital signs (heart rate, blood pressure, respiratory rate, and temperature). Vital signs will be obtained before collection of blood laboratory samples. If >1 temperature is measured within a calendar day, record the highest daily temperature measured. Oral, tympanic, or temporal temperatures are acceptable; the method of measurement will be recorded in the eCRF; the same method of temperature collection for each subject should be used throughout the study.
- Complete the SF-36 Health Survey (Ware 1992)
- Obtain samples for laboratory assessments and send to central laboratory (see Appendix 7 in Section 18.7 for specific tests).
  - Obtain blood samples for hematology, chemistry, and coagulation tests
- Record any new concomitant medications
- Identify, assess, and record any AEs or SAEs

10.11 Late Follow-up

The LFU assessment, designed to provide an assessment of durability of response, is performed 28 to 35 days after EOT. If the primary DFI site has little or no pain, swelling, redness or purulent/seropurulent drainage at the D35 (+2 days) visit, the LFU visit may be performed remotely. Symptoms related to possible relapse of DFI (primary site) will be evaluated as part of the safety assessment. If conducted remotely and clinical relapse/failure is suspected, the subject should be examined and evaluated in-person.

The following will be performed:

- Perform Investigator's assessment of clinical response
- DFI clinical assessments (Section 11.1 and Appendix 4 in Section 18.4):
    - Assess local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent).
    - Evaluate extent of the infection as by the area of redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Record any new concomitant medications
- Identify, assess, and record any AEs or SAEs; during the LFU assessment, symptoms related to possible relapse of DFI will be evaluated as part of the safety assessment.

11.0 ASSESSMENT OF DIABETIC FOOT INFECTIONS

11.1 Clinical Assessments

All subjects must have their primary DFI lesion evaluated by the Investigator. For subjects who have ≥1 DFI lesion at enrollment, the Investigator will decide which is the "primary" lesion to get microbiological samples from and follow for efficacy assessments. All DFI assessments should be performed by the same Investigator on the same subject throughout the study.

When conducting a clinical examination of the primary DFI lesion, the Investigator will perform and record the following:

- Extent of the infection as measured by redness, edema, or induration using manual measurement of the longest length and greatest perpendicular width, with a ruler provided by the Sponsor; for length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable (Appendix 2 in Section 18.2).
- Color digital photograph of the DFI is obtained at Screening/Baseline only.
- Local signs and symptoms of redness (erythema), edema, induration, warmth, tenderness on palpation, pain, and discharge (purulent and nonpurulent) as described in Appendix 4 in Section 18.4.

In addition, record the following information at Screening/Baseline only:

- Primary anatomical site
- Predisposing cause of infection, if any (eg, ulcer, trauma, arthropod bite, fungal dermatosis, surgery, spontaneous)
- Ankle brachial index of the primary DFI limb (if ankle blood pressure cannot be obtained, obtain the toe blood pressure and toe brachial index)

11.2 Microbiological Assessments

All subjects enrolled must undergo microbiological assessments (ie, DFI lesion specimens and blood cultures) at Screening/Baseline and these samples should be obtained from each subject before administration of antibacterial therapy whenever possible.

The Screening/Baseline microbiological assessments are critical, in that microbiological response is an important secondary outcome of the study (Section 5.0). Also, the antibacterial spectrum of study drug (contezolid acefosamil/contezolid or linezolid) is limited to Gram-positive pathogens (eg, staphylococci and streptococci); therefore, it is important to determine whether non-Gram-positive pathogens are involved in the DFI, in addition to Gram-positive pathogens.

- Adjunctive parenteral aztreonam should be administered for confirmed or suspected aztreonam-susceptible aerobic Gram-negative pathogens as causes of the DFI in addition to Gram-positive pathogens (Section 8.3); however, subjects with suspected Gram-negative pathogens **only** must be excluded.

- Adjunctive parenteral metronidazole should be administered for confirmed or suspected metronidazole -susceptible aerobic Gram-negative pathogens as causes of the DFI in addition to Gram-positive pathogens (Section 8.3).

Gram stain and culture specimens (aerobic and anaerobic) of the primary DFI lesion (specific DFI for which the subject was enrolled) must be obtained from all subjects for microbiologic evaluation at Screening/Baseline; the DFI site specimen must be obtained before administration of study antibacterial therapy. DFI site tissue specimens will be aseptically obtained by curettage or biopsy; specimens of purulent secretions obtained by sterile aspiration (but not by swab) are also acceptable. Superficial swabs of infected areas are not acceptable, due to the high probability that such specimens could be contaminated with clinically insignificant, and therefore misleading, isolates.

In addition, 2 sets of blood cultures (each consisting of 1 aerobic and 1 anaerobic blood culture bottle from 2 separate venipuncture sites) will be obtained from all subjects. The blood cultures should be obtained before administration of antibacterial therapy, whenever possible. Blood cultures must be repeated every 3 (±1) days if the previous blood culture was positive, or at any time after Screening/Baseline if clinically indicated. All bacterial isolates that are identified from a blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. If the repeat blood culture remains positive with the bacterial pathogen initially isolated, the Investigator must consider modifying the subject's antibiotic therapy and discuss the case with the Medical Monitor.

After Screening/Baseline, microbiological assessments (DFI lesion and/or blood cultures) should be repeated only when clinically indicated (eg, the subject is deemed a clinical failure or relapse or purulence and discharge from the DFI site continues after Screening/Baseline).

For all microbiological specimens (DFI site specimen and blood), Gram stain and culture (aerobic and anaerobic) should be performed at the local laboratory according to local standards of care. All bacterial isolates that are identified from a DFI site specimen or blood culture at the local laboratory will be sent to a central laboratory for confirmation of species identification and antimicrobial susceptibility testing. The central laboratory will test all Gram-positive isolates for both linezolid and contezolid acefosamil/contezolid susceptibilities. *Staphylococcus aureus* will also be tested for oxacillin susceptibility as a marker for methicillin resistance by both the central and local laboratories. All clinically significant nonanaerobic Gram-negative isolates will be tested for aztreonam susceptibility by both the central and local laboratories. Refer to the Laboratory Manual for specific procedures pertaining to the collection, processing, storage, and shipment of bacterial isolates.

The local laboratory should retain all isolates until confirmation of a viable organism is received from the central laboratory. Backup cultures will be requested when the central laboratory does not receive a viable culture or recovers an organism different from the one recorded by the local laboratory. Refer to the Laboratory Manual for additional details.

12.0 ASSESSMENT OF EFFICACY

12.1 Clinical Response Definitions

The primary endpoint is the Investigator's assessment of clinical response at D35 in the MITT analysis set (Table 7), defined in Section 12.1.1.

Secondary and exploratory efficacy endpoints will be determined at D10, EOT, D35, and LFU according to Table 7. Investigator's assessment of clinical responses (including success and relapse) are defined in Table 8, per-subject microbiological responses are defined in Section 12.2.2, and microbiological responses per Baseline pathogen are defined in Section 12.2.1.

12.1.1 Investigator's Assessment of Clinical Response

The Investigator's assessment of clinical response will be made at D10, EOT, D35, and LFU as defined in Table 8. Investigator assessed clinical failures at EOT will be carried forward as the clinical response at D35. The Investigator's assessment of clinical response should be performed by the same Investigator on the same subject throughout the study.

Data for all subjects will be reviewed to ensure the Investigators are following the protocol defined criteria for clinical response and queries will be issued as needed to clarify any response that does not meet the protocol definition.

Table 7: Efficacy Endpoints by Efficacy Analysis Set

Efficacy Endpoints	Efficacy Analysis Sets						
	ITT	MITT	Micro-MITT	CE-EOT	ME-EOT	CE-D35	ME-D35
Primary:							
Clinical response at D35		√					
Secondary:							
Investigator's assessment of clinical response at EOT		√					
Investigator's assessment of clinical response at D35						√	
Exploratory							
Investigator's assessment of clinical response at D10	√	√					
Investigator's assessment of clinical response at EOT	√			√			
Investigator's assessment of clinical response at D35	√						
Investigator's assessment of sustained clinical success at LFU	√	√				√	
Investigator's assessment of DFI signs and symptoms at EOT				√			
Investigator's assessment of DFI signs and symptoms at D35						√	
Investigator's assessment of clinical response stratified by adjunctive therapies or prior antibiotics at D35						√	
Investigator's assessment of clinical response stratified by presence of ulcer/wound at D35						√	
Percent reduction in surface area of DFI at Day 5, EOT and D35 in subjects who did not receive rescue antibiotics and are alive				√		√	
Per-subject microbiological response at D35			√				√
Per-pathogen microbiological response at D35			√				√
Per-pathogen microbiological response at EOT			√		√		
Investigator's assessment of clinical response at D35 (overall and by Baseline pathogen)			√				√
Investigator's assessment of clinical response at LFU (overall and by Baseline pathogen)			√				√
All-cause mortality at Day 28	√	√					
Composite endpoint of death, unplanned amputation, and infectious complications of the DFI at D35						√	
Composite endpoint of death, unplanned amputation, and infectious complications of the DFI at LFU						√	

CE = Clinically Evaluable; D = day; ; EOT = End-of-Therapy; ITT = Intent-to-Treat; LFU = Late Follow-Up; ME = Microbiologically Evaluable; MITT = Modified Intent-to-Treat; Micro-MITT = Microbiological Modified Intent-to-Treat

Table 8: Clinical Response Definitions – Investigator's Assessment

Timepoint Classification	Definition
D10, EOT, and D35:	
Success	• Resolution or near resolution of Baseline DFI signs and symptoms with none worsening and thus not requiring further antibacterial or surgical therapy (only for EOT and D35) ○ Near resolution is defined as resolution of the signs and symptoms of DFI, except allowing one to persist but with continued improvement such that no further antibacterial or surgical therapy are required to treat the primary DFI • No new signs, symptoms or complications attributable to the primary DFI; no osteomyelitis at the primary DFI site diagnosed >7 days after starting study drug • No post-Baseline surgical procedure (eg, amputation), major surgical debridement, or adjunctive intervention after 24 hours of start of study drug through D10, EOT, or D35, respectively, to treat the primary DFI that was not already planned at Baseline • No intercurrent nonprotocol specified systemic antibacterial therapy with activity against Gram-positive organisms for the treatment of DFI • Did not die of any cause up to D10, EOT, or D35, respectively
Failure	• Lack of resolution or near resolution of DFI signs and symptoms • New signs, symptoms, or complications attributable to the DFI; any amputation or development of osteomyelitis of the primary DFI (>7 days after starting study drug) • Any post-Baseline surgical procedure, major surgical debridement, or adjunctive intervention after 24 hours of start of study drug through D10, EOT, or D35, respectively, to treat the infection that was not already planned at Baseline • Intercurrent nonprotocol specified antibacterial therapy administered for the treatment of the primary DFI lesion or might have potential antibiotic activity directed toward the Gram-positive pathogens implicated in the DFI • Died of any cause up to D10, EOT, and D35, respectively
Indeterminate	• Study data are unavailable for evaluation of efficacy for any reason (eg, missing data, lost to follow-up). • Diagnosed with osteomyelitis ≤7 days of starting study drug
LFU: Subjects who were failures before LFU will be considered failures at LFU:	
Sustained clinical success	• No new signs or symptoms of the primary DFI after D35 in a subject who was a success at D35
Clinical relapse/failure	• New or worsened signs or symptoms of the primary DFI after D35 in a subject who was a success at D35
Indeterminate	• Study data are unavailable for evaluation of efficacy for any reason (eg, missing data, lost to follow-up).

DFI = diabetic foot infections; D = day; EA = Early Assessment; EOT = End-of-Therapy; LFU = Late Follow-Up

12.2 Microbiological Response Definitions

12.2.1 Per-Pathogen Microbiological Response

A microbiological outcome at D35 will be determined in the Micro-MITT and ME-D35 analysis sets for each pathogen isolated from the DFI lesion or blood at Screening/Baseline. Microbiological outcome categories include eradication, presumed eradication, persistence, presumed persistence, and indeterminate, as defined in Table 9. Favorable microbiological outcomes include eradication or presumed eradication. Unfavorable microbiological outcomes include persistence or presumed persistence.

Table 9: Microbiological Outcome Categories

Outcome Category	Definition
Eradication	An adequate source specimen (from DFI lesion and/or blood) demonstrates absence of the original Baseline pathogen
Presumed eradication	An adequate source specimen was not available to culture and the subject was assessed as a clinical success by the Investigator at D35
Persistence	An adequate source specimen demonstrates continued presence of the original Baseline pathogen at D35
Presumed persistence	An adequate source specimen was not available to culture from the DFI site or blood and the subject was assessed as a clinical failure by the Investigator at D35
Indeterminate	An adequate source specimen was not available to culture from the DFI site or blood and the subject's clinical response was assessed by the Investigator as indeterminate at D35

12.2.2 Per-Subject Microbiological Response

A microbiological outcome at D35 will be determined in the Micro-MITT and ME-D35 analysis sets for each subject based on individual outcomes for each Baseline pathogen. For a subject to have a favorable per-subject microbiological response, the outcome for each Baseline pathogen must be favorable (eradicated or presumed eradicated, as defined in Table 9). For a subject to have an unfavorable per-subject microbiological response, the outcome for a Baseline pathogen must be unfavorable (persistence, presumed persistence, as defined in Table 9). If the same pathogen is isolated from multiple sites (eg, blood and DFI lesion culture), the worst response will be used to determine the per-subject microbiological response.

12.2.3 Emergent Infections

Superinfections and new infections of DFI are defined in Table 10.

Table 10: Emergent Infections

Category	Definition
Superinfection	Isolation of a new pathogen(s) (other than the original Baseline pathogen[s]) from the primary DFI lesion (culture) that is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period up to and including EOT (ie, Investigator's assessment of clinical response is failure).
New infection	Isolation of a new pathogen(s) (other than the original Baseline pathogen[s]) from the primary DFI lesion (culture) that is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy after EOT (ie, the Investigator's assessment of clinical response is failure at D35)

DFI = diabetic foot infections; EOT = End-of-Therapy

13.0 ASSESSMENT OF SAFETY

Safety will be assessed through the determination and recording of the occurrence of AEs and AEs of special interest, as well as by adverse changes in physical examinations, vital signs, ECG parameters, and laboratory values. Adverse events will be evaluated by relationship to study drug and severity. Serious adverse events will be identified.

All subjects will be monitored for the occurrence of AEs throughout the study, including AEs of special interest (Section 13.1.8) that are associated with the oxazolidinone class of antibiotics. Each recorded AE will be described by its duration (ie, start and end dates), severity, seriousness, and suspected relationship to the study drug. Adverse events will be graded as mild, moderate, or severe, according to DMID toxicity grading as detailed in Section 13.1.2 and Appendix 1 in Section 18.1. Relationship of the AE to study drug will be characterized as related (including possibly related or definitely related) and unrelated, as detailed in Section 13.1.3.

Vital signs, ECGs, hematology, serum chemistry, coagulation, and UA evaluations will be performed at Screening/Baseline and at various timepoints during and after the dosing period (Table 1).

As detailed in Section 6.5, if study drug is determined not to be safe and tolerated in a specific subject, the study drug assignment for the subject with a significant safety concern may be unblinded after discussion between the Investigator and Sponsor. The blind may also be broken in the case of a medical emergency requiring the Investigator to know the identity of the study drug to appropriately guide the subject's medical management. Prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel.

Reports of AEs will be collected for all subjects from the time informed consent is signed. The Investigator will assess all AEs and SAEs and record the following information on the appropriate eCRF page:

- Date and time of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

The Investigator should distinguish between local and systemic AEs. An example of a possible systemic AE includes generalized rash or pruritus related to an allergic reaction. An example of a possible local AE includes a focal rash or irritation that is localized to a cutaneous area surrounding a venous blood draw.

Clinically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. For example, laboratory workup of an AE of anemia could include iron tests, reticulocyte count, and blood smear, among other local laboratory tests. The Investigator should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

13.1 Adverse Events

13.1.1 Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Adverse events are collected from the time the informed consent is signed.

An AE does *not* include the following:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); the condition that necessitates the procedure is an AE.
- Any pre-existing disease or condition, or laboratory or ECG abnormality, present or detected before administration of study drug that does not worsen.
- Laboratory or ECG abnormalities without clinical manifestations, which do not require medical intervention, or that do not result in termination or delay of study medication (see Section 13.1.9 for further detail).
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, or convenience admissions).
- Overdose of any study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation.
- Worsening of the primary DFI for which the subject was enrolled.

When possible, a constellation of signs and symptoms associated with an underlying condition should be reported as the unifying event. For example, the individual signs and symptoms of elevated WBC, fever, cough and shortness of breath should be reported as pneumonia, if applicable.

13.1.2 Assessment of Severity

Severity of AEs will be assessed by the Investigator was mild, moderate, or severe (Table 11). This assessment is subjective and thus the Investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. It is important to recognize that severity is not equivalent to event seriousness (see Section 13.1.4.2).

Table 11: Guidelines for Severity Assessments

Severity	Grade	Definition[a]
Mild	1	Transient (ie, <48 hours) or mild discomfort, no medical intervention or treatment required, no limitation in activity or daily function.
Moderate	2	Mild to moderate limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required (ameliorated with simple therapeutic measures).
Severe	3	Marked limitation in activity (sufficient severity to cause severe discomfort and interrupt daily activities), some assistance usually required, medical intervention/therapy required, hospitalization possible. A severe AE does not necessarily qualify as an SAE (Section 13.1.4.2).
Life-threatening	4	Extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care probable.

AE = adverse event; SAE = serious adverse event

a. National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases

13.1.3 Relationship to Study Drug

For each reported AE, the Investigator must make an assessment of the relationship of the event to the study drug using the following scale:

- Not related: The AE is definitely caused by the subject's clinical state, or the study procedure/conditions. There is no association between the study drug and the reported event; there is a clear alternative explanation; a causal relationship is nonplausible.
- Unlikely Related: The underlying or concurrent disease or other drugs/exposures provide plausible alternative explanations. Temporal relationship to study drug administration makes a causal relationship improbable.
- Likely Related: There is a reasonable possibility that the drug caused the AE; the event is unlikely attributed to underlying or concurrent disease or other drugs/exposures (ie, alternative explanation). There is a reasonable time sequence to administration of the study drug.
- Definitely Related: A definite causal relationship exists between the drug administration and the AE; including a plausible time relationship to drug administration, and it cannot be explained by underlying or concurrent disease or other drugs/exposures; abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to administration of study drug, then an alternative explanation should be provided.

13.1.4 Serious Adverse Events

An SAE is defined as any adverse experience occurring at any dose of study medication that occurs between the time informed consent is signed and within 30 days after the final administration of study drug that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization (*excluding hospitalization before randomization due to initial management of DFI at Baseline and new hospitalizations due to progression of the underlying primary DFI lesion*) or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Events that jeopardize the subject sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes (eg, bronchospasm requiring urgent management in an emergency room, blood dyscrasias that do not result in hospitalization, seizures that do not result in hospitalization)

13.1.4.1 Serious Adverse Event Reporting

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after administration of study drug. All SAEs must be reported to the Medical Monitor within 24 hours of the investigational site's knowledge of the event.

Any SAE, regardless of expectedness or causality, should be reported by completing the AE eCRF form (ie, when Serious = Yes) electronically in the Electronic Data Capture (EDC) system. When the form is completed, Medpace Clinical Safety will be notified electronically. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE reporting line (provided below), and fax/email the completed paper SAE form to Medpace within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered into the EDC within 24 hours of the system becoming available. Any supporting documentation (eg, subject discharge summary, hospital records, autopsy reports) should be submitted to Medpace Clinical Safety via email or fax.

USA - Medpace SAE reporting line:
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3
Fax: +1-866-336-5320 or +1-513-570-5196
email: Medpace-safetynotification@medpace.com

Europe - Medpace SAE reporting line:
Telephone: +49 89 89 55 718 44
Fax: +49 89 89 55 718 104
email: Medpace-safetynotification@medpace.com

In the event of a fatal or life-threatening SAE, any required information for the initial report must be provided to the SAE Reporting General Delivery email box within 7 calendar days of the Investigator's initial SAE report. For an SAE that is not fatal or life-threatening, any required information for the initial report must be provided within 15 calendar days of the Investigator's initial SAE report.

The Investigator will follow an SAE until it resolves, the Investigator feels the event is stable and chronic in nature, or the subject is lost to follow up. All follow up information relevant to the SAE must be provided within 24 hours of the Investigator's receipt of this information.

Instances of death, cancer, or congenital abnormality, if brought to the attention of the Investigator AT ANY TIME after study drug administration AND considered by the Investigator to be RELATED TO THE STUDY DRUG, must be reported as an SAE.

The information needed for completing a Serious Adverse Event Report (SAER) is as follows:

- Subject identification, Investigator name, and site number.
- SAE information: event term, onset date, severity, and causal relationship.
- The outcomes attributable to the event (eg, death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s]).
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history.
- The first and last dates of administration of study drug. NOTE: As this is a double-blind study, SAERs should not indicate specific study drug assignments.
- Indicate if the study drug was discontinued or if the administration of study drug schedule modified.
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the eCRF.

13.1.4.2 “Serious” Versus “Severe” Adverse Events

To avoid confusion or misunderstanding over the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided (excerpted from International Council for Harmonisation [ICH] E2A):

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

13.1.4.3 SAE Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself.
- All deaths during administration of study drug or occurring within 30 days of the last administration of study drug, if brought to the attention of the Investigator, regardless of cause or relationship, must be reported using the SAER.
- "Occurring at any dose" does not imply that the subject is actively receiving study drug at the time of the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.
- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the AE or SAE, rather than as the individual signs or symptoms.

13.1.5 Treatment-emergent Adverse Event

A TEAE is defined as an AE that occurs during or after the first administration of study drug and up through the last study visit or evaluation, or an SAE that occurs during or after the first administration of study drug up through 30 days after the final administration of study drug.

13.1.6 Life-threatening Adverse Event

A life-threatening AE is an AE that, in the view of either the Investigator or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

13.1.7 Unexpected Adverse Event

An AE is considered “unexpected” if it is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered unexpected until they have been observed with the drug under investigation.

13.1.8 Adverse Events of Special Interest

Adverse events of special interest are those associated with the oxazolidinone class of antibiotics. Warnings and precautions in the linezolid label include the risks for myelosuppression, peripheral and optic neuropathy (any clinically significant decrease in visual acuity should prompt ophthalmology consultation), serotonin syndrome, CDAD, potential drug interactions producing hypertension, and hypoglycemia.

13.1.9 Reporting Laboratory and Electrocardiogram Abnormalities

Laboratory and ECG abnormalities should not be recorded as AEs unless they are associated with clinical signs or symptoms or require medical intervention. However, laboratory and ECG abnormalities (eg, clinically significant changes detected on clinical chemistry, hematology, UA, etc.) independent from the underlying medical condition that require medical or surgical intervention, or lead to study drug interruption or discontinuation, must be recorded as an AE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than an isolated laboratory or ECG abnormality. In addition, laboratory and ECG abnormalities or other abnormal test assessments that are associated with signs or symptoms must be recorded as AEs if they meet the definition of an AE (or SAE).

13.2 Risks for Women of Childbearing Potential

The risks of treatment with contezolid acefosamil/contezolid during pregnancy have not been fully evaluated. The effect of the study drug on a fetus, breast-fed child, or gametocytes is unknown. Therefore, females must be either postmenopausal for ≥2 years or surgically sterile (having undergone tubal ligation, hysterectomy, or bilateral oophorectomy) or, if of childbearing potential, must have a negative serum or urine pregnancy test (β–HCG) at Screening/Baseline and, if sexually active with male partners, be willing to use a highly effective method of contraception throughout the study such as 1 of the following:

- Hormonal contraception (stable dose for 3 months)
- Intrauterine device/intrauterine hormone-releasing system
- Double-barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom)

Additionally, males (if nonsterile and sexually active with female partners of childbearing potential) must use a double-barrier method of contraception (ie, diaphragm, cervical cap, contraceptive sponge, condom) and be willing to continue to use these same birth control measures while participating in the study and for 60 days following participation in the study. Males must also refrain from sperm donations during this time.

