Protocol: PJI001-02

A Phase 2, Double-Blind, Randomized, Multicenter, Parallel, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of TNP-2092 to Treat Acute Bacterial Skin and Skin Structure Infection in Adults

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TITLE PAGE

PROTOCOL TITLE: A PHASE 2, DOUBLE-BLIND, RANDOMIZED, MULTICENTER, PARALLEL, CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF TNP-2092 TO TREAT ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION IN ADULTS

Protocol Number: PJI001-02

Amendment Number: 1

Compound Number: TNP-2092

Study Phase: 2

Short Title: Safety, Tolerability, Pharmacokinetics, and Efficacy of TNP-2092 to Treat Acute Bacterial Skin and Skin Structure Infection

Sponsor Name: **TenNor Therapeutics Limited**

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Sponsor Signatory:

CCI [redacted]	Date
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INVESTIGATOR SIGNATURE PAGE

Protocol Title: Phase 2, Double-Blind, Randomized, Multicenter, Parallel, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of TNP-2092 to Treat Acute Bacterial Skin and Skin Structure Infection in Adults

Signature of Investigator	Date

MEDICAL MONITOR NAME AND CONTACT INFORMATION

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Amendment	Date
Amendment 1	14 February 2019

Amendment 1 Approval Date (14 February 2019)

The TNP-2092 IV 450 mg dose was omitted from the original protocol and the randomization scheme was revised from 1:1:1 to 2:1 TNP-2092 (300 mg) IV versus vancomycin (1g) IV to reflect the change. This change was made to comply with an FDA request. Moreover, clarification on the timing and type of physical examinations and laboratory tests was made and typographical errors were corrected. Use of the local and central laboratories was clarified and a list of prohibited medications was provided.

A description of substantive changes to the protocol are presented as follows:

Section No. and Name	Description of Change	Brief Rationale
1.1 Synopsis	Dose and randomization changed in Table 1 and Table 2	Match current study design
1.2 Schema	Figure 2 revised to remove one treatment arm	Dose omitted
1.3 Schedule of Activities	Activity schedule and footnotes revised	Update table and section numbers, and match study conduct
3 Objectives and Endpoints	Table 4 omitted, hyperlink added to Table 1, and subsequent table numbers changed to reflect omission	Remove redundant table
4.1 Overall Design	Dose omitted and 2:1 randomization added, omitted table, hyperlink added to identical table,	To match current study design and remove redundant table
4.2 Scientific Rationale …	Dose omitted	Match dose regimen
4.3 Justification for Dose	Dose omitted and added nonclinical data	Match dose regimen and provide support for dose regimen
4.3.2 Clinical Data	One treatment arm removed	Match dose regimen
5.1 Inclusion Criteria	Inclusion criteria (#3) revised	Describe skin lesion measurement and clarify surgical procedures.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added exclusion criteria (Section 5.2) for body mass index ≥30 kg/m^2 (#1), list prohibited concomitant medications (#13), modified liver test criteria (#6) and added contraindications for fluoroquinolone use specified (#8), and deleted lesion description (former #10p)	To refine patient population
6.1 Study Interventions Administered	2:1 randomization added, treatment arms revised, drug product storage clarification. Table 5 omitted, hyperlink added to Table 2, and subsequent table changed numbers to reflect omission	Match current study design, clarify the duration of drug product storage, and remove redundant table
6.4 Measures to Minimize Bias	2:1 randomization added	Match current study design
6.6.2 Prohibited Medications	Text to add prohibited medications modified	Match text from prescribing information for approved fluoroquinolone (moxifloxacin) and rifamycin (rifampin)
6.6.3 Adjunctive Therapy	Text for surgical interventions added	Clarify use of surgical intervention
6.6.4 Rescue Medication	Text for rescue medication and premature discontinuation of study intervention added	Clarify use of rescue medications
8.2.1 Physical Examinations	Day 1 exam omitted	Clarify timing of exam
8.2.4 Clinical Safety Laboratory Assessments	Text for central and local laboratory assessment separated	Clarify use of local and central laboratory assessments
8.4.1 Clinical Response and Table 8 (now Table 6)	"No baseline gram-positive organisms for treatment of ABSSSI" statement deleted	Statement untrue
8.4.2 Microbiologic Evaluation	Text regarding cellulitis added	Clarify tissue collection from cellulitis lesions
8.6 Pharmacokinetics	One treatment arm omitted	Dose omitted
9.0 Statistical Considerations	One treatment arm omitted	Dose omitted
9.2 Sample Size Determination	New responder rate calculation added for randomization	Randomization changed
9.6 Safety Analyses	One treatment arm omitted	Dose omitted
9.8 Pharmacokinetic Analyses	One treatment arm omitted	Dose omitted

Section # and Name	Description of Change	Brief Rationale
9.9 Handling of Dropouts…	"No baseline gram-positive organisms for treatment of ABSSSI" statement deleted	Statement untrue
10.2 Clinical Laboratory Tests	Table 11: HIV testing deleted; allowed urine and serum pregnancy test type, and added measurement of haptoglobin	Clarify laboratory assessments including HIV and pregnancy, and added haptoglobin measurements
10.4 Prohibited Medications	Added new section with table of prohibited medications (Table 20)	Response to request for new Exclusion Criteria #13
10.5 Pharmacokinetic Sample… (previously Section 10.4)	One treatment arm omitted	Treatment arm and dose omitted
10.6 List of Abbreviations	Revised abbreviations list	Match protocol abbreviations
10.7 Contraceptive Guidance and ….	Pregnancy Report Form used to follow-up pregnancy outcome.	Clarify where pregnancy outcome should be documented
11 References	Prescribing information for moxifloxacin (2016) added and prescribing information for rifampin updated (2019)	Needed in response to prohibited concomitant medications list