Female subjects must be instructed to inform the Investigator immediately if they become pregnant during the study. Male subjects must also be instructed to inform the Investigator immediately if a female partner becomes pregnant within 60 days after dosing. In the event of a confirmed pregnancy in a female subject, the following actions should be taken:

- Study drug should be stopped immediately.
- The pregnancy should be reported to the Medical Monitor within 24 hours of notification using the Pregnancy Report Form.
- The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.
- The subject must be monitored until the immediate postnatal period or until termination of the pregnancy. The outcome should be reported to the Medical Monitor using the Pregnancy Outcome Form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Medical Monitor.

13.3 Adverse Event Follow-up

All AEs and SAEs will be followed to resolution or stabilization. Adverse events that have not resolved by a study visit, but have stabilized, will be categorized as such in the database. Nonserious AEs that are ongoing at the end of the study will be identified as 'Ongoing'.

13.4 Study Termination or Temporary Suspension

The study may be temporarily suspended or terminated should the Sponsor or health authority determine that the safety of study subjects is significantly jeopardized. The decision for a temporary or permanent study hold will depend on the nature, frequency, and severity of AEs that were observed in all enrolled subjects to date. In a temporary study hold, no additional subjects will be enrolled into the study or dosed with study drug until the Sponsor decides it is safe to proceed with the study. Enrollment will be temporarily suspended until review by the independent Data Monitoring Committee (DMC) and risks can be appropriately addressed if any of the following events, confirmed to be related to study drug, occur in ≥2 subjects receiving contezolid acefosamil/contezolid (as determined after unblinding) during the study period:

- Hy's law criteria met; these are defined as elevations of ALT or AST to >3 times ULN and elevation of serum total bilirubin to ≥2 times ULN with serum alkaline phosphatase <2 times ULN, and no other disease or condition can be found to explain the liver test abnormalities (FDA 2009)
- Clinically significant cardiac arrhythmia (eg, Torsade de Pointes)
- Symptomatic anemia with a hemoglobin level <8.0 g/dL, as confirmed on repeat testing, or requirement for blood transfusion
- Platelet count $<50\times10^3/mm^3$, as confirmed on repeat testing
- WBC count $<2.0\times10^3/mm^3$ or absolute neutrophil count $<1{,}000/mm^3$, as confirmed on repeat testing
- Rash defined as an SAE (Section 13.1.4)
- Peripheral or optic neuropathy
- Serotonin syndrome
- Anaphylaxis or allergy-related angioedema

In a temporary study hold, no additional subjects will be enrolled into the study or dosed with study drug until the Sponsor, in consultation with the Medical Monitor and DMC, decides that it is safe to proceed with the study.

As noted above, safety assessments will be monitored and evaluated on a regular basis by the study team, and any abnormal clinical or laboratory findings or trends will be closely monitored and followed regardless of severity or causality (eg, before an event reaches a severe grading level or reaches a termination criterion cutoff).

13.5 Data Monitoring Committee

An independent unblinded DMC, guided by a charter, will be utilized in this study for the protection of study subjects. The DMC will perform ongoing review of blinded and unblinded data, including both safety and efficacy, at scheduled data review meetings. At each meeting, the DMC will review the available data and make recommendations to the Sponsor to continue, modify, or discontinue study enrollment (if the study is enrolling).

14.0 ASSESSMENT OF PHARMACOKINETICS

Pharmacokinetic assessments will be performed at selected clinical sites that have the appropriate equipment (including refrigerated centrifuges and -70ºC freezers) and experienced personnel to adequately obtain, handle, store, and ship PK samples for bioanalysis. At these selected clinical sites, PK samples will be obtained from as many subjects as possible. Drug exposure will be predicted using the population PK model developed from the Phase 1 and Phase 2 studies based on demographic data (eg, body weight) for subjects from whom PK samples were not obtained.

- 3 PK samples after the first IV dose (to characterize the first dose):
  - Obtain 2 blood samples between 1.5 and 6 hours after the start of the first infusion, with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after the start of infusion)
  - Obtain 1 blood sample (trough level) within 2 hours before the start of the second dose (IV or PO) of study drug
- 3 PK samples on D5 (±1 day) (to characterize drug exposure after multiple doses):
  - Obtain 1 blood sample (trough level) within 2 hours before a designated D5 (±1 day) dose (IV or PO) of study drug
  - Obtain 2 blood samples between 1.5 and 6 hours after the designated D5 (±1 day) dose of study drug (when PO dose is taken or when IV dose is started), with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after PO dose taken or IV infusion started)
- 3 PK samples at EOT (to evaluate potential drug accumulation):
  - Obtain 1 blood sample (trough level) within 2 hours before the last dose (IV or PO) of study drug
  - Obtain 2 blood samples between 1.5 and 6 hours after the last dose of study drug (when last PO dose is taken or when last IV dose is started), with a minimum of 2 hours between the 2 sample collections (ideal sample timepoints are at 1.5 hours and at 4 hours after PO dose taken or IV infusion started)

The PK data acquisition and analysis strategy entails the use of a sparse PK sampling schedule for subjects randomized to contezolid acefosamil/contezolid. This PK sampling strategy is designed to characterize the drug exposure profiles of contezolid after the first dose on D1, a designated D5 (±1 day) dose, and the final dose. Exposures to the contezolid acefosamil metabolite (MRX-1352) and the contezolid metabolite (MRX-1320) will also be evaluated. Two (2) PK samples between 1.5 and 6 hours postdose, plus a trough concentration, will assure that informative individual drug exposures for the area under the time-concentration curve (the most important parameter associated with efficacy) will be obtained. Data analysis will be performed by population PK modeling. Additionally, given the range of demographic data in the expected subject population, these PK data will be used to perform exploratory analyses on the impact of demographic characteristics (eg, weight, body mass index, age, gender, race) upon the PK (including clearance) of the drug and its metabolites. Only those PK samples obtained from subjects randomized to contezolid acefosamil/contezolid will be analyzed.

The bioanalytical laboratory will measure plasma concentrations for the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320 using validated and sensitive bioanalytical methods. Specific instructions for the collection of plasma drug concentration specimens will be provided in the Laboratory Manual and should be reviewed before collection.

When >1 assessment is scheduled at any given timepoint, clinical assessments should precede all blood draws, including ECGs. For subjects managed as outpatients, schedule the clinic visits appropriately to obtain PK samples at the end of IV therapy and the EOT visit as described above.

The PK analysis set is defined in Section 15.2. Selected PK samples may be used in the identification of the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320. Additional details will be provided in the PK Analysis Plan.

15.0 STATISTICAL METHODS

All data will be summarized separately by study drug (contezolid acefosamil/contezolid or linezolid). Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study drug. Frequency distributions (counts and percentages) will be presented for categorical variables. Listings will be provided for individual subject study data. All Baseline data will be summarized by treatment group.

15.1 Determination of Study Sample Size

Approximately 865 subjects (3:2 randomization ratio with 519 subjects each in the contezolid acefosamil/contezolid and 346 subjects in the linezolid treatment arm) will be enrolled.

The sample size determination is based on ensuring sufficient power for the primary endpoint of Investigator's assessment of clinical response at D35 in the MITT analysis set. For the primary efficacy endpoint, assuming an outcome rate of 75% for both treatment groups, a noninferiority (NI) margin of 10%, 90% power, and a 1-sided alpha of 0.025, using a Z-test with unpooled variance, a total of 820 subjects in the MITT analysis set are required. To account for an anticipated nonevaluable rate of 5%, an additional 45 subjects have been added for a total of 865 randomized subjects to achieve 820 subjects in the analysis set evaluated for the primary efficacy outcome (492 subjects in the contezolid acefosamil/contezolid group and 328 subjects in the linezolid group).

15.2 Analysis Sets

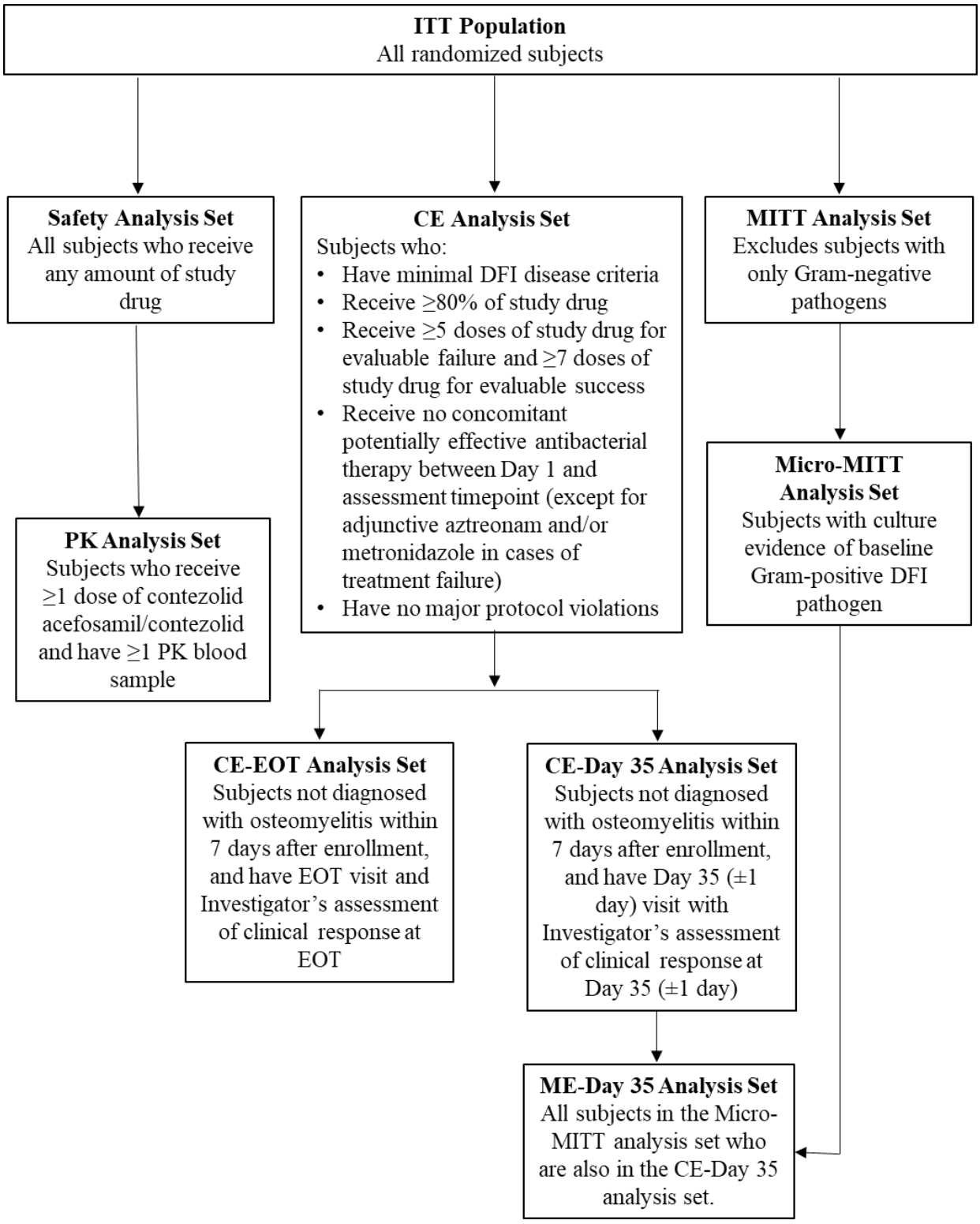
The analysis sets are defined in Table 12, and the relationship between the analysis populations are displayed in Figure 3.

Table 12: Analysis Populations

Analysis Sets	Definitions
ITT analysis set	All randomized subjects will be included in the ITT analysis set, regardless of whether study drug is administered.
MITT (Modified-ITT) analysis set	All subjects in the ITT analysis set with a confirmed or suspected Gram-positive bacterial pathogen (ie, excluding subjects with only a Gram-negative pathogen)
Safety analysis set	All subjects who receive any amount of study drug. Subjects in the safety analysis set will be analyzed according to study drug actually received.
Micro-MITT analysis set	All subjects in the MITT analysis set who have culture evidence of a Baseline Gram-positive bacterial pathogen known to cause DFI
CE analysis sets (CE-D35, CE-EOT)	All subjects in the MITT analysis set who meet the minimal clinical disease criteria for DFI; receive ≥80% of expected doses based on length of therapy; did not receive any potentially effective systemic or topical antibacterial therapies other than protocol specified study drug(s) between D1 and timepoint for assessment (except for adjunctive aztreonam and/or metronidazole, or in cases of treatment failure). To be included in the CE-EOT analysis set, the following conditions must be met: • Have an Investigator's assessment of clinical response at EOT (ie, response cannot be indeterminate) • Had an EOT visit on D14 to D28 (+1 day), or if study drug was prematurely discontinued, within 1 day of discontinuation To be included in the CE-D35 analysis set, the following conditions must be met: • Have an Investigator's assessment of clinical response at D35 (ie, response cannot be missing or indeterminate unless the subject is deemed a clinical failure at EOT) • Had a D35 (+2 days) visit In addition to meeting the above criteria, subjects must meet the following specific conditions to be included in the CE analysis set: • Received ≥5 doses of study drug therapy to be considered an evaluable failure • Received ≥7 doses of study drug therapy to be considered an evaluable success • Did not have any major protocol violations that affected efficacy • Not diagnosed with osteomyelitis within 7 days after randomization
ME analysis sets (ME-D35, ME-EOT)	All subjects in the Micro-MITT analysis set who also are in the CE-D35 or CE-EOT analysis set, respectively.
PK analysis set	All subjects who receive ≥1 dose of contezolid acefosamil/contezolid and had ≥1 blood sample obtained for analysis of the contezolid acefosamil metabolite (MRX-1352), contezolid, and the contezolid metabolite (MRX-1320).

CE = Clinically Evaluable; D = day; DFI = diabetic foot infections; EOT = End-of-Therapy; ITT = Intent-to-Treat; ME = Microbiologically Evaluable; Micro-MITT = Microbiological Modified Intent-to-Treat; MITT = Modified Intent-to-Treat; PK = pharmacokinetic

Figure 3: Overview of Analysis Sets



DFI = diabetic foot infections; CE = Clinically Evaluable; EOT = End-of-Therapy; ITT = Intent-to-Treat; ME = Microbiologically Evaluable; ME = Microbiologically Evaluable; Micro-MITT = Microbiological Modified Intent-to-Treat; MITT= Modified Intent-to-Treat; PK = pharmacokinetic

15.3 Determination of Inclusion in Analysis Sets

Inclusion in the ITT, safety, and PK analysis sets will be determined programmatically from eCRF data. Inclusion in the MITT and Micro-MITT population will be determined programmatically by incorporating the outcome of the review of the isolates by the Medical Monitor. The Medical Monitor will determine whether each isolate (Baseline and post-Baseline) is considered a pathogen. Inclusion in the CE-EOT and CE-D35 analysis sets will be determined programmatically from the eCRF data and manual review conducted by the Medical Monitor. The Medical Monitor may review subject data to confirm that analysis set criteria are satisfied. Inclusion in the MITT and ME-D35 analysis set will be determined programmatically by incorporating the outcome of the review of the isolates by the Medical Monitor. All manual reviews and determinations of analysis set inclusion/exclusion will be done before study unblinding.

15.4 Analysis of Study Analysis Sets and Subject Characteristics

Enrollment, study drug administered, premature discontinuations from study medication, withdrawals from the study, and protocol deviations will be summarized by treatment group. A protocol deviation is defined as any variation from the protocol (eg, enrollment of a subject who did not meet all inclusion and exclusion criteria, failure to perform the assessments and procedures within the required time frame). A major (or important) deviation is defined as one that potentially affects the efficacy and/or safety analyses and will be determined by a review by the Sponsor.

Demographic (eg, age, race, sex), medical history, and Baseline clinical signs and symptoms of DFI will be summarized by treatment group. Baseline pathogens identified at the primary DFI lesion will also be summarized by treatment group.

The number and percentage of subjects in each analysis set and reasons for exclusion from analysis sets will be listed and summarized by treatment group.

15.5 Study Drug Exposure

By treatment group summaries will be provided for the total number of doses, number of IV doses, and number of PO doses. Compliance to study drug will be calculated based on the total number of doses taken, divided by the total number of expected doses in the time period between the dates of the first and last doses of study drug.

15.6 Efficacy Analyses

Primary and secondary efficacy evaluations will be summarized by analysis set, as indicated in Table 7.

15.6.1 Primary Efficacy Evaluation

For all efficacy outcomes, subject data will be analyzed in the group to which the subject was randomized. For the primary analyses, subjects will be analyzed in the stratum to which they were randomized.

15.6.1.1 Primary Efficacy Analysis

The primary efficacy outcome is the Investigator's assessment of clinical response at D35 in the MITT analysis set. The number and percentage of subjects in each treatment group classified as clinical successes, clinical failures, and indeterminates will be summarized. Ninety-five percent CIs will be provided for each clinical success rate. The difference between the clinical success rates will be calculated and a 2-sided 95% CI for the difference in clinical success rates (contezolid acefosamil/contezolid minus linezolid groups) will be calculated using a Z-test. Contezolid acefosamil/contezolid will be considered noninferior to linezolid if the lower bound of the 95% CI is greater than -10%

15.6.1.2 Additional Analyses of the Primary Efficacy Outcomes

The primary efficacy outcome will be assessed separately across the stratification factors of geographic region and severity of infection. For each infection severity stratum and each geographic region stratum, a 2-sided 95% CI for the observed difference in early clinical response rates will be calculated for the MITT analysis set. Additional efficacy endpoints will be summarized by treatment group as detailed in the SAP, which will be prepared and finalized before database lock. Additional subgroup analyses of the primary efficacy outcome may be conducted as descriptive analyses.

15.6.2 Secondary and Exploratory Efficacy Evaluations

All secondary and exploratory efficacy endpoints will be summarized by treatment group as detailed in the SAP. All secondary and exploratory efficacy endpoints are supportive of the primary efficacy endpoint and no conclusion of NI will be made.

Analyses for the secondary outcomes are described below and will be described in more detail in the SAP, which will be prepared and finalized before database lock. Additional exploratory analyses may be conducted and described in the SAP.

15.6.2.1 Clinical Outcomes

The number of subjects with an Investigator's assessment of clinical success, clinical failure, and indeterminate at D35 will be tabulated for both treatment groups for the ITT, MITT, and CE-D35 analysis sets, and at EOT in the ITT, MITT, and CE-EOT analysis sets (by definition, subjects with an indeterminate response will be excluded from summary in the CE-EOT analysis set). The difference in clinical success rates will also be summarized and the 95% CI will be provided for the difference in the success rates. The durability of clinical response (rate of sustained clinical response, clinical relapse/failure, and indeterminate) at LFU will be summarized by treatment group in the Micro-MITT and ME-D35 analysis sets. The difference in sustained clinical response rates will also be summarized and the 95% CI will be provided for the difference in the sustained clinical success rates.

The number and percentage of subjects in each treatment group with an Investigator's assessment of clinical success, clinical failure, and indeterminate at D35 and LFU in the Micro-MITT and ME-D35 analysis sets will be tabulated by Baseline pathogen.

15.6.2.2 Microbiological Outcomes

The number and percentage of subjects with favorable, unfavorable, and indeterminate per-subject microbiological responses at D35 will be summarized in the Micro-MITT and ME-D35 analysis sets. Microbiological responses include eradication, presumed eradication, persistence, presumed persistence, and indeterminate (Table 9). Of these responses, eradication and presumed eradication will be regarded as a favorable outcome. Persistence and presumed persistence will be regarded as an unfavorable outcome. To have an overall, favorable, per-subject, microbiological response at D35 in the Micro-MITT and ME-D35 analysis sets, the outcome for each Baseline pathogen must be favorable. If a subject has >1 Baseline pathogen, all pathogens must have a favorable response to have an overall favorable per-subject response. A 2-sided 95% CI will be calculated for the difference in the per-subject favorable microbiological response.

Microbiologic response at D35 by Baseline pathogen will be determined as the proportion of subjects with a favorable microbiological response for each pathogen isolated at Baseline from the DFI lesion or blood in the Micro-MITT and ME-D35 analysis sets. The number and percentage of subjects in each treatment group with a microbiologically favorable outcome will be tabulated.

Emergent infections (eg, superinfection, new infection) will be listed (Section 12.2.3).

15.7 Safety Analyses

Safety will be evaluated by presenting summaries of AEs, vital signs, laboratory evaluations (hematology, chemistry, and coagulation), and ECG parameters. Adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). An overall summary of AEs will be provided by treatment group. The incidence of TEAEs will be presented by SOC and Preferred Term (PT), and by SOC, PT, and relationship to study drug, and by SOC, PT, and severity. Serious AEs (SAEs) and TEAEs that lead to discontinuation of the study drug will also be presented by SOC and PT. Descriptive statistics for clinical laboratory results, vital signs, and ECG parameters, including change from Baseline, will be presented by timepoint and for the overall most abnormal post-Baseline value (clinical laboratory results and vital signs only). Incidences of potentially clinically significant clinical laboratory results, vital signs, and ECG parameters, as defined in the SAP, will also be summarized by timepoint and the overall most abnormal post-Baseline value (clinical laboratory results and vital signs only). For each safety parameter, the last assessment made before the first administration of study drug will be used as the Baseline for all analyses. For safety analyses for both the FDA and EMA, subjects will be analyzed according to the treatment actually received.

A TEAE is defined as an AE with a start date and time on or after the first dose of study drug. The incidence of TEAEs (defined in Section 13.1.5) will be presented by SOC and PT according to Medical Dictionary of Regulatory Activities (MedDRA®); by SOC, PT, and relationship to study drug; and by SOC, PT, and severity. In addition, the incidence of SAEs and TEAEs leading to discontinuation of study drug will be presented by SOC, PT, and relationship to study drug. If the incidence of SAEs and TEAEs leading to discontinuation of study drug is low, only a listing will be provided.

Descriptive statistics of clinical laboratory tests, vital signs, and ECGs at each timepoint measured, as well as the change from Baseline, will be presented by treatment group. Potentially clinically significant changes will be defined in the SAP. Physical examination results will be presented in by-subject listings.

15.8 Pharmacokinetic Analyses

Characterization of the PK of the contezolid acefosamil metabolite MRX-1352, contezolid, and the contezolid metabolite MRX-1320 is a secondary objective for this study. Plasma samples from subjects in the PK analysis set (Section 15.2) will be analyzed for contezolid and metabolite (MRX-1352and MRX-1320) concentrations using validated and sensitive bioanalytical methods. Only those PK samples obtained from subjects randomized to contezolid will be analyzed.

Pharmacokinetic data will be summarized using descriptive statistics and graphically displayed, and population PK modeling analyses will be performed. Further details of the PK sample collection and analyses are provided the PK Analysis Plan and Laboratory Manual.

15.9 Handling of Dropouts, Missing, Unused and Spurious Data

Every effort will be made to collect all data at specified times. Missing values will not be imputed and only observed values will be used in data analyses and presentations. Where individual data points are missing, categorical data will be summarized based on reduced denominators (ie, only subjects with available data will be included in the denominators).

For the primary outcome measure of the Investigator's assessment of clinical response at D35 in the MITT analysis set, if any data field needed to determine the response is missing, the subject will be assigned an Indeterminate response. For analyses of the primary outcome, subjects with an Indeterminate response are included in the denominator, and thus, are considered early clinical nonresponders. A sensitivity analysis of the primary outcome will be conducted in which subjects with an Indeterminate response are considered early clinical responders and a multiple imputation analysis will be completed.

Missing data for secondary efficacy outcomes will be handled similarly. A detailed description of the handling of dropouts and missing, unused, and spurious data will be provided in the SAP.

16.0 ADMINISTRATIVE CONSIDERATIONS

16.1 Ethical Conduct of Study

This study will be conducted in accordance with applicable US FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, and the IRB/IEC and local legal requirements.

16.2 Informed Consent

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Subjects will give written consent to participate in the study at the first visit, before initiation of any study-related procedure, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. A copy of the informed consent document must be provided to the subject in a language understandable to the subject. Signed consent forms must remain in the subject's study file and be available for verification by the Sponsor or representatives of a competent regulatory agency at any time.

16.3 Institutional Review Board/Independent Ethics Committee Approval

This study will be conducted in compliance with the protocol approved by the IRB/IEC and according to ICH and GCP consolidated guidelines and the ethical principles of the Declaration of Helsinki.

No major deviation from the protocol will be implemented without the prior review and approval of the IRB/IEC or Sponsor except when it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Medical Monitor/Sponsor as soon as possible, and the IRB/IEC in accordance with the IRB/IEC reporting requirements.

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB/IEC for approval. Approval by the IRB/IEC of the protocol, informed consent document, and any advertisement used to recruit study subjects must be obtained before the study may be initiated at a site.

The Investigator and/or Sponsor designee are responsible for informing the IRB/IEC of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator and/or Sponsor designee are also responsible for notifying the IRB/IEC of any SAEs and significant AEs that occur during the study, in accordance with their reporting criteria.

16.4 Investigator Requirements

Each Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor or Sponsor representative must approve any change to the protocol before seeking approval from the IRB/IEC. Each Investigator will be responsible for enrolling only those subjects who have met the protocol inclusion and exclusion criteria.

16.5 Electronic Case Report Forms and Data Capture System

This study will utilize an eCRF system for data recording. All eCRF data are to be completed by designated site personnel. All data entry, modification, or deletion will be recorded automatically in the electronic audit trail. All electronic data entered by the site (including the electronic audit trail) will be maintained or made available at the site in compliance with 21 CFR Part 11 and other applicable retention regulations.

Before the first subject is dosed at an investigational site, the Investigator and the study site's personnel will be trained on recording the data in the eCRFs. The Investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor or Sponsor representative via the system, providing missing or corrected data, and approving all changes performed on the subject data. This approval method will include applying an electronic signature, a uniquely assigned username, and a password that together will represent a traditional handwritten signature. This electronic signature will be certified as outlined in 21 CFR Part 11. The Sponsor will retain the original eCRF data and audit trail. An electronic or certified paper copy of all completed eCRF data, including query resolution correspondence, will be provided to the Investigator at the end of the study.

Queries may be issued electronically to the clinical study site and answered electronically by that study site's personnel. The identifying information (assigned username, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records.

16.6 Source Data and Document Maintenance

All data collected on the eCRFs must have an original source record.

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. The Sponsor or Sponsor's representative has ethical, legal, and scientific obligations to monitor this study in a detailed and orderly manner in accordance with established research principles and applicable local regulations. As part of a concerted effort to fulfill these obligations, the Sponsor's monitors or representatives will visit the study site on a regular basis during the conduct of the study, in addition to maintaining telephone and written communication.

The Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records. The Investigator must retain a comprehensive and centralized filing system of all clinical study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities. The Investigator will allow the Sponsor or its representative, or an appropriate representative of the competent authorities, to inspect all clinical study-related documentation for confirmation of data throughout the study period.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor and by the IRB/IEC as appropriate. At a subject's request, blinded medical information (unless previously unblinded) may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from subjects during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

16.7 Study Monitoring Requirements

The Sponsor or Sponsor representative will conduct site visits to inspect study data, subjects' medical records, and eCRFs in accordance with current ICH E6 GCP guideline, and the respective US or local regulations and guidelines, as applicable. The Sponsor or Sponsor representative will also review data and query status remotely, which may warrant additional communication with the Investigator and the study site's personnel. The Investigator will make available to the Sponsor, or Sponsor representative, source documents, signed Informed Consent Forms, and all other study-related documents.

The Investigator will allow the Sponsor or Sponsor representative and applicable regulatory authorities to inspect facilities and records relevant to this study.

16.8 Study Completion

The Sponsor requires the availability of the following data and materials before the study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from Baseline through LFU for subjects enrolled.
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the Investigator.
- Complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material).
- Copies of protocol amendments and IRB/IEC approval(s) and notification(s), if appropriate.

This study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 GCP: Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, FDA GCP guidelines, and any additional IRB/IEC-required procedures.

16.9 Quality Control and Quality Assurance

Written SOPs will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol and amendment(s) with GCP, and with the applicable regulatory requirements
- Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study

To fulfill the quality assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

The purpose of an audit is to:

- Ensure subject safety
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs
- Assure data quality

16.10 Retention of Records

Essential documents pertaining to the conduct of this study and the distribution of investigational drugs including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records should be retained until ≥2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or ≥2 years have elapsed since the formal discontinuation of clinical development of an investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to notify the Investigator/institution as to when these documents no longer require retention.

16.11 Finance and Insurance

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

16.12 Publication Policy

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. The Sponsor will make all reasonable efforts to publish the results of the study in an appropriate peer-reviewed journal. Authorship on the primary publication of the results from this study will be based on contributions to study design, enrollment, data analysis, and interpretation of results.

17.0 REFERENCES

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18.0 APPENDICES

18.1 Appendix 1: DMID Toxicity Table

The National Institute of Allergy and Infectious Diseases (NIAID), Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (modified) (Table 13).

Estimating Severity Grade

For abnormalities NOT found elsewhere in the Toxicity Tables, use the scale below to estimate grade of severity:

- GRADE 1 (Mild): Transient or mild discomfort (<48 hours); no medical intervention/therapy required
- GRADE 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
- GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
- GRADE 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Serious or Life-threatening AEs

ANY clinical event deemed by the investigator to be serious or life-threatening should be considered a Grade 4 event.

Laboratory Ranges

Where discrepancies in the ULN and lower limit of normal of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

Table 13. Adult Toxicity Table

HEMATOLOGY	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	9.5-10.5 g/dL	8.0 -9.4 g/dL	6.5-7.9 g/dL	<6.5 g/dL
Absolute neutrophil count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75,000-99,999/mm^3	50,000-74,999/mm^3	20,000-49,999/mm^3	<20,000/mm^3
WBCs	11,000-13,000/ mm^3	13,000-15,000 /mm^3	15,000-30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorpho-nuclear leucocytes +band cells	>80%	90–95%	>95%	---------
Activated partial thromboplastin	1.01-1.66 ×ULN	1.67-2.33 ×ULN	2.34-3 ×ULN	>3 ×ULN
CHEMISTRIES	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement therapy or hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/l	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116-160 mg/dL	161- 250 mg/dL	251-500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/Dl or abnormal calcium *with* life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life threatening arrhythmia
Hypomagnesemia	1.4-1.2 mEq/L	1.1-0.9 mEq/L	0.8-0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL or replacement therapy required	1.0-1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1-<1.25 ×ULN	1.25-<1.5 ×ULN	1.5–1.75 ×ULN	>1.75 ×ULN
Hyperbilirubinemia (when other liver function in the normal range)	1.1-<1.5 ×ULN	1.5-<2.0 ×ULN	2.0 –3.0 ×ULN	>3.0 ×ULN
BUN	1.25-2.5 x ULN	2.6-5 ×ULN	5.1-10 ×ULN	>10 ×ULN
Hyperuricemia (uric acid)	7.5–10.0 mg/dL	10.1–12.0 mg/dL	12.1–15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1-1.5 ×ULN	1.6-3.0 ×ULN	3.1-6 ×ULN	>6 ×ULN or dialysis required
ENZYMES	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**

AST (SGOT)	1.1-<2.0 ×ULN	2.0–<3.0 ×ULN	3.0–8.0 ×ULN	>8 ×ULN
ALT (SGPT)	1.1-<2.0 ×ULN	2.0–<3.0 ×ULN	3.0–8.0 ×ULN	>8 ×ULN
Alkaline Phosphatase	1.1-<2.0 ×ULN	2.0–<3.0 ×ULN	3.0–8.0 ×ULN	>8 ×ULN
URINALYSIS	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 0.2-1g loss/day	2-3+ or 1-2 g loss/day	4+ or 2-3.5 g loss/day	nephrotic syndrome or >3.5 g loss/day
Hematuria	microscopic only <10 RBC/hpf	gross, no clots >10 RBC/hpf	gross, ±clots, OR RBC casts	obstructive or required transion
CARDIOVASCULAR	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac rhythm		asymptomatic, transient signs, no therapy required	recurrent/persistent symptomatic therapy required	unstable dysrythmia; hospitalization and treatment required
Hypertension	transient increase >20 mmHg; no treatment	recurrent, chronic increase >20 mmHg, treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 bpm or decreased by <10 mmHg systolic BP, no treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mmHg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60 mmHg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, blood loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused
RESPIRATORY	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, acute	transient; no treatment; 70-80% FEV1 of peak flow	requires treatment; normalizes with bronchodilator; FEV1 50-70% (of peak flow)	no normalization with broncho-dilator; FEV1 25-50% of peak flow; or retractions present	cyanosis: FEV1 <25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	dyspnea at rest	dyspnea requiring oxygen therapy

GASTROINTESTINAL	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last <1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral discomfort/ dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids
NEUROLOGICAL	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neurocerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle strength	subjective weakness, no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neurosensory	mild impairment in sensation (decreased sensation, eg, vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision, and/or hearing	moderate impairment (moderate decreased sensation, eg, vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (ie, upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL	Grade 1	Grade 2	Grade 3	Grade 4
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema, or joint swelling, but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function but not with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis
SKIN	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	erythema; pruritus	diffuse, maculo-papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme, or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15 mm	15-30 mm	>30 mm	
Erythema	<15 mm	15-30 mm	>30 mm	
Edema	<15 mm	15-30 mm	>30 mm	
Rash at injection site	<15 mm	15-30 mm	>30 mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy
Fever: oral	37.7-38.5°C or 100.0-101.5°F	38.6-39.5°C or 101.6-102.9°F	39.6-40.5°C or 103-105°F	>40°C or >105°F
Fatigue	normal activity reduced <48 hours	normal activity decreased 25-50%, >48 hours	normal activity decreased >50%, can't work	unable to care for self

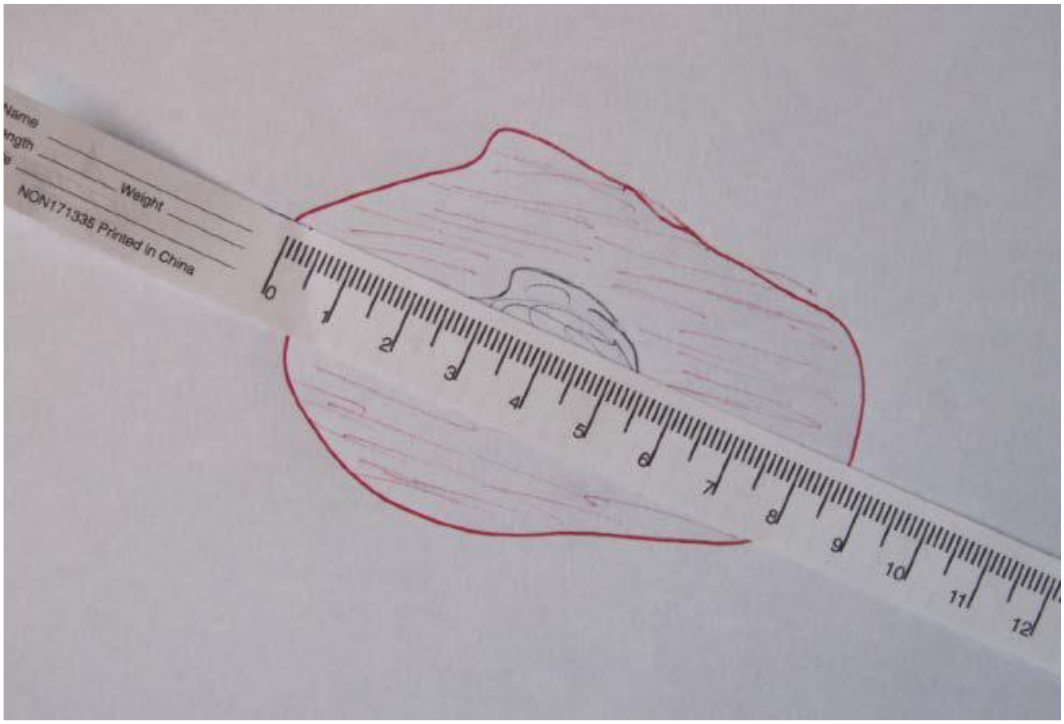
ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; bpm = beats per minute; ECG = electrocardiogram; FEV1 = forced expiratory volume in 1 second; hpf = high power field; IV = intravenous; LLN = lower limit of normal; mmHg = millimeter mercury; RBC = red blood cell; ULN = upper limit of normal
Source: National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases, Adult Toxicity Table, modified. November 2007.

18.2 Appendix 2. Instructions for Primary Diabetic Foot Infection Site Measurement

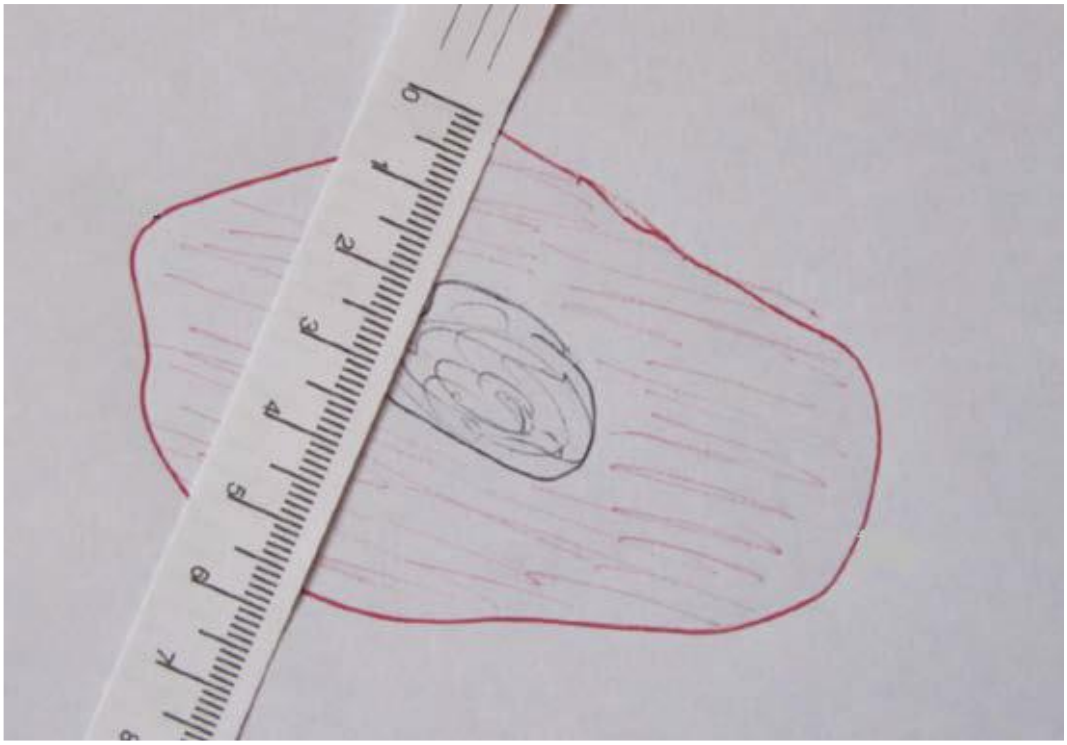
1. Measurements of erythema, edema, or induration, whichever is largest, should be done by measuring the longest length and then the widest width perpendicular to that length (Figure 4). Note: the furthest edges of erythema, edema, and/or induration, whichever is largest should be the focus of the measurement. For length (cm) of redness extending from the wound margin, measure the same direction from rim of wound as used at Baseline assessment, if applicable. Note: in subjects with darker skin, the perimeter of erythema, edema, and/or induration may be difficult to delineate. Palpation may help delineate the perimeter of the inflammatory lesion.
2. Measure in this manner and document the measurement in the source document and eCRF.

Figure 4: Primary Diabetic Foot Infection Site Measurement – Example

Longest length:



Widest width perpendicular:



18.3 Appendix 3: American Diabetes Association Criteria for the Diagnosis of Diabetes

Criteria for the diagnosis of diabetes (American Diabetes Association 2011) is provided below:

- Glycated hemoglobin (A1C) ≥6.5% (in the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test samples)

  OR

- Fasting plasma glucose ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for ≥8 hours (in the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test samples)

  OR

- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (in the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test samples)

  OR

- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

18.4 Appendix 4. Local Signs and Symptoms of Diabetic Foot Infections

Local signs and symptoms will be assessed for the primary DFI lesion. The Investigator will provide a categorical assessment and comparison to Baseline of the following DFI signs and symptoms using the scale in Table 14.

Table 14. Diabetic Foot Infection Signs and Symptoms

Parameter	Description	Absent	Present		
Purulent drainage	viscous, yellowish-white or greenish fluid formed in infected tissue	Absent	Present		
Parameter	**Description**	**Absent**	**Mild**	**Moderate**	**Severe**
Nonpurulent drainage	serous, sanguineous, or serosanguineous collection of fluid in tissue surrounding wound	absent	scant drainage on dressing (<0.5 cm diameter) not requiring additional dressings	> scant but < copious drainage on dressing (>2 cm diameter) requiring additional dressing changes	copious drainage on dressing (>2 cm diameter) requiring additional dressing changes
Other signs and symptoms of inflammation		**Score of 0**	**Score of 1**	**Score of 2**	**Score of 3**
Erythema	congestive or exudative redness surrounding wound caused by engorgement of capillaries in lower layers of skin	absent	pink, barely perceptible	pale red with defined edges	red to dark red
Edema	observable and/or palpable soft tissue swelling, often "pitting" with pressure, caused by soft tissue fluid accumulation	absent	localized to infection site	limited extension from infection site	extending from infection site to involve substantial portion of affected lower extremity
Induration	inflammatory hardening or thickening of tissues; ‘‘brawny edema.’’	absent	localized to infection site	limited extension from infection site	extending from infection site to involve substantial portion of affected lower extremity
Warmth	increase in skin temperature relative to the uninfected contralateral foot	absent; temperature of the 2 sides the same	temperature slightly, but perceptibly warmer	temperature clearly warmer (perceived as 1–2 °F)	marked difference in temperature (perceived as >2 °F)
Tenderness	palpation of infection site elicits subject report of tenderness. Measured on 0 (none) to 10 (worst imaginable) scale	absent	score of ≤5	score of 6–8	score of ≥9
Pain	subjective reporting of discomfort or perception of pain at infection site reported by patient. Measured on 0 (none) to 10 (worst imaginable) scale	absent	score of ≤5	score of 6–8	score of ≥9

18.5 Appendix 5. Restricted Medications

Oxazolidinones are reversible, nonselective MAOIs; therefore, they have the potential for interaction with adrenergic and serotonergic agents (Zyvox® Prescribing Information, 2021). Exclusion Criterion 20 states that prior (within the past 2 weeks) or expected/required concomitant (from the start of the study drug to EOT) administration of systemic adrenergic or serotonergic medications are excluded (Section 7.2). Such agents include the following:

Adrenergic Agents

Adrenergic agents, including indirect-acting sympathomimetic agents, vasopressors, and dopaminergic agents, should be used with caution when administered concomitantly with oxazolidinones— subjects receiving concomitant linezolid may experience a reversible enhancement of the pressor response to such adrenergic agents (Zyvox® Prescribing Information, 2021). Examples of such agents include:

- ***Adrenergic receptor agonists***; examples include dobutamine, dopamine, epinephrine (adrenaline), norepinephrine, phenylpropanolamine, pseudoephedrine
- ***Norepinephrine reuptake inhibitors***; examples include bupropion and methylphenidate
- ***Azapirones***; examples include buspirone and gepirone

Serotonergic Agents

Spontaneous reports of serotonin syndrome, including fatal cases, have been reported with the co-administration of linezolid and serotonergic agents (eg, antidepressants such as serotonin reuptake inhibitors [SSRIs]). Symptoms and signs of serotonin syndrome include hyperthermia, rigidity, myoclonus, autonomic instability, and mental status changes that include extreme agitation progressing to delirium and coma. In this study, study drug (contezolid acefosamil/contezolid or linezolid) should not be administered to subjects taking any of the following medications:

- ***SSRIs***; examples include paroxetine, sertraline, fluoxetine, fluvoxamine, and citalopram
- ***Tricyclic antidepressants***; examples include clomipramine and imipramine
- ***Serotonin 5-HT1 receptor agonists*** (***triptans***); examples include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan

18.6 Appendix 6. Avoidance of High-tyramine Foods and Drinks

As linezolid and other oxazolidinones are MAOIs, a significant pressor response has been observed in normal adult subjects receiving linezolid and concomitant tyramine doses of >100 mg (Zyvox® Prescribing Information, 2021); therefore, subjects receiving linezolid or contezolid acefosamil/contezolid need to avoid consuming large amounts of foods or beverages with high-tyramine content. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling, or smoking to improve flavor, such as aged cheeses, fermented or air-dried meats, sauerkraut, soy sauce, and tap beers (Table 15). The tyramine content of any protein-rich food may be increased if stored for long periods or improperly refrigerated.

The following table of high-tyramine foods and drinks to avoid in large amounts during study drug administration in this study has been modified from "Meal Ideas and Menus: Avoiding High-tyramine Foods Made Easy" (Holden, 2006), and serves as a general guidance. Questions as to whether additional foods or beverages must be avoided should be directed to the Medical Monitor.

Table 15: Foods and Beverages to Avoid[a] During Study Drug Administration[b]

Cheeses	Beverages	Meat, Poultry, Fish	Produce	Condiments
Canadian or New York Cheddar Stilton Camembert Swiss Blue/Gorgonzola	Vermouth Tap beer Korean beer	Dry sausages (eg, mortadella, salami) Chinese dried duck Aged chicken livers Smoked or pickled fish (eg, lox) Pickled herring Caviar Soups, gravies, or sauces containing meat extracts (eg, bouillon, beef broth)	Sauerkraut Fava beans and broad beans (Italian green beans) Banana peel Kimchi Miso soup, fermented soybean/bean curd, tofu	Soy sauce Concentrated yeast extract (Marmite®, Vegemite®) Thai or Vietnamese fish sauce

[a] Similar aged, fermented, pickled, or smoked foods or beverages not shown in this table (eg, unlisted cheeses or alcoholic beverages) should be generally avoided or consumed rarely with caution.
[b] Foods that need to be avoided from Day 1 until End-of-Therapy

18.7 Appendix 7. Safety Laboratory Tests (Central Laboratory)

Hematology: • Hemoglobin • Hematocrit • Erythrocyte count • Leukocyte count (total white blood cells and immature granulocytes/bands) • Neutrophils (with immature neutrophils/bands) • Lymphocytes • Monocytes • Eosinophils • Basophils • Platelets • Erythrocyte sedimentation rate **Coagulation:** • Prothrombin time/International normalized ratio • Partial thromboplastin time • Activated partial thromboplastin time **Urinalysis:** • Specific gravity • pH • Protein • Glucose • Ketones • Bilirubin • Occult blood • Nitrites • Urobilinogen • Leukocyte esterase **Urine Microscopy [a]:** • White blood cells • Red blood cells • Casts • Bacteria • Crystals	**Chemistry (Serum Concentrations):** • Glucose • Calcium • Albumin • Total protein • Sodium • Potassium • Bicarbonate • Chloride • Urea nitrogen • Creatinine • Alkaline phosphatase • Alanine aminotransferase • Aspartate aminotransferase • Total and direct bilirubin • Magnesium • Lactate dehydrogenase • Phosphorus • Uric Acid • Creatine kinase • Gamma-glutamyl transferase • Indirect bilirubin • Cholesterol • Triglycerides • β-Human chorionic gonadotropin for females • C-reactive protein **SCREENING/BASELINE ONLY:** • Creatinine clearance • Hemoglobin A1c • Anti-hepatitis B core antigen • Anti-hepatitis B surface antigen • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus antibody

a. Performed if urinalysis is positive for red blood cells, white blood cells, or protein.

18.8 Appendix 8: International Working Group on the Diabetic Foot Infection Guideline

Table 16. Classification System for Defining the Presence and Severity of an Infection of the Foot in a Person with Diabetes

Clinical classification of infection with definitions	International Working Group on the Diabetic Foot Infection Guideline classification
Uninfected: No systemic or local symptoms or signs of infection	**1 (uninfected)**
Infected: At least 2 of these items are present: • Local swelling or induration • Erythema >0.5 cm around the wound [a] • Local tenderness or pain • Local increased warmth • Purulent discharge AND No other cause(s) of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis or venous stasis)	**2 (mild infection)** Infection with no systemic manifestations (see below) involving: • Only the skin or subcutaneous tissue (not any deeper tissues) AND • Any erythema present does not extend >2 cm around the wound [b]
	3 (moderate infection) Infection with no systemic manifestations AND involving: • Erythema extending ≥2 cm from the wound margin [a] AND/OR Tissue deeper than skin and subcutaneous tissues (eg. tendon, muscle, joint, bone)
	4 (severe infection) Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome), as manifested by ≥2 of the following: • Temperature >38°C or <36°C • Heart rate >90 beats/minute • Respiratory rate >20 breaths/minute or $PaCO_2$ <4.3 kPa (32 mmHg) White blood cell count >12,000/mm^3 or <4000 mm^3, or >10% immature (band) forms

a. Infection refers to any part of the foot, not just of a wound or an ulcer

b. In any direction from the rim of the wound. The presence of clinically significant foot ischemia makes both diagnosis and treatment of infection considerably more difficult

Source: Table adapted from Lipsky 2019.

CONTRATTO PER LA CONDUZIONE DELLA SPERIMENTAZIONE CLINICA SU MEDICINALI "Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi"	**CLINICAL INVESTIGATION AGREEMENT FOR THE DRUGS "A Phase 3, Multicenter, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections"**
TRA	BETWEEN
A.ULSS 7 PEDEMONTANA (d'ora innanzi denominato/a"**Ente**"), con sede legale in via dei Lotti, n. 40 , 36061 BASSANO DEL GRAPPA (VI) C.F. e P. IVA n 00913430245, in persona del Legale Rappresentante, Dr Carlo Bramezza, in qualità di Direttore Generale	Aulss 7 Pedemontana (hereinafter the "**Entity**"), headquartered in Lotti, n. 40 , 36061 BASSANO DEL GRAPPA (VI), tax code and VAT no. 00913430245, through its Legal Representative Carlo Bramezza, in the capacity *Director General*
E	AND
Medpace Clinical Research LLC, con sede legale in 5375 Medpace Way, Cincinnati, Ohio 45227 USA USA, C.F. n.LLC81-4138570, in persona del proprio firmatario autorizzato Laura Omoboni , (d'ora innanzi denominata "**CRO**"), che agisce per contonell'interesse di _Micurx Pharmaceuticals Inc.(d'ora innanzi denominato "**Promotore**"), in forza di idonea delega/mandato/procura conferita in data 1 Aprile 2022	Medpace Clinical Research LLC, headquartered in 5375 Medpace Way, Cincinnati, Ohio 45227 USA USA, tax code and VAT no. LLC81-4138570, through its authorized signatory, Laura Omoboni (hereinafter the "**CRO**"), acting on behalf of/ the interests of Micurx Pharmaceuticals Inc (hereinafter the "**Sponsor**"), by virtue of the authority/mandate/power of attorney granted on 1st of April 2022
di seguito per brevità denominati/e singolarmente/collettivamente "la **Parte**/le **Parti**"	hereinafter individually/collectively "the **Party**/the **Parties**"
Premesso che:	Whereas:
A. è interesse del Promotore effettuare, ai sensi del Regolamento (UE) n. 536/2014 (di seguito "Regolamento"), la sperimentazione clinica dal titolo: "**Uno studio di fase 3, multicentrico, randomizzato, in doppio cieco per**	A. the Sponsor is interested, pursuant to Regulation (EU) no. 536/2014 (hereinafter the "Regulation"), in conducting the clinical trial entitled: "**A Phase 3, Multicenter,**

valutare la sicurezza e l'efficacia di Contezolid Acefosamil e Contezolid rispetto al Linezolid somministrato per via endovenosa e orale ad adulti con infezioni del piede diabetico moderate o gravi" (di seguito "**Sperimentazione**"), avente ad oggetto il Protocollo versione n. 1del 28 Febbraio 2022 e suoi successivi emendamenti e successive versioni di Protocollo o suoi emendamenti, debitamente approvati (di seguito "**Protocollo**"), codice EuCT n. 2022-500257-16 presso l'Ente, sotto la responsabilità del Dott./Prof Alberto Marangoni, in qualità di Responsabile scientifico della sperimentazione oggetto del presente Contratto (di seguito "**Sperimentatore Principale**"), nell'U.O.S. Diabetologia dell'Ospedale di Bassano (di seguito "**Centro di Sperimentazione**");	**Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Contezolid Acefosamil and Contezolid Compared to Linezolid Administered Intravenously and Orally to Adults with Moderate or Severe Diabetic Foot Infections**" (the "**Trial**"), relating to the Protocol version no. Amendment_1 of 28 of February 2022and as amended with any successive protocol version , or Protocol amendment that are, duly approved (the "**Protocol**"), EuCT code no. 2022-500257-16 at the Entity, under the responsibility of Dr./Prof. Alberto Marangoni, as the scientific Director of the trial covered by this Agreement (the "**Principal Investigator**"), at nell'U.O.S. Diabetologia dell'Ospedale di Bassano (the "Trial Centre");
B. il Promotore ha individuato quale referente scientifico per la parte di propria competenza il dott. Barry Hafkin. Il Promotore può modificare il referente scientifico per la parte di propria competenza con notifica scritta all'Ente;	B. the Sponsor has appointed Dr. Barry Hafkin as scientific and technical contact for the part under its responsibility. The Sponsor may change the scientific and technical contact by giving written notice to the Entity;
C. il Centro di sperimentazione possiede le competenze tecniche e scientifiche per la Sperimentazione ed è struttura adeguata alla conduzione della Sperimentazione nel rispetto della normativa vigente;	C. the Trial Centre has the technical and scientific know-how to carry out the Trial and is a suitable facility for the Trial to be conducted in accordance with the applicable regulations;
D. lo Sperimentatore Principale ed i suoi diretti collaboratori, qualificati in base al Protocollo ad intervenire con poteri discrezionali nell'esecuzione di esso (di seguito "Co-sperimentatori"), così come tutti gli altri soggetti che svolgano qualsiasi parte della Sperimentazione sotto la supervisione dello Sperimentatore Principale sono idonei alla conduzione della Sperimentazione in conformità alla normativa applicabile, conoscono il Protocollo e le norme di buona pratica clinica e possiedono i	D. the Principal Investigator and his/her direct healthcare staff qualified according to the Protocol to intervene with discretionary powers in the execution of it (hereinafter "Co-investigators"), as well as all other subjects playing any part in the Trial under the supervision of the Principal Investigator are qualified to conduct the Trial in accordance with the applicable regulations, are familiar with the Protocol and the standards of good clinical practice and possess the

requisiti normativi e regolamentari necessari compreso il rispetto della normativa vigente riguardante il conflitto di interessi;	necessary regulatory and legal requirements including compliance with the current regulations regarding the conflict of interest;
E. salvo quanto eventualmente, successivamente, diversamente concordato per iscritto dalle Parti, l'Ente dovrà condurre la Sperimentazione esclusivamente presso le proprie strutture;	E. Except where agreed eventually, subsequently, otherwise in writing by the Parties, the Entity shall only conduct the Trial on its own facilities;
F. l'Ente è dotato di apparecchiature idonee, necessarie all'esecuzione della Sperimentazione secondo quanto indicato nel Protocollo;	F. the Entity has the equipment necessary to execute the Trial in accordance with the Protocol;
G. *(i) (per sperimentazioni proposte ai sensi del Regolamento):* la Sperimentazione è stata regolarmente autorizzata a norma del Capo II del Regolamento, previo provvedimento di autorizzazione nazionale AIFA caricato sul portale UE di cui all'art. 80 del Regolamento in data 5 dicembre 2022, che include il parere emesso dal Comitato Etico Unico, la Fondazione Policlinico Universitario A.Gemelli;	G. *(i) (for trials proposed pursuant to the Regulation):* the Trial has been duly authorized in accordance with Chapter II of the Regulation, subject to the provision of national AIFA authorization uploaded on the EU portal pursuant to art. 80 of the Regulation on 5 december 2022, which includes the opinion issued by the Ethics Committee Comitato Etico Unico, la Fondazione Policlinico Universitario A.Gemelli ;
H. ai sensi dell' art. 76 del Regolamento e delle disposizioni nazionali applicabili, il Promotore ha stipulato la polizza assicurativa come meglio precisato all'art. 8 del presente Contratto.	H. in accordance with art. 76 of the Regulation and the applicable national provision, Sponsor took out an insurance policy as described in Article 8 below.
I. (se il caso ricorre) nella negoziazione del presente Contratto, le Parti si sono basate sullo schema approvato dal Centro di coordinamento nazionale dei Comitati etici territoriali ai sensi dell'art. 2, comma 6, della legge 11 gennaio 2018 n. 3 e, nel rispetto dell'omogeneità degli aspetti amministrativi, economici, assicurativi ivi richiamata, hanno ritenuto di integrare e/o modificare le relative previsioni, ai fini della disciplina delle specificità e	I. (if applicable) during negotiation of this Agreement, the Parties relied on the scheme approved by the National Coordination Center of Territorial Ethics Committees pursuant to art. 2, paragraph 6, of the l. 11 January 2018 n. 3 and, in compliance with the homogeneity of the administrative, economic, insurance aspects referred to therein, have decided to integrate and / or modify the relative provisions,

peculiarità della Sperimentazione, sulla base delle seguenti motivazioni (➔ precisare): ……...,	for the purposes of regulating the specificities and peculiarities of the Trial, on the basis of the following reasons (➔specify) : …… .....,
Tra le Parti si conviene e si stipula quanto segue:	In consideration of the foregoing, it is hereby agreed as follows:
Art. 1 - Interezza del Contratto 1.1 Le premesse, il Protocollo, anche se non materialmente accluso, e tutti gli allegati, incluso il budget (Allegato A) e il glossario relativo alla protezione dati personali (Allegato B), fanno parte integrante e sostanziale del presente Contratto.	**Art. 1 – Entirety of Agreement.** 1.1 The recitals, the Protocol – even if not physically attached – and all the annexes including the budget (Annex A) and the data protection glossary (Annex B) form an integral and substantial part of this Agreement.
Art. 2 - Oggetto 2.1 Il Promotore affida all'Ente l'esecuzione della Sperimentazione alle condizioni indicate nel presente Contratto, in accordo col Protocollo, con gli eventuali successivi emendamenti, nonché con le modifiche al presente Contratto/budget da questi derivanti e formalizzate mediante i necessari atti di modifica tempestivamente sottoscritti.	**Art. 2 – Subject of the agreement** 2.1 The Sponsor hereby entrusts the Entity with the execution of the Trial under the terms of this Agreement, in accordance with the Protocol and any subsequent amendments, and with the amendments to this Agreement/budget resulting from such amendments formalised by the necessary deeds of amendment, duly signed.
2.2 La Sperimentazione deve essere condotta nel più scrupoloso rispetto del Protocollo, nella versione vigente, accettata dallo Sperimentatore Principale e approvata dal Comitato Etico e dall'Autorità Competente, in conformità alla vigente normativa in materia di sperimentazioni cliniche di medicinali e ai principi etici e deontologici che ispirano l'attività medica dei professionisti a vario titolo coinvolti.	2.2 The Trial is to be conducted in strict compliance with the Protocol, in the version in force as accepted by the Principal Investigator and approved by the Ethics Committee and the Competent Authority in conformity with the laws applicable to clinical drugs trials and the principles of ethics and medical practice followed by the healthcare staff involved in the Trial in any capacity.
2.3 La Sperimentazione deve essere altresì condotta in conformità ai principi contenuti nella Convenzione sui Diritti dell'Uomo e la Biomedicina, nella Dichiarazione di Helsinki nella versione aggiornata, nelle vigenti regole della Buona Pratica Clinica, e in conformità delle leggi applicabili in tema di trasparenza e prevenzione della corruzione, nonché di protezione dei dati personali secondo la normativa vigente.	2.3 The Trial shall also be conducted in accordance with the principles of the Convention on Human Rights and Biomedicine, the updated version of the Helsinki Declaration, the current rules of good clinical practice, and in accordance with the applicable laws on transparency, anti-corruption and the current data protection regulations.

2.4 Con la sottoscrizione del presente Contratto, le Parti dichiarano di conoscere e accettare il contenuto di quanto sopra richiamato.	2.4 By signing this Agreement, the Parties declare that they know and accept the contents of the above rules and regulations.
2.5 Il Promotore e lo Sperimentatore Principale, avendo l'obbligo di tutelare la salute dei pazienti, quando ricorrano le circostanze, possono adottare urgenti e adeguate misure a tutela della sicurezza dei pazienti, quali la sospensione temporanea dello studio (interruzione del trattamento per i pazienti già coinvolti nella Sperimentazione, ovvero interruzione dell'inclusione di nuovi soggetti), con le modalità previste dall'art. 38 del Regolamento (UE) n. 536/2014,, fermo restando l'obbligo per il Promotore di informare immediatamente il Comitato Etico, l'Autorità Competente ed i centri di sperimentazione , oltre che i partecipanti allo studio in merito ai nuovi eventi, alle misure intraprese e al programma di provvedimenti da adottare, completando tempestivamente le procedure previste dalla vigente normativa. Il Promotore, avuta comunicazione dallo Sperimentatore Principale di un evento avverso grave, comunica tempestivamente alla banca dati elettronica tutte le reazioni sospette avverse gravi e inattese nei termini di cui al comma 2 dell'art. 42 del Regolamento (UE) n. 536/2014, anche ai sensi del comma 3 mediante segnalazione.	2.5 The Sponsor and the Principal Investigator, having an obligation to protect patients' safety, where required in the circumstances, may take urgent, appropriate measures to protect patients' safety such as temporarily suspending the study (interruption of treatment for patients already enrolled or interruption of the enrolment of new patients), in the manner provided for by art. 38 of Regulation (EU) 536/2014, subject to the Sponsor's obligation to immediately inform the Ethics Committee, the Competent Authority and the trial centers as well as the partecipants in the study, of any new events, the measures taken, and the programme of measures to be taken in the future, and will duly complete the procedures required by the applicable laws. The Sponsor, having been informed by the Principal Investigator of a serious adverse event, promptly communicates to the electronic database all the serious and suspected adverse events within the terms referred to in paragraph 2 of art. 42 of Regulation (EU) 536/2014, also pursuant to paragraph 3 by reporting.
2.6 Poiché la Sperimentazione prevede l'inclusione competitiva dei pazienti, è prevista da parte dell'Ente l'inclusione di circa 4 soggetti, con il limite del numero massimo di 865 pazienti candidabili alla Sperimentazione a livello globale e dei termini previsti dal Promotore. Il periodo previsto di inclusione è suscettibile di modifiche in funzione del suo andamento anche a livello internazionale. Al raggiungimento del numero totale dei pazienti previsti per l'intera Sperimentazione, l'inclusione di ulteriori pazienti verrà automaticamente chiusa, indipendentemente dal numero di pazienti inclusi presso l'Ente, a eccezione dei pazienti che hanno già fornito il loro consenso a partecipare	2.6 As the Trial involves the competitive inclusion of patients, the Entity expects to include approximately 4 patients, with a global maximum of 865 patients eligible for the Trial, and limited to the terms provided for by the Sponsor. The enrolment period may be changed depending on the national or international trend in enrolment. When the total number of patients permitted for the entire Trial has been reached, the inclusion of further patients will be closed automatically, regardless of the number of patients enrolled at the Centre, apart from patients who have already provided their consent to take part in

alla Sperimentazione, a meno che essi stessi non ritirino il consenso. Il Promotore provvederà a inviare all'Ente adeguata e tempestiva comunicazione.	the Trial, unless the patients themselves withdraw their consent. The Sponsor will timely notify the Entity accordingly.
2.7 L'Ente e il Promotore conserveranno la documentazione inerente la Sperimentazione (fascicolo permanente "*trial master file"*) per il periodo di tempo e secondo le specifiche indicate dalla vigente legislazione(o per un periodo più lungo, qualora ciò sia richiesto da altre norme applicabili o da un accordo economico tra Ente e Promotore). Il Promotore ha l'obbligo di comunicare al Centro Sperimentale l'avvenuta scadenza del termine dell'obbligo di conservazione. A richiesta del Promotore, dopo lo spirare del termine suddetto, le Parti potranno concordare le condizioni di un ulteriore periodo di conservazione, rendendo previamente anonimi i dati.	2.7 The Entity and the Sponsor will keep the Trial documentation (the t*rial master file*") for the period of time and as specified in the applicable laws (or for a longer period if required by other applicable laws or by a financial agreement between Entity and the Sponsor). The Sponsor is obligated to inform the Centre of the expiry of the mandatory conservation period Atthe request of the Sponsor, after expiry of the mandatory conservation period, the Parties may agree the terms of a further conservation period, anonimizing the data in advance.
2.8 L'Ente e il Promotore, ciascuno per gli ambiti di propria competenza, si obbligano inoltre a conservare la citata documentazione adottando delle forme di digitalizzazione (o dematerializzazione) documentale, ove applicabile. Indipendentemente dal fatto che l'archiviazione della documentazione inerente la Sperimentazione riguardi o meno dati personali (di natura particolare o meno), secondo le definizioni del Regolamento (UE) n. 679/2016 (di seguito "GDPR") , l'Ente e il Promotore dovranno adottare tutte le misure fisiche e tecniche di cui all'art. 32 del citato GDPR ed effettuare gli eventuali controlli di sicurezza previsti dalla normativa vigente, a protezione di dati, informazioni e documenti (sia cartacei che elettronici). Il sistema di archiviazione adottato dovrà garantire non solo l'integrità dei dati, delle informazioni e dei documenti cartacei ed elettronici, ma altresì la loro futura leggibilità per tutto il periodo previsto dall'obbligo di conservazione. Per l'espletamento di tale obbligazione, sia il Promotore che l'Ente potranno avvalersi di soggetti esterni che gestiscano tale obbligo di archiviazione.	2.8 The Entity and the Sponsor, each within their own sphere of responsibility, shall also use forms of digitalisation (or dematerialisation) to conserve the documentation, if applicable. Regardless of whether or not the archived Trial documentation contains personal data (of a special nature or otherwise), according to the definitions in Regulation (EU) No. 679/2016 (herein after "GDPR"), the Entity and the Sponsor shall take all the physical and technical measures referred to in Article 32 of said GDPR and shall carry out any security checks as required by the applicable regulation to protect the data, information and documents (both printed and digital). The archiving system shall guarantee not only the integrity of the data, information and printed/digital documents but also their future legibility throughout the mandatory conservation period. To fulfil such obligation both the Sponsor and the Entity may rely on external service providers to manage the archiving obligation.

2.9 Il Promotore, l'Ente e lo Sperimentatore Principale devono rispettare le direttive, le indicazioni, le istruzioni e le raccomandazioni impartite dal Comitato Etico e dall'Autorità competente.	2.9 The Sponsor, the Entity and the Principal Investigator shall comply with the directions, indications, instructions and recommendations given by the Ethics Committee and by the Competent Authority.
Art. 3 - Sperimentatore Principale e Co-sperimentatori	**Art. 3 - Principal Investigator and Co-investigators**
3.1 Lo Sperimentatore Principale sarà coadiuvato nell'esecuzione della Sperimentazione da collaboratori diretti, qualificati in base al Protocollo ad intervenire con poteri discrezionali nell'esecuzione di esso nonché dal personale, sanitario e non sanitario, incaricati dall'Ente , Co-sperimentatori ed altro personale opereranno sottola responsabilità dello Sperimentatore Principale per gli aspetti relativi alla Sperimentazione,;essi dovranno essere qualificati per la conduzione della Sperimentazione, ed aver ricevuto preventivamente adeguata formazione secondo la normativa vigente dal Promotore ciascuno di essi dovrà aver manifestato la propria disponibilità a partecipare alla Sperimentazione	3.1 The Principal Investigator shall be supported in the execution of the Trial by direct collaborators, qualified according to the Protocol to intervene with discretionary powers in the execution of it as well as by the healthcare and non-healthcare personnel engaged by the Entity, Co-Investigator and other personnel will operate under the responsibility of the Principal Investigator for all aspects pertaining to the Trial, they will have to be qualified to conduct the Trial, and have previously received adequate training in accordance with the applicable law, by the Sponsor and each of them must have declared their willingness to take part in the Trial
3.2 Le Parti prendono atto che lo Sperimentatore Principale è tenuto a ogni responsabilità e obbligo imposti a tale figura dalla normativa vigente in materia di sperimentazioni cliniche di medicinali.	3.2 The Parties acknowledge that the Principal Investigator is bound by all the responsibilities and obligations imposed on their role by the applicable regulations on clinical drug trials.
3.3 Il presente rapporto intercorre tra il Promotore/CRO e l'Ente. Il Promotore/CRO è estraneo a rapporti esistenti tra l'Ente, lo Sperimentatore Principale e, i Co-sperimentatori, e tutto l'altro personale partecipante alla Sperimentazione restando quindi sollevato da qualsiasi pretesa che costoro dovessero avanzare in relazione alla Sperimentazione.	3.3 This Agreement is made between the Sponsor/CRO and the Entity. The Sponsor/CRO is extraneous to the relations between the Entity, the Principal Investigator and the Co-investigators, and all other personnel participating in the Trial and is thus indemnified in respect of any claim that they may make in relation to the Trial.
3.4 In relazione alla Sperimentazione oggetto del presente Contratto, le Parti si danno atto di aver adempiuto a quanto previsto dall'art. 7 del Regolamento, nonchè dall'art. 6, comma 4 del D. Lgs. 14 maggio 2019, n. 52, come modificato dall'art. 11-*bis* della L. 17 luglio 2020, n. 77, di	3.4 In relation to the Trial covedered by this Agreement, the Parties acknowledge that they have complied with the provisions of Art. 7 of the Regulation as well as art. 6, paragraph 4 of Legislative Decree no. 52 of 14 May 2019, as amended by art. 11-bis of Law no. 77 of 17

conversione del D.L. 19 maggio 2020, n. 34 ("Decreto Rilancio").	July 2020, converting Legislative Decree no. 34 of 19 May 2020 ("Decreto Rilancio").
3.5 Qualora il rapporto tra lo Sperimentatore Principale e l'Ente dovesse per qualsiasi ragione concludersi, l'Ente deve informarne tempestivamente per iscritto il Promotore, indicando il nominativo di un sostituto e segnalandolo nella banca dati elettronica europea.L'indicazione del sostituto deve essere oggetto di approvazione da parte del Promotore e del Comitato Etico competente. L'Ente garantisce che il nuovo Sperimentatore Principale abbia i requisiti idonei a proseguirla, accetti i termini e le condizioni del presente Contratto e assuma l'impegno di rispettare il Protocollo nell'esecuzione della Sperimentazione. Nelle more dell'approvazione dell'emendamento sostanziale di cambio dello Sperimentatore Principale, lo sperimentatore indicato dall'Ente garantisce la necessaria continuità dell' attività sperimentale. Nel caso in cui il Promotore non intenda accettare il nominativo del sostituto proposto dall'Ente oppure questi non proponga un sostituto, il Promotore/CRO potrà recedere dal presente Contratto in accordo a quanto previsto dall'art. 7.	3.5 If the relationship between the Principal Investigator and the Entity ends for any reason, the Entity will inform the Sponsor in writing and indicate the name of a replacement and reporting it in the European electronic database. The named replacement must be approved by the Sponsor and by the competent Ethics Committee. The Entity guarantees that the new Principal Investigator is qualified to continue the Trial, that they will accept the terms and conditions of this Agreement and that they will agree to respect the Protocol when executing the Trial. Pending approval of the substantial amendment for the change of Principal Investigator, the investigator indicated by the Entity shall carry out the necessary continuity in the Trial activities. If the Sponsor does not intend to accept the name of the replacement proposed by the Entity, or if the Entity does not propose a substitute, the Sponsor/CRO may terminate this Agreement in accordance with the provisions of Article 7.
3.6 Lo Sperimentatore Principale prima di iniziare la Sperimentazione, deve acquisire il consenso informato del paziente o del suo rappresentante legale, secondo quanto previsto dalla vigente normativa in materia di sperimentazioni cliniche ed il consenso al trattamento dei dati personali ai sensi e per gli effetti della vigente normativa nazionale e comunitaria in materia di protezione dei dati personali come successivamente declinato all'art. 11.	3.6 Before starting the Trial, the Principal Investigator shall obtain the informed consent of the patient or his/her legal representative in accordance with the current laws on clinical trials as well as theconsent for the processing of personal data in accordance with the current Italian and EU laws on data protection and as outlined in Article 11 below.
3.7 Lo Sperimentatore Principale ha l'obbligo di registrare e documentare, dettagliatamente tutti gli eventi avversi ed eventi avversi gravi e di darne comunicazione al Promotore nei termini previsti dalla legislazione vigente.	3.7 The Principal Investigator is obliged to register and document, in detail of all adverse events and serious adverse events and to report them to the Sponsor/ within the terms established by current legislation.
Inoltre lo Sperimentatore Principale deve fornire ogni altra informazione clinica di rilievo indicata nel Protocollo (ad esempio gravidanza) direttamente o indirettamente correlabile	Furthermore, the Principal Investigator, has to provide any other clinical information indicated in the Protocol (e.g: pregnancy) that is directly or indirectly related to the

all'esecuzione della Sperimentazione, secondo quanto previsto dal Protocollo , dalle norme di Buona Pratica Clinica e dalla normativa applicabile in materia di farmacovigilanza e sperimentazione clinica di medicinali.	execution of the Trial, in accordance with the provisions of the Protocol, the rules of Good Clinical Practice and the laws applicable to pharmacovigilance and clinical drugs trials.
3.8 L'Ente garantisce il corretto svolgimento della Sperimentazione da parte dello Sperimentatore Principale e del personale posto sotto la sua responsabilità secondo i più elevati standard di diligenza. In particolare:	3.8 The Entity guarantees the correct performance of the Trial by the Principal Investigator and the personnel under his responsibility in accordance with the highest standards of diligence. In particular:
3.8.1 Lo Sperimentatore Principale deve consegnare tutte le Schede Raccolta Dati (Case Report Forms-CRF) correttamente compilate, secondo termini e modalità previsti dal Protocollo della sperimentazione e dalla normativa applicabile, in formato cartaceo o elettronico, e comunque con tempestività come da GCP, entro i termini previsti dal Protocollo della Sperimentazione.	3.8.1 The Principal Investigator shall keep all of the Case Report Forms (CRF), duly compiled, in accordance with the terms and conditions of the Protocol for the trial and with the applicable regulations, in printed or digital form and in any case they shall be delivered promptly in accordance with the GCP, by the date indicated in the Trial Protocol.
3.8.2 Lo Sperimentatore Principale si impegna altresì a risolvere le richieste di chiarimento (*queries*) generate dal Promotore entro i termini previsti dal Protocollo della sperimentazione.	3.8.2 The Principal Investigator shall also resolve any queries raised by the Sponsor by the date indicated in the trial Protocol.
3.8.3 Per verificare la corrispondenza tra i dati registrati nelle Schede Raccolta Dati e quelli contenuti nei documenti originali (per es. cartella clinica), l'Ente e lo Sperimentatore Principale consentono l'accesso diretto ai dati originali durante le visite di monitoraggio e nel corso di eventuali *audit* promossi da Promotore e ispezioni da parte delle Autorità Competenti, incluse le modalità da remoto, purché non vengano violate le norme in materia di riservatezza e di protezione dei dati personali dei pazienti.	3.8.3 To verify the correspondence between the data recorded on the CRF and the data contained in the original clinical records, the Entity and the Principal Investigator shall allow direct access to the source data during the monitoring visits and any audits by the Sponsor and inspections by the Competent Authorities, including remote methods, provided that the laws on confidentiality and patient privacy are respected.
3.8.4 L'Ente e lo Sperimentatore Principale, informati con congruo preavviso, devono consentire il corretto svolgimento dell'attività di monitoraggio e di auditing e di ispezioni presso il Centro di Sperimentazione UOS Diabetologia	3.8.4 The Entity and the Principal Investigator, having been informed sufficiently in advance, shall allow the correct execution of the monitoring and auditing and inspections at the Trial Centre UOS Diabetologia dell'Ospedale

dell'Ospedale di Bassano da parte del personale del Promotore e da parte dell'Autorità Competente, attività effettuate per garantire la regolare esecuzione della Sperimentazione.	di Bassano by the Sponsor and by the Competent Authority, such activities to be carried out to guarantee the proper execution of the Trial.
3.9 L'Ente avviserà tempestivamente il Promotore qualora un'Autorità Competente comunichi all'Ente un avviso di ispezione/*audit* relativo alla Sperimentazione e, se non negato espressamente dall'Autorità Competente, l'Ente autorizzerà il Promotore a parteciparvi, inviando nel contempo al Promotore ogni comunicazione scritta ricevuta e/o trasmessa ai fini o in risultanza dell'ispezione/*audit*.	3.9 The Entity shall promptly inform the Sponsor if a regulatory authority informs the Entity of an inspection/ audit in relation to the Trial and, unless expressly refused by the Competent Authority, the Entity will authorise the Sponsor to take part, while sending the Sponsor all the written communications received for the purposes of the inspection/audit.
3.10 Tali attività non devono però pregiudicare in alcun modo lo svolgimento dell'ordinaria attività istituzionale dell'Ente.	3.10 These activities must in no way prejudice the ordinary institutional activities of the Entity.
3.11 L'Ente ed il Promotore garantiscono che i campioni biologici (sangue, urine, saliva ecc.) dei pazienti coinvolti nella Sperimentazione di cui al presente Contratto saranno utilizzati esclusivamente per la Sperimentazione oggetto del presente Contratto, secondo le previsioni del Protocollo e della vigente normativa. L'eventuale conservazione e successivo utilizzo sono vincolati all'acquisizione di uno specifico consenso informato da parte del paziente (o del genitore/tutore legale), al parere favorevole del Comitato Etico, nei limiti e con le garanzie previste dalle norme vigenti e dalle linee di indirizzo di cui all'art. 1 del D. Lgs 14 maggio 2019 n. 52.	3.11 The Entity and the Sponsor guarantees that the biological samples (blood, urine, saliva etc.) that may be collected from patients undergoing the Trial covered by this Agreement shall only be used for the purposes of the Trial in accordance with the provisions of the Protocol and of the current regulations. Any conservation and subsequent use are subject to the acquisition of specific informed consent from the patient (or the parent/legal guardian), to the favourable opinion of the Ethics Committee in accordance with the limits and guarantees provided for in the current regulations and guidelines referred to in Article 1 of legislative decree 52 of 14 May 2019.
Art. 4 - Medicinali Sperimentali Materiali e Servizi	**Art. 4 - Trial Drugs Materials and Services**
4.1 Il Promotore si impegna a fornire gratuitamente all'Ente, per tutta la durata della Sperimentazione e nelle quantità necessarie e sufficienti all'esecuzione della Sperimentazione, il/i prodotto/i farmaceutico/i oggetto della Sperimentazione (Contezolid Acefosamil/contezolid) e, gli altri farmaci previsti	4.1 The Sponsor shall provide the Entity, free of charge and for the duration of the Trial, with the necessary and sufficient quantities of the pharmaceutical product/s relating to the Trial (Contezolid Acefosamil/contezolid) and shall provide the other drugs provided for in the Protocol (Linezolid), in accordance with

dal protocollo (Linezolid) in ottemperanza al D.M. 21 dicembre 2007, Allegato 1, punto 3 Tabella I, inclusi i medicinali da utilizzarsi in associazione o combinazione tra loro, ogniqualvolta oggetto dello studio sia appunto l'associazione o combinazione (in seguito "Medicinali Sperimentali"), e a provvedere con oneri a proprio carico alla fornitura dei medicinali ausiliari e della terapia di background, cioè lo standard terapeutico per la patologia oggetto di Sperimentazione, qualora inclusa, secondo il protocollo di Sperimentazione, nel confronto fra le diverse strategie terapeutiche oggetto di sperimentazione. Le quantità dei Medicinali Sperimentali, dei medicinali ausiliari e della terapia di background a carico del Promotore devono essere adeguate alla numerosità della casistica trattata. La ricezione e il tracciamento dei farmaci dovranno avvenire con la registrazione dei lotti. Restano a carico dell'Ente le terapie di background non incluse nelle strategie terapeutiche di confronto. Il Promotore si impegna altresì a fornire con oneri a proprio carico ogni altro materiale necessario all'esecuzione della Sperimentazione (di seguito "Materiali nonché gli esami di laboratorio, diagnostici o di monitoraggio, inerenti l'utilizzo dei Medicinali Sperimentali o gli obiettivi primari e secondari della Sperimentazione (di seguito, "Servizi").	Ministerial Decree of 21 December 2007, Annex 1, para. 3 Table I, including the drugs to be used in association or combination, whenever the object of the study relates to such an association or combination (the "Trial Drugs"),and to provide at its own expense the supply of auxiliary medicines and the background therapy, that is the therapeutic standard for the pathology subject of the Trial, if included, according to the Trial protocol, in the comparison among the different therapeutic strategies being tested. The quantities of Trial Drugs, auxiliary medicines and background therapy charged to the Sponsor must be adequate to the number of cases treated. The receipt and tracking of drugs must take place with the registration of the batches. Background therapies not included in the comparison therapeutic strategies remain the responsibility of the Entity. Sponsor, also, undertakes to provide, at its own expenses, any other materials necessary for the execution of the Trial (the "Materials") as well as laboratory, diagnostic or monitoring tests relating to use of the Trial Drugs or primary and secondary objectives of the Trial (hereinafter "Services")
4.2 Al ricorrere delle condizioni previste dalla normativa vigente in materia di uso terapeutico di medicinale sottoposto a sperimentazione clinica, con particolare riguardo alla dichiarazione di Helsinki e alle buone prassi in materia di continuità terapeutica, il Promotore si impegna, laddove applicabile e salvo motivi in contrario da precisarsi per iscritto, a rendere disponibile il farmaco oggetto della Sperimentazione clinica al termine della Sperimentazione oltre il periodo di osservazione, per i pazienti che abbiano ottenuto un beneficio clinico dal farmaco sperimentale, valutato in base al giudizio dello Sperimentatore Principale (indipendentemente dall'applicabilità o meno del D. M. 7 settembre 2017 "Disciplina dell'uso terapeutico di medicinale sottoposto a	4.2 Subject to the conditions provided for by the current legislation on the therapeutic use of medicinal products subjected to clinical trials, with particular regard to , the declaration of Helsinki and good practices in the field of therapeutic continuity, Sponsor, where possible, and except for reason to be specified in writing shall make available the drugs for the clinical Trial after conclusion of the Trial beyond the observation period, for any patients who have obtained a clinical benefit from the investigational drug, assessed based on the judgment of the the Principal Investigator (regardless of the applicability or otherwise of the Ministerial Decree of 7 September 2017 "Discipline of the therapeutic use of medicinal products

sperimentazione clinica"). Nei pazienti con beneficio clinico la fornitura del farmaco sarà proseguita fino a quando esso non sarà reso disponibile tramite gli ordinari canali di dispensazione, in modo da garantire la continuità terapeutica. In accordo con la Dichiarazione di Helsinki l'informazione circa la disponibilità all'accesso post-trial da parte dello Sponsor dovrà essere, resa palese ai partecipanti alla Sperimentazione nei documenti di consenso informato.	undergoing clinical trials"). In patients with clinical benefit, the provision of the drug will be continued, until it is available through the ordinary dispensing channels, in order to ensure continuity of treatment. In accordance with the Declaration of Helsinkithe information about the availability of post-trial access by the Sponsor must be clear to the participants in the Trial in the informed consent documents.
4.3 I Medicinali Sperimentali devono essere inviati dal Promotore alla Farmacia dell'Ente che provvederà alla loro registrazione, appropriata conservazione e consegna allo Sperimentatore Principale, così come previsto dal Protocollo e dalla normativa vigente.	4.3 The Trial Drugs shall be sent by the Sponsor to the Pharmacy of the Entity, which will record them, store them appropriately and deliver them to the Principal Investigator in accordance with the provisions of the Protocol and the current regulations.
4.4 I Medicinali Sperimentali dovranno essere muniti di adeguato documento di trasporto destinato alla Farmacia, con la descrizione del tipo di farmaco, della sua quantità, del lotto di preparazione, dei requisiti per la conservazione, della scadenza e i riferimenti alla Sperimentazione (codice di Protocollo, Sperimentatore Principale e Centro di Sperimentazione interessato).	4.4 The Trial Drugs shall be accompanied by an adequate transport note addressed to the Pharmacy, describing the type of drug, the quantity, batch, storage requirements, expiry date and references to the Trial (Protocol code, Principal Investigator and Trial Centre).
4.5 L'Ente e lo Sperimentatore Principale devono utilizzare i Medicinali Sperimentali e i Materiali forniti dal Promotore esclusivamente nell'ambito e per l'esecuzione della Sperimentazione. L'Ente non deve trasferire o cedere a terzi i Medicinali Sperimentali e/o i Materiali/Servizi forniti dal Promotore ai sensi del presente Contratto.	4.5 The Entity and the Principal Investigator shall use the Trial Drugs and Materials supplied by the Sponsor exclusively in the context of, and to conduct the Trial. The Entity shall not transfer or assign to a third party the Trial Drug/s and Materials/Services supplied by the Sponsor under the terms of this Agreement.
4.6 (a) (*In caso di ritiro dei Medicinali Sperimentali da parte del Promotore*) I Medicinali Sperimentali scaduti o non altrimenti utilizzabili, ovvero non utilizzati al	4.6 (a) (*In the case of collection of the Trial Drugs by the Sponsor)* All the expired or otherwise unusable Trial Drugs or those that have not been used on

termine della Sperimentazione, saranno integralmente ritirati dal Promotore (o suo incaricato) e successivamente smaltiti a sue spese.	conclusion of the Trial will be collected by the Sponsor (or its representative) and will subsequently be disposed of at the Sponsor's expense.
Art. 5 - Comodato d'uso (NON applicabile) 5	**Art. 5 – Loan (NOTapplicable)**
Art. 6 - Corrispettivo	**Art. 6 – Remuneration**
6.1 Il corrispettivo pattuito, preventivamente valutato dall'Ente, per paziente eleggibile, valutabile e che abbia completato il trattamento sperimentale secondo il Protocollo e per il quale sia stata compilata validamente la relativa CRF/eCRF, comprensivo di tutte le spese sostenute dall'Ente per l'esecuzione della Sperimentazione e dei costi di tutte le attività ad essa collegate, è pari ad € 8.093 per paziente e (complessivi € 32.372,00 + per n. 4 pazienti stimato), come meglio dettagliato nel Budget qui allegato (Sub A).	6.1 The remuneration agreed, previously evaluated by the Entity, for each eligibleassessable patient and who has completed the trial treatment according to the Protocol and for whom the related CRF/eCRF has been duly compiled, including all the costs incurred by the Entity in execution of theTrial and the costs to cover all the related activities, is €8.093 per patient (a total of € 32.372,00) for an estimated 4 patients) as specified in more detail in the Budget annexed (Sub A).
6.2 Il Promotore si impegna a corrispondere quanto dovuto ai sensi del presente articolo sulla base di quanto risulta da adeguato prospetto/rendiconto giustificativo, concordato tra le Parti, dopo che lo Sponsor abbia approvato il pagamento. Il CRO, in qualità di agente di pagamento dello Sponsor, effettuerà i pagamenti con i fondi forniti dallo Sponsor. Il budget contenuto nell'Allegato A è comprensivo di tutte le imposte applicabili. Il pagamento del compenso di cui sopra verrà effettuato con la cadenza indicata nel Budget (Allegato A sulla base del numero dei pazienti coinvolti nel relativo periodo, dei trattamenti da loro effettuati secondo Protocollo e in presenza delle relative CRF/eCRF debitamente compilate e ritenute valide dal Promotore in base alle attività svolte. Al completamento o alla risoluzione del presente Contratto, in nessun caso la CRO sarà obbligata a pagare le fatture presentate dopo la scadenza del periodo di tempo per la presentazione delle fatture definitive di cui all'Allegato A.	6.2 The Sponsor will pay the amount due under the terms of this article on the basis of a valid statement of account/supporting document agreed between the Parties, after Sponsor has approved the payment. CRO, as Sponsor's payment agent, shall make payments from funds provided by Sponsor. The budget contained in Annex A is inclusive of all applicable taxes. The above amount will be paid at the intervals indicated in the Budget (Annex A), on the basis of the number of patients enrolled during the period, the treatments carried out according to the Protocol, and in the presence of the duly completed CRF/eCRF duly compiled and validated by the Sponsor based on the activities carried out. Upon completion or termination of this Agreement, in no event shall CRO be obligated to pay any invoices submitted after the time period for submitting final invoices set forth in the Annex A has expired.
L'Ente e l'Investigatore Principale dichiarano che	Entity and Principal Investigator represent that neither Principal Investigator nor Entity

né l'Investigatore Principale né l'Ente sono cittadini o residenti degli Stati Uniti, o società o partnership che è ed è stata trattata come una società o partnership statunitense, e che tutti i pagamenti che l'Ente riceve ai sensi del presente Contratto saranno destinati a servizi resi al di fuori degli Stati Uniti. Nel caso in cui le leggi fiscali richiedano una trattenuta, la Parte legalmente responsabile sarà responsabile per le trattenute.	are a citizen or resident of the United States, or a corporation or partnership that is and has been treated as a U.S. corporation or U.S. partnership, and that all payments Entity receives under this Agreement will be for services rendered outside the United States. Should any tax laws require withholding, the Party legally responsible shall be liable for withholdings.
6.3 *(a) (Nel caso in cui gli esami vengano eseguiti da un Centro esterno all'Ente)* Gli esami di laboratorio/strumentali, indicati in Allegato A, richiesti dal Protocollo, così come approvato dal Comitato Etico, non graveranno in alcun modo sull'Ente in quanto effettuati centralmente. *(b) (Nel caso in cui gli esami vengano eseguiti presso l'Ente*) Tutti gli esami di laboratorio/strumentali e ogni altra prestazione/attività aggiuntiva non compresa nel corrispettivo pattuito per paziente eleggibile, richiesta dal Promotore, così come approvato dal Comitato Etico e dall'Autorità Competente e come dettagliato in Allegato A , saranno rimborsati e fatturati dal Promotore in aggiunta al corrispettivo pattuito per paziente eleggibile.	6.3 *(a) (If the tests are done by a centre external to the Entity)* All the laboratory/instrument tests indicated in Annex A, required by the Protocol and approved by the Ethics Committee, will not burden the Entity as they will be carried out centrally. *(b) (If the tests are carried out on the Entity's premises*) All the laboratory/instrument tests and any other services or additional activities not covered by the price agreed per eligible patient, and requested by the Sponsor as approved by the Ethics Committee and Competent Authority and as detailed in Annex A (), shall be reimbursed and invoiced by the Sponsor in addition to the price paid for each eligible patient.
6.4 L'Ente non riceverà alcun compenso per pazienti non valutabili a causa di inosservanza del Protocollo, di violazione delle norme di Buona Pratica Clinica o di mancato rispetto della normativa vigente in materia di sperimentazioni cliniche di medicinali. L'Ente non avrà diritto ad alcun compenso anche per pazienti coinvolti successivamente alla comunicazione di interruzione e/o conclusione della Sperimentazione da parte del Promotore od oltre il numero massimo di soggetti da includere ai sensi del presente Contratto, ove non concordati con il Promotore.	6.4 The Entity will not receive any remuneration for patients who cannot be assessed due to failure to observe the Protocol, violation of the rules of Good Clinical Practice or failure to comply with the laws applicable to clinical drug trials. The Entity will have no right to receive any remuneration for any patient enrolled after notification of interruption and/or conclusion of the Trial by the Sponsor/, or any number beyond the maximum number of patients stipulated under the terms of this Agreement, if not agreed with the Sponsor.

6.5 Il Promotore provvederà, inoltre, a rimborsare all'Ente tutti i costi aggiuntivi risultanti da attività mediche/diagnostiche, compresi eventuali ricoveri, non previste nel Protocollo o nei successivi emendamenti allo stesso, e non già coperti dai compensi sopra elencati, qualora tali attività si rendano indispensabili per una corretta gestione clinica del paziente in Sperimentazione. Il rimborso sarà effettuato solo a condizione che tali attività e i relativi costi vengano tempestivamente comunicati, giustificati e documentati per iscritto al Promotore e approvati per iscritto dallo stesso, ferma restando la comunicazione in forma codificata dei dati personali del paziente.	6.5 The Sponsor shall also reimburse the Entity with all the additional costs of medical/diagnostic activities, including hospital admissions, which are not provided for in the Protocol or amendments to the Protocol, and which are not already covered by the above payments, if such activities are essential for the proper clinical treatment of a patient undergoing the Trial. The reimbursement will only be paid on condition that such activities and costs have been properly communicated, with justification, and have been documented in writing to the Sponsor and approved in writing by the Sponsor, and provided that the patient's personal data is communicated in anonymized form.
6.6 Se nel corso dello svolgimento della Sperimentazione si rendesse necessario aumentare il supporto economico a favore dell'Ente, il Promotore/CRO potrà integrare, con un addendum/emendamento, il presente Contratto, prevedendo l'adeguato aumento del Budget qui allegato.	6.6 If, during the Trial, it is necessary to increase the financial support to the Entity, the Sponsor/CRO may supplement this Agreement, by and addendum/amendment, by authorising the appropriate increase to the attached Budget.
6.7 In ottemperanza alla normativa sull'obbligo della fatturazione elettronica per le cessioni di beni e per la prestazione di servizi anche tra privati, l'Ente emetterà fatture	6.7 In accordance with the regulation on mandatory e-invoicing for sales of goods and services among private individuals, the Entity shall issue invoices
Lo Sponsor/CRO comunica i dati necessari per l'emissione della fattura: Medpace Clinical Research, LLC Attn: Clinical Operations Site Payments 5375 Medpace Way Cincinnati, Ohio 45227 Tax ID LLC81-4138570 Email: siteinvoices@medpace.com Telefono: 513-579-9911	The Sponsor/CRO shall provide the data necessary for the issue of the invoice: Medpace Clinical Research, LLC Attn: Clinical Operations Site Payments 5375 Medpace Way Cincinnati, Ohio 45227 Tax ID LLC81-4138570 Email: siteinvoices@medpace.com Telefono: 513-579-9911
6.8 I pagamenti effettuati per i servizi svolti dall'Ente (i) rappresentano il corretto valore di mercato di detti servizi, poiché adeguati rispetto al tariffario applicabile presso l'Ente, (ii) sono	6.8 The payments made for the Entity's services (i) represent the fair market value for those services, as they reflect the tariff scale applied by the Entity, (ii) were negotiated

stati negoziati a condizioni commerciali normali e (iii) non sono stati definiti sulla base del volume o valore di prescrizioni o comunque in riferimento a tali prescrizioni o altre attività economiche che si generino fra le Parti. A fronte delle attività svolte o delle spese sostenute includendo i pazienti in Sperimentazione, al cui pagamento il Promotore sia tenuto, né l'Ente né lo Sperimentatore Principale chiederanno altri rimborsi o corrispettivi ad altri soggetti.	under normal market conditions, and (iii) were not agreed on the basis of the volume or value of prescriptions or in reference to those prescriptions or other financial activities between the Parties. Neither the Entity nor the Principal Investigator shall request any compensation or reimbursement from any other party in return for the activities performed or costs incurred by including the patients in the Trial, which the Sponsor is obligated to pay for.
Tutti i costi relativi a voci non specificate nell'Allegato A non verranno rimborsati. Le Parti concordano che le eventuali spese e commissioni bancarie dovute per i bonifici esteri dovranno essere addebitate interamente all'ordinante e in nessun caso potranno essere dedotte dall'importo che viene accreditato al beneficiario.	The costs relating to items not listed in Annex A will not be reimbursed. Parties agree that any bank charges and commissions due for foreign wire transfers shall be charged entirely to the originator and in no case can they be deducted from the amount that is credited to the payee.
Art. 7 - Durata, Recesso e Risoluzione	**Art. 7 - Duration, termination and cancellation**
7.1 Il presente Contratto produrrà effetti a partire dalla data di ultima sottoscrizione ("Data di decorrenza") e rimarrà in vigore sino all'effettiva conclusione della Sperimentazione presso l'Ente, così come previsto nel Protocollo di studio, salvo eventuali modifiche concordate tra le Parti. Fermo restando quanto sopra, il presente Contratto produrrà i suoi effetti a seguito del rilascio di formale autorizzazione da parte dell'Autorità Competente. 7.2 L'Ente si riserva il diritto di recedere dal presente Contratto mediante comunicazione scritta e con preavviso di 30 giorni da inoltrare al Promotore/CRO con raccomandata A.R. o PEC. nei casi di:	7.1 This Agreement shall take effect from the date of the last signature ("Effective Date") and shall remain in force until conclusion of the Trial at the Entity, as provided for in the study Protocol, subject to any amendments agreed by the Parties. Without affecting the foregoing provision, this Agreement shall remain in full force and effect following the issue of formal authorisation by the Competent Authority. 7.2 The Entity may terminate this Agreement in writing with notice of 30 days, sent to the Sponsor/CRO by registered post or certified email, in the following cases:
- insolvenza dei Promotore/CRO, proposizione di concordati anche stragiudiziali con i creditori del Promotore o avvio di procedure esecutive nei confronti del Promotore/CRO. Qualora la situazione sopra indicata riguardi la CRO, il	- insolvency of the Sponsor/CRO, proposal of composition arrangements, also extrajudicially, with the creditors of the Sponsor or the commencement of enforcement action against the

Promotore sarà tenuto a subentrarle e proseguire l'attività, qualora non procuri l'intervento di un'altra CRO, approvata dall'Ente, in sostituzione di quella divenuta insolvente;	Sponsor/CRO. If the situation indicated above relates to the CRO, the Sponsor is obligated to take over from the CRO and to continue the activities, unless the intervention of another CRO – approved by the Entity – is obtained to replace the insolvent CRO;
- cessione di tutti o di parte dei beni del Promotore/CRO ai creditori o definizione con gli stessi di un accordo per la moratoria dei debiti.	- the sale of all or part of the assets of the Sponsor/CRO to the creditors or the agreement of a moratorium with creditors.
Il preavviso avrà effetto dal momento del ricevimento da parte del Promotore/CRO della comunicazione di cui sopra.	The notice will take effect from the time when the Sponsor/CRO receives the above communication.
7.3 Il Promotore/CRO, ai sensi dell'art. 1373, comma secondo, Codice Civile, si riserva il diritto di recedere dal presente Contratto in qualunque momento, per giustificati motivi, mediante comunicazione scritta inviata a mezzo raccomandata A.R. o PEC, con preavviso di 30 giorni. Tale preavviso avrà effetto dal momento del ricevimento da parte dell'Ente di detta comunicazione.	7.3 The Sponsor/CRO, in accordance with Article 1373(2) of the Italian Civil Code, may terminate this Agreement at any time, for justifiable reasons, by sending 30-day notice in writing by registered post or certified email. The notice will take effect from the time when the Entity receives such communication.
In caso di recesso del Promotore/CRO sono comunque fatti salvi gli obblighi assunti e le spese effettuate dall'Ente alla data della comunicazione di recesso. In particolare, il Promotore/CRO corrisponderà all'Ente tutte le spese documentate e non revocabili, contenute nell'Allegato A, che questo abbia sostenuto al fine di garantire la corretta ed efficace esecuzione della Sperimentazione (*ove applicabile*, incluse le spese sostenute dall'Ente nei confronti dei pazienti-partecipanti), nonché i compensi sino a quel momento maturati. In caso di recesso anticipato, il Promotore ha diritto di ricevere, quale proprietario a titolo originario, tutti i dati e risultati, anche parziali, ottenuti dall'Ente nel corso della Sperimentazione e anche successivamente, se derivanti da o correlati a essa.	The termination by the Sponsor/CRO will not affect the obligations assumed and costs paid by the Entity on the date of notification of termination. In particular, the Sponsor/CRO will pay the Entity all the documented, non-revocable expenses, contained in Annex A, that it has incurred in order to ensure the correct, efficient execution of the Trial (*where applicable*, including the costs incurred by the Entity towards the patients/participants) and all the payments accruing up until that time. In the case of early termination the Sponsor may, as the original owner, receive all the complete and partial data and results obtained by the Entity during the Trial and also thereafter, if deriving from or related to the Trial.
7.4 In caso di interruzione della Sperimentazione, ai sensi della normativa applicabile il Promotore corrisponderà all'Ente i	7.4 In case of termination of the Trial, in accordance with the applicable regulation, Sponsor will pay the Entity the expenses and

rimborsi delle spese e i compensi, contenuti nell'Allegato A, effettivamente maturati e documentati fino a quel momento.	payments contained in Annex A that have accrued and are documented up until that time.
7.5 Resta peraltro inteso che lo scioglimento anticipato del Contratto non comporterà alcun diritto di una Parte di avanzare nei confronti dell'altra pretese risarcitorie o richieste di pagamento ulteriori rispetto a quanto convenuto.	7.5 It is also agreed that the early termination of this Agreement shall not give either Party any right to claim from the other Party any compensation or requests for payment other than those already agreed.
7.6 Gli effetti del presente Contratto cesseranno automaticamente ai sensi dell'art. 1454 del Codice Civile nel caso in cui una delle Parti non abbia adempiuto a uno degli obblighi previsti dal presente Contratto entro 30 giorni dalla richiesta scritta di adempimento presentata dall'altra parte. Resta in ogni caso salva l'applicabilità degli artt1218 e seguenti del Codice Civile.	7.6 This Agreement shall cease to have effect automatically pursuant to Article 1454 of the Civil Code in the event that either Party has not fulfilled one of its obligations as provided for herein, within 30 days from a written notice to perform sent by the other Party. The provisions of Articles 1218 et seq. of the Italian Civil Code shall apply in any event.
7.7 In caso di risoluzione del presente Contratto, non derivante da inadempimento dell'Ente, quest'ultimo avrà diritto al rimborso delle spese effettivamente sostenute per la Sperimentazione prima del ricevimento della notifica di risoluzione e a un compenso per i servizi proporzionale all'attività svolta sino al momento della risoluzione. L'Ente si impegna a restituire al Promotore/CRO eventuali importi già liquidati e relativi ad attività non svolte.	7.7 If this Agreement is terminated for reasons not due tononcomplianceby the Entity, the Entity shall have the right to reimbursement of the expenses incurred in relation to the Trial prior to receipt of the notice of termination, and to payment for the services in proportion to the activities completed up until the time of termination. The Entity shall repay the Sponsor/CRO any amounts already paid in relation to activities that were not completed.
7.8 In tutti i casi di interruzione o di risoluzione del presente Contratto, sarà attuata ogni precauzione per garantire la massima tutela dei pazienti già coinvolti, in accordo con quanto previsto dal Protocollo approvato dal Comitato Etico, garantendo, nei limiti e con le modalità previste dall'art. 4.2, la continuità terapeutica.	7.8 In all cases of interruption or termination of this Agreement, full precautions will be taken to protect the patients already involved, in accordance with the Protocol approved by the Ethics Committee, guaranteeing, within the limits and the modality set in the art. 4.2 continuity of treatment
Art. 8 - Copertura assicurativa	**Art. 8 - Insurance cover**
8.1 Il Promotore è tenuto a garantire, secondo la legislazione vigente, il risarcimento dei danni subiti dai pazienti e riconducibili alla partecipazione alla Sperimentazione clinica, secondo il Protocollo commisurato alla natura e	8.1 The Sponsor is required to guarantee, according to current legislation, compensation for damages suffered by patients and attributable to participation in the clinical Trial, in accordance with the

alla portata dei rischi conseguenti.	Protocol, commensurate with the nature and extent of the consequent risks.
8.2 Fatte salve le previsioni dell'art 76 del Regolamento e della Legge 8 marzo 2017, n. 24 e dei rispettivi provvedimenti attuativi, la copertura assicurativa fornita dal Promotore garantisce rispetto alle ipotesi di responsabilità civile del Promotore, dell'istituzione sanitaria sede della Sperimentazione, dello Sperimentatore Principale, e degli altri Sperimentatori coinvolti presso dell'Ente.	8.2 Without prejudice to the provisions of Article 76 of the Regulation and of Law 8 March 2017, n. 24 and the respective implementing measures, the insurance coverage provided by the Sponsor guarantees with respect to the hypotheses of civil liability of the Sponsor, the health entity where the Trial is conducted, the Principal Investigator, and the other Investigators involved at the f the Entity.
8.3 Il Promotore dichiara, di aver stipulato adeguata polizza assicurativa (n. 390-76574325-30011, con la Compagnia HDI Global SE) per la responsabilità civile verso terzi, a copertura del rischio di eventuali danni derivanti ai pazienti dalla partecipazione alla Sperimentazione, secondo quanto previsto dal D.M. 14 luglio 2009. La polizza assicurativa è stata ritenuta dal Comitato Etico rispettosa dei termini di legge e adeguatamente tutelante i soggetti coinvolti nella Sperimentazione clinica.	8.3 The Sponsor confirms, that it has taken out a third party liability insurance policy (no. 390-76574325-30011, with the insurer HDI Global SE) to cover the risk of injury to patients from taking part in the Trial, in accordance with M.D. of 14 July 2009. The Ethics Committee considers that the insurance policy complies with the provisions of the law and adequately protects the patients taking part in the Trial.
8.4 Il Promotore, , dichiara di farsi carico delle conseguenze connesse a eventuali inadeguatezze, anche sopravvenute, della copertura assicurativa in argomento, integrandole ove necessario in coerenza con quanto previsto all'art. 8.1.	8.4 The Sponsor, confirms, that it is liable for any consequences resulting from any present or future deficiencies in the insurance cover mentioned above, integrating them where necessary in accordance with the provisions of art. 8.1.
8.5 Il Promotore in particolare, nel caso in cui intenda recedere dal Contratto, garantisce che la Società assicuratrice assicuri in ogni caso la copertura dei soggetti già inclusi nello studio clinico anche per il prosieguo della Sperimentazione ai sensi dell'art. 2 comma 3 del D.M. 17/07/09.	8.5 In particular, in the event that the Sponsor intends to withdraw from the Agreement, the Sponsor warrants that the insurer shall in all cases guarantee the cover of the patients already included in the clinical trial also during the continuation of the Trial, in accordance with Article 2 par. 3 of M.D. of 17/07/09.
8.6 All'atto del sinistro, Ente è tenuto a comunicare l'esistenza di coperture assicurative per la responsabilità RCT Medical Malpractice (a copertura dell'Ente, sia del personale medico che ha somministrato il farmaco), ai sensi dell'articolo 1910 codice civile.	8.6 At the time of the accident, the Entity is required to disclose the existence of policies for liability RCT Medical Malpractice (to cover the Entity and the medical staff administering the drug) in accordance with article 1910 of the Italian Civil Code.

Art. 9 - Relazione finale, titolarità e utilizzazione dei risultati	Art. 9 - Final report, ownership and use of results
9.1 Il Promotore si impegna a divulgare tutti i risultati dello studio anche qualora negativi.	9.1 The Sponsor will publish the results of the Study even if the results are negative.
9.2 Il Promotore assume la responsabilità della preparazione del rapporto clinico finale e dell'invio entro i termini previsti dalla vigente normativa allo Sperimentatore Principale e al Comitato Etico del riassunto dei risultati della Sperimentazione stessa. Indipendentemente dall'esito di una sperimentazione clinica, entro un anno (e sei mesi nel caso di studi pediatrici) dalla sua conclusione, il Promotore trasmette una sintesi dei risultati della Sperimentazione alla banca dati EU secondo le modalità previste dall'Art 37.4 del Regolamento (UE) n. 536/2014.	9.2 The sponsor is liable for preparing the final clinical report and for sending a summary of the results of the Trial to the Principal Investigator and Ethics Committee by the applicable legal deadline. Regardless of the outcome of a clinical Trial, within one year (and six months in the case of pediatric studies) from its conclusion, the Sponsor sends a summary of the results of the Trial to the EU database in accordance with the procedures set out in Article 37.4 of the Regulation (UE) n. 536/2014.
9.3 Tutti i dati, i risultati, le informazioni, i materiali, le scoperte e le invenzioni derivanti dall'esecuzione della Sperimentazione nel perseguimento degli obiettivi della stessa, , sono di proprietà esclusiva del Promotore, salvo il diritto degli Sperimentatori, ricorrendone i presupposti, di esserne riconosciuti autori. A fronte di una procedura attivata dal Promotore per il deposito di una domanda di brevetto avente a oggetto invenzioni ricavate nel corso della Sperimentazione, l'Ente e lo Sperimentatore Principale si impegnano a fornire al Promotore tutto il supporto, anche documentale, utile a tal fine.	9.3 All the data, the results, information, materials, discoveries and inventions deriving from the execution of the Trial in pursuit of its objectives, is the exclusive property of the Sponsor , without prejudice to the right of the Investigators, if the conditions are met, to be recognized as authors. If the Sponsor takes action to file an application for a patent relating to inventions obtained during the course of the Trial, the Entity and the Principal Investigator shall provide to Sponsor all the assistance and documentary support necessary for that purpose.
9.4 L'Ente può utilizzare i dati e i risultati della Sperimentazione, del cui trattamento è autonomo titolare ai sensi di legge, unicamente per propri scopi istituzionali scientifici e di ricerca. Tale utilizzo non deve in alcun caso pregiudicare la segretezza degli stessi e la tutela brevettuale dei relativi diritti di proprietà intellettuale spettanti al Promotore.	9.4 The Entity may use the data and the results of the Trial, for which processing it is automomous data controller pursuant the applicable regulation for its own institutional, scientific and research purposes only. Such use must not under any circumstance affect the secrecy and the patent protection of the related intellectual property rights due to Sponsor

Le Parti e il Promotore riconoscono reciprocamente che resteranno titolari dei diritti di proprietà industriale e intellettuale relativi alle proprie pregresse conoscenze (*background knowledge*) e alle proprie conoscenze sviluppate o ottenute nel corso della Sperimentazione, ma a prescindere e indipendentemente dalla sua conduzione e dai suoi obiettivi (*sideground knowledge*).	The Parties and Sponsor mutually acknowledge they will still be the owners of industrial and intellectual property rights relating to their background knowledge and to their own knowledge developed or obtained in the course of the Trial, but regardless and irrespectively from the way it is conducted (sideground knowledge).
9.5 Le disposizioni del presente articolo resteranno valide ed efficaci anche dopo la risoluzione o la cessazione degli effetti del presente Contratto.	9.5 The provisions of this article will remain valid and binding even after termination or cancellation of this Agreement.
Art. 10 Segretezza di informazioni tecnico-commerciali e diffusione dei risultati	**Art. 10 - Secrecy of technical and commercial information and dissemination of data**
10.1 Con la sottoscrizione del presente Contratto, ciascuna delle Parti si impegna a mantenere riservate per l'intera durata del presente Contratto *(termine* estensibile in sede negoziale fino alla, loro caduta in pubblico dominio, qualora necessario in base ad eventuali accordi con licenzianti) tutte le informazioni di natura tecnica e/o commerciale, messe a disposizione dall'altra Parte e/o sviluppate nel corso della Sperimentazione e nel perseguimento degli obiettivi della stessa, che siano classificabili come "Segreti Commerciali" ai sensi degli art. 98 e 99 del Codice della Proprietà Industriale (D. Lgs. n. 30/2005, come modificato dal D. Lgs. n. 63/2018 in recepimento della Direttiva UE 2016/943), adottando ogni misura (di carattere contrattuale, tecnologico o fisico) idonea per la loro protezione, anche nei confronti di propri dipendenti, collaboratori, sub-appaltatori, danti o aventi causa.	10.1 By signing this Agreement, each Parties undertakes to treat as private for the entire duration of this Agreement (time limit extendable in the course of negotiation until their fall into public domain, if necessary on the basis of any agreements with the licensors), all the technical and/or commercial information provided by the other Party and/or developed during the course of the Trial and in pursuit of its objectives, which may be classified as "Commercial Secrets" within the meaning of articles 98 and 99 of the Industrial Property Code (legislative decree 30/2005 as amended by legislative decree 63/2018 enacting Directive EU 2016/943), and shall take all the contractual, technological or physical measures necessary to protect such information, also with regard to their own employees, contractors, subcontractors, successors or assigns.
Ciascuna delle Parti inoltre dichiara e garantisce quanto segue: (i) i propri Segreti Commerciali sono stati acquisiti, utilizzati e rivelati lecitamente e non	Each Party also represents and warrants as follows: (i) its own Commercial Secrets have been acquired, used and disclosed legally and

vi sono – per quanto ad essa noto – azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.	there are not – as far as is known to it – any legal actions, disputes, claims for compensation or indemnity, whether judicial or extrajudicial, brought by any third party claiming ownership of such secrets.
(ii) essa pertanto terrà indenne e manleverà l'altra Parte da azioni giudiziarie, contestazioni, richieste di risarcimento o di indennizzo promosse anche in via stragiudiziale, da parte di terzi rivendicanti la titolarità di tali segreti.	(ii) It shall therefore indemnify the other Party in respect of any legal actions, complaints, claims for compensation or indemnity, whether judicial or extrajudicial, brought by any third party claiming ownership to such secrets.
10.2 Le Parti sono obbligate all'adeguata e corretta diffusione e pubblicazione dei risultati della Sperimentazione nonchè alla loro adeguata comunicazione ai pazienti partecipanti ed ai rappresentanti dei pazienti. Il Promotore, ai sensi della vigente normativa, è tenuto a rendere pubblici tempestivamente i risultati, anche se negativi, ottenuti a conclusione della Sperimentazione, non appena disponibili da parte di tutti i Centri partecipanti e comunque non oltre i termini a tal fine stabiliti dalle disposizioni applicabili dell'Unione Europea.	10.2 The Parties are obligated to adequately and accurately disclose and publish the results of the Trial as well as to communicate them adequately to the patients taking part and to the patients' representatives. Under the terms of the applicable regulations, the Sponsor is required to promptly publish the results of the Trial even if negative, obtained at the end of the Trial as soon as they become available from all the participating Centres and any case no later than the deadlines for this purpose established by the applicable provisions of the European Union
10.3 Ai sensi dell'art. 5, comma secondo, lett. c) del D.M. 8 febbraio 2013, lo Sperimentatore Principale ha diritto di diffondere e pubblicare, senza limitazione alcuna, i risultati della Sperimentazione ottenuti presso l'Ente, nel rispetto delle disposizioni vigenti in materia di riservatezza dei dati sensibili, di protezione dei dati personali e di tutela della proprietà intellettuale, nonché nel rispetto dei termini e delle condizioni di cui al presente Contratto.	10.3 Pursuant to Article 5(2) (c) of M.D. of 8 February 2013, the Principal Investigator has the right to disseminate and publish, without limitation, the results of the Trial obtained from the Entity, in accordance with the current laws on the confidentiality of sensitive data, data protection and intellectual property, and in accordance with the terms and conditions of this Agreement.
Per garantire la correttezza della raccolta e la veridicità dell'elaborazione dei dati e dei risultati della Sperimentazione ottenuti presso l'Ente, in vista della loro presentazione o pubblicazione, almeno 60 giorni prima di esse lo Sperimentatore Principale dovrà trasmettere al Promotore il testo del documento destinato ad essere presentato o pubblicato Ove dovessero sorgere questioni relative all'integrità scientifica del documento e/o questioni afferenti agli aspetti	To ensure that the data processing is correct and accurate and the results of the Trial obtained at the Entity, in view of their presentation or publication, at least 60 days before them, the Principal Investigator will send the Sponsor the text of the document Intended to be presented or published , Should issues arise in relation to the scientific integrity of the document and/or issues regarding regulatory aspects, patents or the

regolatori, brevettuali o di tutela della proprietà intellettuale, le Parti e lo Sperimentatore Principale procederanno nei 60 giorni successivi al riesame del documento.Lo Sperimentatore Principale accetterà di tenere conto dei suggerimenti del Promotore nella presentazione o pubblicazione, solo se necessari ai fini della tutela della riservatezza delle informazioni, dei dati personali e della tutela della proprietà intellettuale, purché non in contrasto con l'attendibilità dei dati, con i diritti, la sicurezza e il benessere dei pazienti.	protection of intellectual property, the the Parties and the Principal Investigator will proceed over the next 60 days to review the document The Principal Investigator shall agree to take into account the Sponsor's suggestions in the publication or presentation, only if necessary to protect the confidentiality of information, personal data, and to protect intellectual property, provided that the amendments do not conflict with the reliability of the data, or the rights, safety and well-being of the patients.
10.4 Il Promotore riconosce di non aver diritto di chiedere l'eliminazione delle informazioni contenute nel documento salvo quando tali richieste e modifiche siano necessarie ai fini della tutela della riservatezza dei dati, della protezione dei dati personali e della tutela della proprietà intellettuale.	10.4 The Sponsor acknowledges that they do not have the right to request the deletion of the information contained in the document,, except where such requests and amendments are necessary for , data confidentiality, data protection and the protection of intellectual property.
10.5 Il Promotore, allo scopo di presentare una richiesta di brevetto e qualora risulti necessario, potrà chiedere allo Sperimentatore Principale di differire di ulteriori 90 giorni la pubblicazione o presentazione del documento.	10.5 The Sponsor may, for the purposes of presenting a patent application and if necessary, ask the Principal Investigator to delay the publication or presentation of the document by a further 90 days.
In caso di sperimentazione multicentrica lo Sperimentatore Principale non potrà pubblicare i dati o i risultati del proprio Centro sino a che tutti i dati e risultati della Sperimentazione siano stati integralmente pubblicati ovvero per almeno 12 mesi dalla conclusione della Sperimentazione, dalla sua interruzione o chiusura anticipata.	(*For multi-centre trials*) The Principal Investigator may not publish the data or the results of his or her own Centre until all data and results of the Trial have been published in full or for at least 12 months from conclusion of the Trial, its interruption or early termination.
Laddove la pubblicazione recante i risultati di una sperimentazione multicentrica ad opera del Promotore, o del terzo da questi designato, non venga effettuata entro 12 mesi (*secondo la normativa vigente almeno dodici mesi*) dalla fine della Sperimentazione multicentrica, lo Sperimentatore potrà pubblicare i risultati ottenuti presso l'Ente, nel rispetto di quanto contenuto nel presente articolo.	If a publication containing the results of a multi-centre trial, published by the Sponsor or by the third party designated by the Sponsor is not completed within 12 months (*at least twelve months under the current regulations*) from the end of the multi-centre Trial, the Investigator may publish the results obtained at the Entity, in accordance with the contents of this article.

Art. 11 - Protezione dei dati personali	Art. 11 - Data protection
11.1 Le Parti nell'esecuzione delle attività previste dal presente Contratto si impegnano a trattare i dati personali, di cui vengano per qualsiasi motivo a conoscenza durante la Sperimentazione clinica, nel rispetto degli obiettivi di cui ai precedenti articoli e in conformità a quanto disposto dal Regolamento (UE) 2016/679 del Parlamento Europeo e del Consiglio del 27 aprile 2016 (GDPR),, nonché dalle correlate disposizioni legislative e amministrative nazionali vigenti, con le loro eventuali successive modifiche e/o integrazioni (di seguito, collettivamente, "Leggi in materia di Protezione dei dati") nonché degli eventuali regolamenti degli enti "). nonché delle "Linee guida per i trattamenti di dati personali nell´ambito delle sperimentazioni cliniche di medicinali\ - 24 luglio 2008 G.U. n. 190 del 14 agosto 2008" del Garante per la Protezione dei Dati Personali e autorizzazioni generali in materia di ricerca scientifica e dati genetici del 5 giugno 2019.	11.1 In executing the contractual activities the Parties shall treat all the personal data they receive for any reason in relation to the clinical Trial in accordance with the objectives of the foregoing articles and in conformity with the provisions of Regulation (EU) 2016/679 of the European Parliament and Council of 27 April 2016 (GDPR),, and with the related provisions of law and orders of national administrations, including any subsequent amendments (collectively the "Data Protection Laws") as well as any regulations of the entities as well as the "Guidelines for the processing of personal data in the context of clinical trials of medicines \ - July 24, 2008 G.U. n. 190 of 14 August 2008 "of the Guarantor for the Protection of Personal Data and general authorizations in the field of scientific research and genetic data of 5 June 2019.
11.2 I termini utilizzati nel presente articolo, nel Contratto, nella documentazione di informativa e consenso e in ogni altro documento utilizzato per le finalità della Sperimentazione clinica devono essere intesi e utilizzati secondo il significato a essi attribuito nell'Allegato B.	11.2 The terms used in this article, in this Agreement, in the informed consent documents and in any other documents used for the purposes of the Trial shall be construed and utilised in accordance with the meanings given in Annex B.
11.3 L'Ente e il Promotore si qualificano come autonomi titolari del trattamento ai sensi dell'art. 4 paragrafo 17 del GDPR. Ciascuna delle Parti provvederà a propria cura e spese, nell'ambito del proprio assetto organizzativo, alle eventuali nomine di Responsabili del trattamento e attribuzione di funzioni e compiti a soggetti designati, che operino sotto la loro autorità, ai sensi del GDPR e della normativa vigente.	11.3 The Entity and Sponsor are independent data controllers for the purposes of article 4 paragraph 17 of the GDPR. Each of the Parties will arrange at its own expense, as part of its organizational structure, for the appointment of Data Processors and assignment of functions and tasks to designated subjects, who operate under their authority, in accordance with the GDPR and current legislation.
11.4 Per le finalità della Sperimentazione saranno trattati dati personali riferiti alle seguenti categorie di interessati: soggetti partecipanti alla Sperimentazione; e loro stakeholders persone che operano per le Parti. Tali interessati sono	11.4 For the purposes of the Trial, personal data relating to the following categories of data subject will be processed: persons taking part in the trial; and their stakeholders persons operating on the Parties' behalf. Such

informati sul trattamento che li riguarda a mezzo di idonea informativa. Per le finalità della Sperimentazione saranno trattati le seguenti tipologie di dati personali: dati di cui all'art. 4 n. 1 del GDPR; dati rientranti nelle categorie "particolari" di dati personali - e in particolare dati relativi alla salute e alla vita sessuale, dati genetici - di cui all'art. 9 del RGPD. Tali dati saranno trattati nel rispetto dei principi di liceità, correttezza, trasparenza, adeguatezza, pertinenza e necessità di cui all'art.5, paragrafo 1 del GDPR.	data subjects will be appropriately informed of the processing of their data. For the purposes of the Trial, the following types of personal data will be processed: the data referred to in article 4 paragraph 1 of the GDPR; data classified as "sensitive" – and in particular, data relating to health, sexual preferences and genetic data – referred to in Article 9 GDPR. Such data shall be processed in accordance with the principles of legality, fairness, transparency, adequacy, relevance and necessity as contained in Article 5 paragraph 1 of the GDPR.
11.5 Il Promotore potrà trasmettere i dati ad affiliate del gruppo del Promotore e a terzi operanti per suo conto, anche all'estero, in paesi al di fuori dell'Unione Europea soltanto nel rispetto delle condizioni di cui agli artt. 44 e ss. del GDPR. In questo caso il Promotore garantirà un adeguato livello di protezione dei dati personali anche mediante l'utilizzo delle Standard Contractual Clauses approvate dalla Commissione Europea. Ove il Promotore abbia sede in uno Stato che non rientra nell'ambito di applicazione del diritto dell'Unione Europea e che la Commissione Europea abbia deciso che tale Paese non garantisce un livello di protezione adeguato ex artt. 44 e 45 del GDPR UE 2016/679, il Promotore e l'Ente dovranno compilare e sottoscrivere il documento Standard Contractual Clauses (quest'ultimo non viene allegato al presente Contratto).	11.5 The Sponsor may send the data to other affiliates of the Sponsor's group and to third parties operating on its behalf, including those abroad, in countries outside of the EU, only in compliance with the conditions set out in Articles 44 and ss. of the GDPR. In this case, the Sponsor will guarantee an adequate level of protection of personal data also through the use of the Standard Contractual Clauses approved by the European Commission. Where the Sponsor is established in a State that does not fall within the scope of European Union law and that the European Commission has decided that this country does not guarantee an adequate level of protection pursuant to Articles 44 and 45 of the EU GDPR 2016/679, the Sponsor and the Entity must complete and sign the Standard Contractual Clauses document.(this last document is not attached to this Agreement)
11.6 Le Parti garantiscono che le persone da esse autorizzate a trattare dati personali per le finalità della Sperimentazione rispettino i principi posti a tutela del diritto alla protezione dei dati personali e del diritto alla riservatezza, e che le persone che hanno accesso ai dati personali siano obbligati a trattarli in conformità alle istruzioni dettate, in coerenza con il presente articolo, dal titolare di riferimento.	11.6 The Parties warrant that the persons authorised by them to process personal data for the purposes of the Trial will comply with the principles in place to safeguard data protection and the right to confidentiality and that any persons having access to the personal data will be obligated to process the data in accordance with the instructions given, in accordance with this article, by the data controller.
11.7 Lo Sperimentatore Principale è individuato dall'Ente quale persona autorizzata al trattamento ai sensi dell'art. 29 del GDPR e quale	11.7 The Principal Investigator has been identified by the Entity as a person authorised for the data processing for the purposes of

soggetto designato ai sensi dell'art. 2 quaterdecies del Decreto Legislativo n. 196/2003.	Article 29 GDPR and as a designated party for the purposes of Article 2 quaterdeciesof the Italian Law Decree 196/2003.
11.8 Lo Sperimentatore Principale, deve informare in modo chiaro e completo, prima che abbia inizio la Sperimentazione (incluse le relative fasi prodromiche e di screening) ogni paziente circa natura, finalità, risultati, conseguenze, rischi e modalità del trattamento dei dati personali; in particolare il paziente deve inoltre essere informato che Autorità nazionali e straniere, nonché il Comitato Etico, potranno accedere, nell'ambito di attività di monitoraggio, verifica e controllo sulla ricerca, alla documentazione relativa alla Sperimentazione così come anche alla documentazione sanitaria originale del paziente, e che ad esse potranno anche eccedere in visione, nell'ambito delle rispettive competenze, Monitor e Auditor.	11.8 The Principal Investigator shall provide clear, complete information to all patients before the Trial starts (also before the preliminary phases or screening) to all patients, regarding the nature, purpose, results, consequences, risks and methods of the processing of personal data; in particular, all patients must be informed that the national and international authorities and the Ethics Committee may, in connection with the monitoring, checking and control of the Trial, have access to the related documentation and also to the original healthcare records of the patient, and that the data may also be accessed by the Monitors and Auditors in connection with their respective duties.
11.9 Lo Sperimentatore Principale deve acquisire dal paziente debitamente informato il documento di consenso oltre che alla partecipazione alla Sperimentazione, anche al trattamento dei dati. L'Ente è responsabile della conservazione di tale documento.	11.9 After the patient has been duly informed the Principal Investigator shall obtain the consent form for participation in the Trial and also the consent to the processing of personal data. The Entity is responsible for keeping the consent forms.
11.10 Qualora uno dei titolari del trattamento accerti una violazione dei dati personali, si impegna a comunicarlo all'-altro titolare del trattamento entro 48 ore dall'accertamento della violazione, ferma restando l'autonomia di alcuno dei titolari del trattamento nella valutazione della sussistenza delle condizioni e nell'adempimento degli obblighi previsti dagli artt. 33 e 34 del GDPR	11.10 If either data controller discovers a data protection breach, the other data controller shall be informed within 48 hours from the breach having been verified, without affecting either data controller's independent assessment of the existence of the conditions and fulfilment of the obligations contained in Articles 33 and 34 GDPR.
11.11 L'Ente accetta che la CRO possa compilare un database di informazioni dell'Ente e del suo personale (incluso lo Sperimentatore Principale) da utilizzare in relazione alla Sperimentazione (inclusi, a titolo esemplificativo ma non esaustivo, questionari di fattibilità, CV, licenze, specialità mediche, partecipazione a studi clinici, moduli di informativa finanziaria) e/o possa utilizzare tali informazioni per scopi connessi alla propria attività. L'Ente deve aver ottenuto tutti i	11.11 Entity agrees that CRO may compile a database of information from Entity and its personnel (including Principal Investigator) for use in connection with the Trial (including but not limited to feasibility questionnaires, CVs, licenses, medical specialties, participation in clinical trials, financial disclosure forms) and/or may use this information for purposes related to its business. Entity shall have secured any necessary consents from its

consensi necessari dal proprio personale per consentire tale condivisione di informazioni. Tali informazioni sono utilizzate esclusivamente in relazione all'avvio di studi e studi di fattibilità e sono accessibili solo al Promotore del rispettivo studio e al personale incaricato della gestione dello studio e per il quale le informazioni sono necessarie nell'espletamento dei loro compiti (ulteriormente descritto come "**Personale Autorizzato**"). Poiché alcuni studi delle CRO sono condotti in tutto il mondo, le informazioni personali raccolte sono a disposizione del Personale Autorizzato che può trovarsi in paesi al di fuori dell'Unione Europea. Al fine di garantire la protezione dei dati personali, la CRO ha stabilito politiche e procedure che disciplinano la sicurezza e l'accesso limitato a tali dati che sono uniformi per tutta la CRO e le sue affiliate e che rispettano gli standard di protezione dei dati personali applicabili all'interno dell'Unione Europea. Ove applicabile, la CRO stipula accordi di trattamento dei dati con i promotori in linea con le leggi dell'Unione Europea in materia di protezione dei dati. In conformità con le leggi relative alla protezione dei dati personali, i soggetti interessati i cui dati sono raccolti hanno il diritto di accedere, modificare, rettificare e sopprimere i loro dati personali, semplicemente richiedendoli all'attenzione del Responsabile della Protezione dei Dati di Medpace all'indirizzo privacy@Medpace.com, o al seguente indirizzo: Medpace Privacy Officer, Medpace, Inc., 5375 Medpace Way, Cincinnati, Ohio, 45227.	personnel to allow for this sharing of information. Such information is used solely in connection with the initiation of studies and feasibility studies and is accessible only to the Sponsor of the respective study and personnel assigned to study management and for whom the information is needed in the performance of their duties (further described as "**Authorized Personnel**"). As some CRO studies are being conducted worldwide, the personal information collected is available to Authorized Personnel who may be located in countries outside the European Union. In order to provide for the protection of personal data, CRO has established policies and procedures governing the security of and limited access to this data that are uniform throughout CRO and its affiliates and comply with the standards of personal data protection applicable within the European Union. When applicable, CRO enters into data processing agreements with sponsors in line with applicable European Union data protection Laws. In accordance with the laws pertaining to the protection of personal data, the individuals' whose data is collected have a right to access, to modify, to rectify, and to suppress their personal data, simply by requesting it to the attention of the Medpace Privacy Officer at privacy@Medpace.com, or to the following address: Medpace Privacy Officer, Medpace, Inc., 5375 Medpace Way, Cincinnati, Ohio, 45227.
Art. 12 - Modifiche	**Art. 12- Amendments**
12.1 Il presente Contratto e i relativi allegati/addendum, unitamente al Protocollo quale parte integrante, costituiscono l'intero accordo tra le Parti.	12.1 This Agreement and its annexes/addenda together with the Protocol, form an integral part hereof, constitute the entire agreement between the Parties.
12.2 Il Contratto può essere modificato/integrato solo con il consenso scritto di entrambe le Parti. Le eventuali modifiche saranno oggetto di addendum al presente Contratto e decorreranno	12.2 This Agreement may only be amended/supplemented with the written consent of both Parties. Any amendments will be contained in an addendum to this

dalla data della loro sottoscrizione, salvo diverso accordo tra le Parti.	Agreement and will take effect from the date of signature, unless agreed otherwise by the Parties.
Art. 13 - Disciplina anti-corruzione e per la prevenzione di reati	**Art. 13 - Anti-corruption provisions and for the prevention of crimes**
13.1 L'Ente e il Promotore/CRO si impegnano a rispettare la normativa anticorruzione applicabile in Italia.	13.1 The Entity and the Sponsor/CRO will comply with the anticorruption laws applicable in Italy.
13.2 Il Promotore dichiara di aver adottato misure di vigilanza e controllo ai fini del rispetto e dell'attuazione delle previsioni del D. Lgs. 8 giugno 2001 n. 231, nonché, in quanto applicabili e non in contrasto con la normativa vigente in Italia, dei principi del *Foreign Corrupt Practices Act* degli Stati Uniti, e loro successive modifiche e integrazioni. L'Ente e le sue strutture cliniche e amministrative, si impegnano a collaborare in buona fede, nei limiti di quanto previsto dalla normativa italiana di cui sopra, con il personale e il management del Promotore al fine di facilitare la piena e corretta attuazione degli obblighi che ne derivano e l'attuazione delle procedure operative a tal fine messe a punto dal Promotore.	13.2 The Sponsor confirms that it has taken supervisory and control measures to ensure compliance with, and implementation of, the provisions of Italian legislative decree no. 231 of 8 June 2001 and, where applicable and not conflicting with laws in Italy, that covers the principles of the US Foreign Corrupt Practices Act and its amendments. The Entity and its clinical and administrative facilities undertake to collaborate in good faith in accordance with the provisions of Italian law as mentioned above, and will collaborate with the Sponsor's personnel and management to facilitate full, accurate implementation of the resulting obligations and the implementation of the operational procedures developed by the Sponsor for that purpose.
13.3 Ai sensi e per gli effetti della L. n. 190 del 6 novembre 2012 ("Legge Anticorruzione") e sue successive modificazioni, l'Ente dichiara di avere adottato il Piano Triennale per la prevenzione della corruzione.	13.3 For the purposes of Law 190 of 6 November 2012 ("Anticorruption Act") as amended, the Entity confirms that it has adopted the Three-Year Anti-corruption Plan.
(*Ove applicabile e non in contrasto con la normativa vigente*) Il Promotore dichiara di aver adottato il proprio Codice etico, di cui è possibile prendere visione alla pagina web www.micurx.com	(*If applicable and if not conflicting with current regulations)* The Sponsor declares that it has adopted its own code of ethics which can be viewed at the webpage www.micurx.com
13.4 L'Ente e il Promotore s'impegnano reciprocamente a informare immediatamente l'altra Parte circa ogni eventuale violazione del presente articolo di cui venga a conoscenza e a rendere disponibili tutti i dati informativi e la documentazione per ogni opportuna verifica.	13.4 The Entity and the Sponsor shall immediately inform each other of any violation of this article by the other Party, of which they become aware, and will provide full information and documents, for all the appropriate investigations.
13.5 Il Promotore può divulgare per qualsiasi scopo legittimo, nei limiti della normativa sul	13.5 the Sponsor may disclose the terms of this Agreement or any amendments to this

trattamento dei dati, i termini del presente Contratto o di qualsiasi suo emendamento.	Agreement for any legitimate purpose, within the limits of the data protection laws.
13.6 La violazione di quanto previsto da questo articolo costituisce grave inadempimento del presente Contratto ai sensi e per gli effetti di cui all'art. 1456 Codice Civile, risultando pregiudicato il rapporto di fiducia tra le Parti.	13.6 The violation of any provisions of this article will constitute serious breach of this Agreement pursuant to Article 1456 of the Italian Civil Code, if the relationship of trust between the Parties is affected.
Art. 14 - Trasferimento diritti, cessione del Contratto e sub-appalto	**Art. 14 - Transfer of rights, assignment of contract and subcontracting**
14.1 Il presente Contratto ha carattere fiduciario e, pertanto, le Parti non possono cedere o trasferire lo stesso a terzi, senza il preventivo consenso scritto dell'altra Parte. Ogni Parte acconsente a che l'altra Parte possa cedere e/o trasferire in tutto o in parte i diritti e gli obblighi a lui pervenuti direttamente o indirettamente dalla firma del presente Contratto a un suo successore o ad una società od entità ad essa collegata , previa accettazione da parte del cessionario di tutte le condizioni e i termini del presente Contratto. Qualsiasi trasferimento di diritti in assenza delle suddette condizioni sarà considerato nullo e mai avvenuto.	14.1 This Agreement is fiduciary in nature and therefore the Parties may not assign or transfer this Agreement to any third party without the prior consent of the other Party. Each Party will allow the other Party to assign and/or transfer all or part of the rights and obligations received directly or indirectly from the signing of this Agreement to a successor or to a company or entity affiliated to it , on condition by the transferee of acceptance ts all the terms and conditions herein. Any transfer of rights taking place in the absence of such conditions shall be considered null and void and shall be disregarded.
14.2 In caso di cambio di denominazione dell'Ente non si renderà necessario l'emendamento alla presente convenzione. L'Ente sarà comunque tenuto a notificare tempestivamente al Promotore tale cambio di denominazione.	14.2 In the event of a change of name of the Entity, no amendment to this Agreement shall be necessary. However the Entity is required to duly inform the Sponsor/ of its change of name.
Art. 15 - Oneri fiscali	**Art. 15 - Fiscal obligations**
15.1 Il presente Contratto viene sottoscritto con firma digitale ai sensi della normativa vigenteLe imposte e tasse inerenti e conseguenti alla stipula del presente Contratto, ivi comprese l'imposta di bollo sull'originale informatico di cui all'art. 2 della Tabella Allegato A – tariffa parte I del DPR n. 642/1972 e l'imposta di registro devono essere versate, nel rispetto della normativa applicabile. In particolare, le imposte di bollo saranno assolte dallo CRO, per conto dello Sponsor, in modo virtuale ai sensi dell'art. 15 del D.P.R. 642/72 (Autorizzazione n.173787/2020)	15.1 This Agreement is signed digitally in accordance with the applicable regulation. All the taxes and duties relating to or resulting from the stipulation of this Agreement, including the revenue stamp on the digital original as referred to in Article 2 of the table in Annex A – tariff part I of Presidential Decree 642/1972, and the registration tax, must be paid in accordance with the applicable regulations. In particular, the stamp duties will be digitally fulfilled by CRO, on behalf of Sponsor, in compliance with art. 15 of Italian

	Decree 642/1972 (Authorization n. 173787/2020).
Art. 16 Legge regolatrice e Foro competente	**Art. 16 – Governing law and forum**
16.1 La normativa applicabile al presente Contratto è quella dello Stato italiano.	16.1 This Agreement is governed by the laws of Italy.
16.2 Per tutte le eventuali controversie che dovessero sorgere in relazione all'interpretazione, applicazione ed esecuzione del presente Contratto, fermo restando l'impegno delle Parti ad esperire un preventivo tentativo di conciliazione in sede stragiudiziale, sarà competente, in via esclusiva, il Foro dell'Ente (Vicenza)	16.2 The Court of the Entity (Vicenza) will have exclusive jurisdiction for all disputes that may arise in relation to the interpretation, application and execution of this Agreement, without prejudice to the commitment of the Parties to carry out a preventive attempt at conciliation in out-of-court.
Art. 17 – Lingua	**Art. 17 – Language**
17.1 In caso di difformità tra la versione in lingua inglese e quella in lingua italiana del presente Contratto, la versione in italiano prevarrà.	17.1 In the event of any discrepancy between the English language version and the Italian version of this Agreement, the Italian version shall prevail.
Art. 18 – Il Promotore come Beneficiario	**Art. 18 Sponsor as beneficiary**
Le Parti del presente Contratto riconoscono e convengono che il Promotore godrà dei benefici derivanti dal presente Contratto in quanto beneficiario e che potrà applicare tali diritti sia direttamente sia indirettamente tramite la CRO.	The Parties to this Agreement recognize and agree that Sponsor takes the benefit of this Agreement as beneficiary and agree that Sponsor may enforce such rights either directly itself or indirectly through CRO.

Le Parti si danno reciprocamente atto, per reciproca chiarezza, che il presente Contratto , redatto sulla base dei contenuti minimi individuati ai sensi dell'art. 2 comma 6 della legge 11 gennaio 2018, n.3, è da considerarsi conosciuto ed accettato in ogni sua parte e che non trovano pertanto applicazione le disposizioni di cui all' art. 1341 e 1342 del Codice Civile	The Parties confirm, for mutual clarity, that this Agreement, drawn up on the basis of the minimum contents identified pursuant to art. 2 paragraph 6 of the law 11 January 2018, n.3, is to be considered known and has been accepted in its entirely and therefore the provisions of Article 1341 and 1342 of the Italian Civil Code will not apply.
La CRO per conto del Promotore Il firmatario autorizzato Dott.ssa Laura Omoboni Firmato digitalmente	**The CRO on behalf of Sponsor** authorized signautory Dr. Laura Omoboni Digitally Signed
Per l'Ente Rappresentante suo delegato Dott. Carlo Bramezza Direttore Generale Firmato digitalmente	**For the Entity** Representative or his/her delegate Dr. Carlo Bramezza Direttore Generale Digitally Signed
Lo Sperimentatore Principale per presa visione e accettazione Dott. Alberto Marangoni firmato digitalmente	The Principal Investigator for acknowledgment and acceptance Mr. Alberto Marangoni Digitally Signed

SCHEDULE A	**ALLEGATO A**
MICURX	**MICURX**
PROTOCOL ID: MRXC-302	**ID PROTOCOLLO: MRXC-302**
//ALBERTO MARANGONI//	**//ALBERTO MARANGONI//**
SITE: //1302//	**CENTRO: //1302//**
SCHEDULE A VERSION: VERSION 1	**VERSIONE ALLEGATO A: VERSIONE 1**
COUNTRY: ITALY	**PAESE: ITALIA**
SCHEDULE A	**ALLEGATO A**
A1 STUDY BUDGET	**A1 BUDGET DELLO STUDIO**
Medpace, as Sponsor's payment agent, shall make payment to the payee specified in the Payee Information Table ("Payee") under this Agreement from funds provided by Sponsor for services provided according to the payment schedule below. All fees listed include overhead, taxes, and subject stipend or travel reimbursement, as applicable. VAT is not applicable	Medpace, in qualità di agente preposto ai pagamenti dello Sponsor, s'impegna ad effettuare i pagamenti a favore del Beneficiario indicato nella Tabella Dati del Beneficiario ("Beneficiario"), così come disposto dalla presente Convenzione, utilizzando i fondi erogati dallo Sponsor per i servizi forniti nel rispetto del prospetto dei pagamenti sottostante. Tutti i corrispettivi indicati includono i costi

because Medpace Clinical Research, LLC is a US-based corporation. Should any changes to VAT law occur during the term of this Agreement, the party legally responsible shall be liable for VAT. Payments are based on electronic case report forms ("eCRFs"), laboratory data, IVRS data or other specific data source. All amounts shown herein are calculated in EUR.	operativi, le imposte e il compenso o il rimborso delle spese di viaggio sostenute dai soggetti, a seconda del caso. L'IVA non è applicabile poiché Medpace Clinical Research, LLC è una società con sede negli Stati Uniti. Qualora la legge sull'IVA venisse modificata durante il periodo di validità della presente Convenzione, la parte giuridicamente responsabile sarà assoggettata all'IVA. I pagamenti si basano sulle schede di raccolta dati elettroniche (eCRF), sui dati di laboratorio, sui dati del sistema interattivo di risposta vocale (IVRS) o su altre specifiche fonti di dati. Tutti gli importi riportati nel presente atto sono espressi in EURO.
A1.1 Fee for Each Evaluable Subject EUR 8,093	**A1.1 Compenso per ciascun soggetto valutabile € 8.093**
An "evaluable subject" is one who has been enrolled (randomized to treatment) and in whom all the applicable terms and conditions of the Protocol and this Agreement have been satisfied. Randomization occurs at Screening.	Si definisce "soggetto valutabile" qualunque individuo arruolato (randomizzato al trattamento) che soddisfi tutti i termini e condizioni applicabili del Protocollo e della presente Convenzione. La randomizzazione avviene allo Screening.
A2 SETUP FEES & VISIT PAYMENTS	**A2 COMPENSI PER LE ATTIVITÀ PRELIMINARI E PAGAMENTI PER LE VISITE**
☑ Please check box if Payee must submit an invoice to Medpace prior to receiving payment. Payment will be made within forty-five (45) days of receipt of invoice.	☑ Spuntare la casella se il Beneficiario è tenuto a presentare una fattura a Medpace prima di ricevere il pagamento. Il pagamento sarà effettuato entro quarantacinque (45) giorni dal ricevimento della fattura.
2.1.1 Pharmacy Set-up Fee EUR 425	***2.1. 1 Compenso di avvio della farmacia € 425***
2.1.2 Non-refundable Administration Set-up Fee EUR 800	***2.1. 2 Costo di avvio amministrativo non rimborsabile € 800***
2.1.3 Monitoring fee – una tantum EUR 1.500 (DGR 1066/2013 all B – Regione Veneto) to be paid at the signing of the agreement	2.1.3 Quota Monitoraggio una tantum EUR 1.500 (DGR 1066/2013 all B – Regione Veneto)da pagarsi alla sottoscrizione del contratto
Payment will be made within forty-five (45) days of:	Il pagamento sarà effettuato entro quarantacinque (45) giorni da:
• Medpace's receipt of the fully executed Agreement.	• Ricevimento da parte di Medpace della Convenzione formalizzata e sottoscritta da entrambe le parti.
A2.2 Ongoing Payments	**A2.2 Pagamenti periodici**

Payments for Study subject visits, as set forth in Table below, will be paid on a quarterly basis for the actual number of Study subjects for whom eCRFs have been completed less ten percent (10%) of each quarterly payment, which will be withheld until and paid with the final payment. Quarterly payments will be made within forty-five (45) days after the end of each quarter. The quarterly schedule may be offset from the calendar quarter.

Tutti i pagamenti per le visite da effettuarsi sui soggetti partecipanti allo Studio, come indicato nella tabella sottostante, saranno corrisposti su base trimestrale per il numero effettivo di soggetti partecipanti allo Studio per i quali siano state compilate le schede eCRF, meno il dieci percento (10%) di ciascun pagamento trimestrale, che sarà trattenuto fino al pagamento finale e corrisposto con esso. I pagamenti trimestrali saranno eseguiti entro quarantacinque (45) giorni successivi la fine di ciascun trimestre. La periodicità trimestrale potrebbe non coincidere con il trimestre solare.

Table 1 – Fees for Completed Clinical Visits for Randomized Subjects

VISIT	FEE
Screening	EUR 1,487.00
Day 1	EUR 1,104.00
Day 5	EUR 815.00
Day 10	EUR 620.00
Day 14	EUR 779.00
Day 17	EUR 501.00
Day 21	EUR 815.00
EOT (D14-28)	EUR 866.00
D35	EUR 650.00
LTFU	EUR 456.00
TOTAL PER PATIENT	**EUR 8,093.00**

Tabella 1 – Compensi per le visite mediche completate per i soggetti randomizzati

VISITA	COMPENSO
Screening	EUR 1,487.00
Giorno 1	EUR 1,104.00
Giorno 5	EUR 815.00
Giorno 10	EUR 620.00
Giorno 14	EUR 779.00
Giorno 17	EUR 501.00
Giorno 21	EUR 815.00
EOT (G14-28)	EUR 866.00
G35	EUR 650.00
Follow-up a lungo termine (LTFU)	EUR 456.00
TOTALE PER PAZIENTE	**EUR 8,093.00**

A2.3 Screen Failures

Table 2 – Screen Failures

VISIT OF FAILURE	COST
Visit Screening	EUR 1,487

Screen failures will be paid per procedure performed once the required number of subject(s) have been enrolled per ratio (2 failures : 1 enrolled) for whom Medpace has received all appropriate documentation of procedures/visits completed. An itemized invoice listing the subject ID number, screen failure date and list of procedures performed with itemized costs must be

A2.3 Screen failure

Tabella 2 – Screen failure

VISITA DI SCREEN FAILURE	COSTO
Visita di screening	€ 1.487

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I pagamenti per i casi di screen failure saranno effettuati per procedura eseguita una volta che il numero richiesto di soggetti è stato arruolato per rapporto (2 failures: 1 enrolled) per i quali Medpace ha ricevuto tutta la documentazione appropriata delle procedure/visite completate. Deve essere presentata una fattura dettagliata che elenchi il numero di identificazione del soggetto, la data dello screen failure e l'elenco delle procedure

submitted. Eligible screen failure payment will be based on the order (by date) of when the subject is consented. Additional screen failures may be payable with prior written approval from Sponsor.	eseguite con i costi dettagliati. Il pagamento per gli screen failure si baserà sull'ordine (per data) di quando il soggetto ha acconsentito. Ulteriori screen failure aggiuntivi potranno essere pagati previa approvazione scritta dello Sponsor.
A2.4 Final Payment	**A2.4 Pagamento finale**
Final payment for all services performed under this Agreement will be paid to Payee by Medpace after:	Medpace corrisponderà al Beneficiario il pagamento finale per tutti i servizi svolti nell'ambito della presente Convenzione dopo:
• Final resolution of all queries;	• Risoluzione definitiva di tutte le query;
• Upon final acceptance of all eCRFs;	• Accettazione definitiva di tutte le schede eCRF;
• The receipt and approval of any outstanding regulatory documents as required by Sponsor;	• Ricevimento e approvazione degli eventuali documenti regolatori mancanti e richiesti dallo Sponsor;
• The return of all unused Study Drug, Study supplies (including any equipment provided by Sponsor) and Confidential Information to Sponsor; and	• Restituzione allo Sponsor di tutti i Farmaci in studio non utilizzati, dei Materiali forniti per lo Studio (incluse le eventuali apparecchiature fornite dallo Sponsor) e delle Informazioni riservate; e
• Upon completion of all other applicable conditions set forth in the Agreement.	• Ottemperanza di tutte le altre condizioni applicabili di cui alla presente Convenzione.
A2.5 Archiving Fee EUR 575	**A2.5 Compenso per archiviazione € 575**
Payable with final payment.	Da corrispondere con il pagamento finale.
A3 INVOICEABLE ITEMS	**A3 VOCI FATTURABILI**
Payment will be made within forty-five (45) days of receipt of invoice and supporting documentation if applicable and requested.	Il pagamento sarà effettuato entro quarantacinque (45) giorni dal ricevimento della fattura e della relativa documentazione, ove pertinente e richiesto.
A3.1 Additional Subject Procedures	**A3.1 Procedure aggiuntive dei soggetti**

Table 3 – Unitized Procedures

FEES	COST	UNIT (IF APPLICABLE)
Study Drug IV Infusion and Pharmacy Dispensing	EUR 174	For IV infusions beyond the first required infusion
Study Drug Oral Pharmacy Dispensing	EUR 32	For all oral study drug dispensing
Foot X-Ray	EUR 74	At screening and EOT
Probe to Bone	EUR 27	At screening

Tabella 3 – Procedure unitarie

COMPENSI	COSTO	UNITÀ (SE APPLICABILE)
Infusione EV del farmaco dello studio e relative dispensazioni della farmacia	€ 174	Per le infusioni EV oltre la prima infusione richiesta
Dispensazione del farmaco dello studio orale da parte della farmacia	€ 32	Per tutte le dispensazione del farmaco dello studio orale
Radiografia del piede	€ 74	Durante lo screening, e a EOT
Test sonda-osso	€ 27	Durante lo screening,

Table 4 – Laboratory Procedures

FEES	COST	UNIT (IF APPLICABLE)
Blood Cultures	EUR 13	Invoiceable if clinically indicated beyond Screening. Procedure is included in the Screening visit cost.
DFI Specimen Gram Stain and Culture	EUR 85	Invoiceable if clinically indicated beyond Screening. Procedure is included in the Screening visit cost.
Single Drug Level PK Collection and Handling	EUR 57	If applicable at site, each timepoint

Tabella 4 – Procedure di laboratorio

COMPENSI	COSTO	UNITÀ (SE APPLICABILE)
Emocolture	€ 13	Fatturabile se clinicamente indicato, oltre lo Screening. La procedura è inclusa nel costo della Visita di screening.
Colorazione e coltura di Gram del campione DFI	€ 85	Fatturabile se clinicamente indicato, oltre lo Screening. La procedura è inclusa nel costo della Visita di screening.
Raccolta e trattamento PK a livello di singolo farmaco	€ 57	Se applicabile presso il centro, ogni punto temporale

A3.2 Additional Study-necessitated Fees

Payee will be reimbursed at actual cost for any other unforeseen but reasonable procedures or costs necessitated by the Study or Protocol (and any amendments thereto) and pre-approved by Medpace/Sponsor.

A3.2 Ulteriori compensi necessari ai fini dello Studio

Il Beneficiario sarà rimborsato in base ai costi effettivamente sostenuti per eventuali altre procedure o spese ragionevoli impreviste richieste dallo studio o dal protocollo (e da qualunque emendamento dei medesimi) e preventivamente approvate da Medpace/dallo Sponsor.

A3.3 Nominal equipment

Entity may be provided during the course of the Study small items of equipment necessitated by the Study or Protocol and pre-approved by Medpace/Sponsor.

A3.3 Apparecchiature di valore nominale

Durante il corso dello Studio, all'Ente potranno essere fornite piccole apparecchiature necessarie ai fini dello

	Studio o del Protocollo e preventivamente approvate da Medpace/dallo Sponsor.
A4 MEDPACE RIGHTS	**A4 DIRITTI DI MEDPACE**
Medpace reserves the right to suspend payments due to Payee, if Principal Investigator and/or Institution do not complete data entry, query resolutions, and electronic signatures on eCRFs and/or provide regulatory documents to Medpace within timelines defined by the project team. Payments will resume once the missing or incomplete information is resolved.	Medpace si riserva il diritto di sospendere i pagamenti dovuti al Beneficiario nel caso in cui lo Sperimentatore principale e/o l'Istituto non completino l'inserimento dei dati, le risoluzioni delle query e le firme elettroniche sulle eCRF e/o non forniscano a Medpace i documenti regolatori entro i termini definiti dall'equipe del progetto. I pagamenti riprenderanno una volta fornite le informazioni mancanti o incomplete.
A5 MEDPACE INVOICING	**A5 FATTURAZIONE A MEDPACE**
All payment inquiries and invoices submitted shall include the Protocol number and Principal Investigator name and be sent to the following:	Tutte le richieste relative ai pagamenti e le fatture devono riportare il numero di Protocollo e il nome dello Sperimentatore principale ed essere inviate a:
Email: siteinvoices@medpace.com Phone: 513-579-9911 **Medpace Clinical Research, LLC** Attn: Clinical Operations Site Payments 5375 Medpace Way Cincinnati, Ohio 45227 All invoices must be submitted to Medpace within ninety (90) days of occurrence or up to thirty (30) days after receipt of the final payment.	E-mail: siteinvoices@medpace.com Telefono: +1-513-579-9911 **Medpace Clinical Research, LLC** Attn: Clinical Operations Site Payments 5375 Medpace Way Cincinnati, Ohio 45227 Stati Uniti Tutte le fatture devono essere presentate a Medpace entro novanta (90) giorni dall'emissione o entro e non oltre trenta (30) giorni successivi dal ricevimento del pagamento finale.
A6 PAYEE INFORMATION	**A6 DATI DEL BENEFICIARIO**
All payments made by Medpace as set forth herein shall be payable solely to Payee at the address set forth below. Any such payments which are due to any other party performing services in connection with the Study shall be a matter solely between Payee and such party.	Tutti i pagamenti effettuati da Medpace, come indicato nella presente Convenzione, saranno corrisposti esclusivamente al Beneficiario presso l'indirizzo indicato di seguito. Gli eventuali pagamenti dovuti a qualunque altra parte che offre servizi connessi con lo studio devono essere gestiti esclusivamente tra il Beneficiario e la parte interessata.

Table 5 - For sites receiving payment by foreign wire transfer

PAYEE INFORMATION	
Beneficiary Name	A.ULSS 7 PEDEMONTANA
Payee Mailing Address	VIA DEI LOTTI, N. 40 – 36061 BASSANO DEL GRAPPA (VI)
Contact Name	Nucleo Ricerca Clinica
Email Address	nucleoricercaclinica@aulss7.veneto.it
Bank	UNICREDIT BANCA SPA
Account №	000040458253
IBAN №	T44J0200860165000040458253
BIC Code/Swift Code	UNCRITM1M62
Transit № (Canada)	
IFSC Code (India)	
Tax ID#**	00913430245

**Requested for Medpace Accounting tracking purposes only

Tabella 5 – Per i centri che ricevono il pagamento a mezzo bonifico bancario estero

DATI DEL BENEFICIARIO	
Nome del beneficiario	A.ULSS 7 PEDEMONTANA
Indirizzo postale del beneficiario	VIA DEI LOTTI, N. 40 – 36061 BASSANO DEL GRAPPA (VI)
Nome del contatto	Nucleo Ricerca Clinica
Indirizzo e-mail	nucleoricercaclinica@aulss7.veneto.it
Banca	UNICREDIT BANCA SPA
Numero di conto corrente	000040458253
Codice IBAN	IT44J0200860165000040458253
Codice BIC/Swift	UNCRITM1M62
Transit number (Canada)	
Codice IFSC (Codice del sistema finanziario indiano) (India)	
Codice fiscale n.**	00913430245

**Richiesto al solo scopo di tracciatura da parte del sistema contabile di Medpace

ALLEGATO B – GLOSSARIO RELATIVO ALLA PROTEZIONE DEI DATI PERSONALI (terminologia riferita al GDPR – Reg. UE n. 2016/679 – ed alle norme attuative italiane)	ANNEX B - GLOSSARY RELATING TO THE PROTECTION OF PERSONAL DATA (terminology referring to the GDPR - UE Reg. n. 2016/679 - ad to the Italian implementing rules)
• **Dato personale** - qualsiasi informazione riguardante una persona fisica identificata o identificabile (l'"Interessato"); si considera identificabile la persona fisica che può essere identificata, direttamente o indirettamente, con particolare riferimento a un identificativo come il nome, un numero di identificazione, dati relativi all'ubicazione, un identificativo online o a uno o più elementi caratteristici della sua identità fisica, fisiologica, genetica, psichica, economica, culturale o sociale;	• **Personal Data** - any information relating to an identified, or identifiable, natural person (the "Data Subject"). An identifiable natural person is a person who can be identified directly or indirectly using an identifier such as: a name, an identification number, location data, an online identifier or one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of the individual;
• **Trattamento** - qualsiasi operazione o insieme di operazioni, compiute con o senza l'ausilio di processi automatizzati e applicate a dati personali o insiemi di dati personali, come la raccolta, la registrazione, l'organizzazione, la strutturazione, la conservazione, l'adattamento o la modifica, l'estrazione, la consultazione, l'uso, la comunicazione mediante trasmissione, diffusione o qualsiasi altra forma di messa a disposizione, il raffronto o l'interconnessione, la limitazione, la cancellazione o la distruzione;	• **Processing** - any operation or set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organization, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction;
• **Pseudonimizzazione** - il trattamento dei dati personali tale che i dati non possano più essere attribuiti a un interessato specifico senza l'utilizzo di informazioni aggiuntive, a condizione che tali informazioni aggiuntive siano conservate separatamente e soggette a misure tecniche e organizzative intese a garantire che tali dati personali non siano attribuiti a una persona fisica identificata o identificabile;	• **Pseudonymisation** - the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable individual;

• **Interessato** – la persona fisica cui si riferiscono i dati personali (art. 4 n.1 GDPR);	• **Data Subject -** the natural person to whom the personal data refer (art. 4 n.1 GDPR);
• **Titolare del trattamento** - la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che, singolarmente o insieme ad altri, determina le finalità e i mezzi del trattamento di dati personali; quando le finalità e i mezzi di tale trattamento sono determinati dal diritto dell'Unione o degli Stati membri, il titolare del trattamento o i criteri specifici applicabili alla sua designazione possono essere stabiliti dal diritto dell'Unione o degli Stati membri (art. 4 n. 7 GDPR);	• **Data Controller** - the natural or legal person, public authority, agency or any other entity which, alone or jointly with others, determines the purposes and means of the processing of personal data; where the purposes and means of such processing are determined by Union or member State law, the controller or the specific criteria for its nomination may be provided for by Union or member State law (art. 4 n. 7 GDPR) ;
• **Responsabile del trattamento** - la persona fisica o giuridica, l'autorità pubblica, il servizio o altro organismo che tratta dati personali per conto del Titolare del Trattamento;	• **Data Processor** - a natural or legal person, public authority, agency or other body which processes personal data on behalf of the data controller;
• **Altri soggetti che trattano dati personali** – le persone autorizzate al trattamento dei dati personali sotto l'autorità diretta del Titolare o del Responsabile (artt. 28, n. 3, lettera b, 29 e 32, n. 4 GDPR), ivi incluse quindi le persone fisiche alle quali il Titolare o il Responsabile abbiano attribuito specifici compiti e funzioni connessi al trattamento, che operano sotto l'autorità del Titolare e nell'ambito dell'assetto organizzativo, ai sensi dell'art. 2 quaterdecies del D.lgs . 196/2003 così come modificato dal D.Lgs. 101/2018;	• **Other Subjects processing personal data** - persons authorized to process personal data under the direct authority of the Data Controller or the Data Processor (art. 28, n. 3, letter b, 29 and 32, n. 4 GDPR), including therefore the natural persons to whom the Data Controller or the Data Processon has assigned specific tasks and functions related to the processing, who operate under the Data Controller's authority and within the organizational structure, pursuant to art. 2 quaterdecies " of Legislative Decree 196/2003 as amended by Legislative Decree 101/2018;
• **Consenso dell'interessato** - qualsiasi manifestazione di volontà libera, specifica, informata e inequivocabile dell'interessato, con la quale lo stesso manifesta il proprio assenso, mediante dichiarazione o azione positiva inequivocabile, che i dati personali che lo riguardano siano oggetto di trattamento;	• **Consent of the Data Subject** - any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her;
• **Violazione dei dati personali** - la violazione di sicurezza che comporta accidentalmente o in modo illecito la	• **Personal Data Breach** - any breach of security leading to the accidental or unlawful destruction, loss, alteration,

distruzione, la perdita, la modifica, la divulgazione non autorizzata o l'accesso ai dati personali trasmessi, conservati o comunque trattati;	unauthorized disclosure, or access to, personal data transmitted, stored or otherwise processed;
• **Dati relativi alla salute** - i dati personali attinenti alla salute fisica o mentale di una persona fisica, compresa la prestazione di servizi di assistenza sanitaria, che rivelano informazioni relative al suo stato di salute;	• **Medical Data** - personal data pertaining to the physical or mental health of an individual including the provision of medical services, which may reveal information about his or her state of health;
• **Dati genetici** - i dati personali relativi alle caratteristiche genetiche ereditarie o acquisite di una persona fisica che forniscono informazioni univoche sulla fisiologia o sulla salute di detta persona fisica, e che risultano in particolare dall'analisi di un campione biologico della persona fisica in questione;	• **Genetic data** - personal data relating to the hereditary genetic or acquired characteristics of an individual which provides unequivocal information about the physiology or health of that individual and which results, in particular, from the testing of a biological sample from the individual in question;
• **Campione biologico** - ogni campione di materiale biologico da cui possano essere estratti dati genetici caratteristici di un individuo;	• **Biological sample** - any sample of biological material from which the characteristic genetic data of an individual can be extracted;
• **Sponsor/Promotore** - la persona, società, istituzione oppure organismo che si assume la responsabilità di avviare, gestire e/o finanziare una sperimentazione clinica;	• **Sponsor/Promoter** - the person, company, institution or body that is responsible for starting, managing and/or funding a clinical trial;
• **CRO** – organizzazione di ricerca a Contratto alla quale lo sponsor può affidare una parte o tutte le proprie competenze in tema di sperimentazione clinica;	• **CRO** – the contractual research organisation to which the sponsor may entrust all or part of its competencies relating to clinical trials;
• **Monitor** – il responsabile del monitoraggio della Sperimentazione individuato dallo sponsor/CRO;	• **Monitor** – the party responsible for monitoring the Trial, appointed by the sponsor/CRO;
• **Auditor** – il responsabile della esecuzione della verifica sulla conduzione della Sperimentazione, come parte integrante della assicurazione di qualità, individuato dallo sponsor/CRO.	• **Auditor** – the party responsible for auditing the conduct of the Trial as an integral part of quality assurance, appointed by the sponsor/CRO.