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Double-Blind, Randomized, Multicenter, Parallel, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of TNP-2092 to Treat Acute Bacterial Skin and Skin Structure Infection in Adults

Short Title: Safety, Tolerability, Pharmacokinetics and Efficacy of TNP-2092 to Treat Acute Bacterial Skin and Skin Structure Infection

Rationale:

Antibiotic resistance poses a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared toward discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains. Additional novel antibiotic choices are needed to treat bacterial infections suspected or confirmed to be caused by antibiotic-resistant, gram-positive pathogens (eg, methicillin-resistant *Staphylococcus aureus* [MRSA]).

TNP-2092 is being developed for the treatment of serious or life-threatening bacterial infections including those caused by gram-positive pathogens that have developed or acquired resistance to commonly used antibiotics. CCI

[redacted]

TNP-2092 is predicted to be efficacious against acute bacterial skin and skin structure infections (ABSSSI) suspected or confirmed to be caused by antibiotic resistant gram-positive pathogens, and biofilm-associated foreign body infections, including those medicated by multidrug-resistant pathogens.

Objectives and Endpoints:

This is the first study in which TNP-2092 is administered to participants with ABSSSI suspected or confirmed to be caused by gram-positive pathogens. Safety and tolerability will be the primary objectives of this study, pharmacokinetics (PK) and efficacy will comprise secondary objectives. The objectives and endpoints are presented in Table 1.

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of TNP-2092 300 mg q12h and vancomycin 1g q12h	• Incidence, causality, and severity of AEs • Investigator assessment of thrombotic events and local infusion site reactions and tolerability (Table 18) • Assessment of vital signs, laboratory data, and ECG findings
Secondary	
To determine the PK of TNP-2092 300 mg q12h	Primary PK parameters will be calculated from concentration versus time data with noncompartmental techniques. PK parameters include C_{max}, t_{max}, AUC_{0-12}, and CL (after last dose)
To evaluate the efficacy of TNP-2092 300 mg q12h and vancomycin 1 g q12h	• Evaluate the programmatic clinical response of TNP-2092 and vancomycin at EA visit (48 to 72 hours after the first dose of study intervention) in the ITT, mITT, and micro-ITT populations • Evaluate per participant microbiological response at PTE in the micro-ITT and ME-PTE populations • Evaluate per pathogen microbiological response at PTE in the micro-ITT and ME-PTE populations • Evaluate the investigator's assessment of clinical response at EOIV, EOT, and PTE visits in the mITT, micro-ITT and CE populations (CE-EOIV, CE-EOT, and CE-PTE, as appropriate)

AE = adverse event; AUC_{0-12} = area under the curve versus time from 0 to 12 hours; CE = clinically evaluable; CL = clearance; C_{max} = maximum concentration; EA = early assessment; ECG = electrocardiogram; EOIV = end of IV; EOT = end of treatment; IV = intravenous; ITT = intent-to-treat; LTFU = long-term follow-up; ME = microbiologically evaluable; mITT = modified intent-to-treat; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetics; PTE = posttreatment evaluation; q12h = every 12 hours; t_{max} = time to maximal concentration

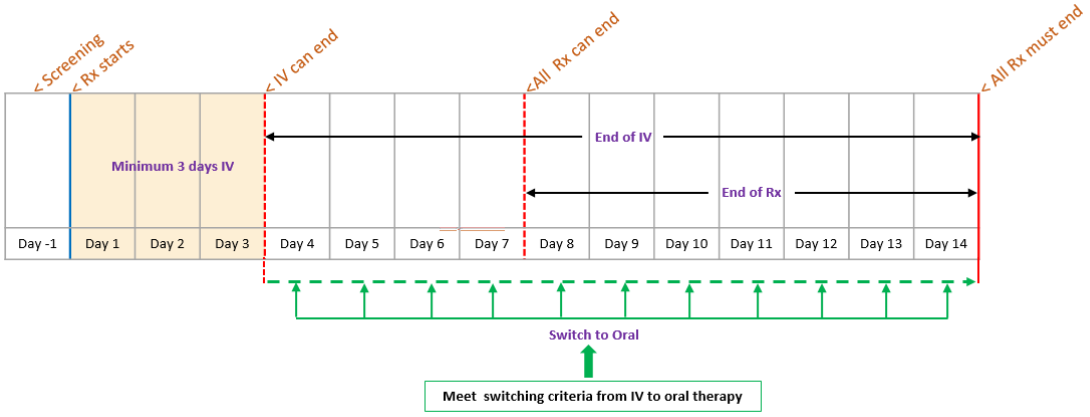
Detailed schedules of study assessments and PK collection time points are provided in Section 1.3 and Section 10.5, respectively.

Overall Design:

This Phase 2, double-blind, randomized, multicenter, parallel, controlled study will be conducted to evaluate safety, tolerability, PK, and efficacy of TNP-2092 300 mg IV q12h and vancomycin 1 g IV q12h in adults with ABSSSI suspected or confirmed to be caused by gram-positive pathogens. The entire duration of the treatment period (IV or IV plus oral switch, if applicable) is a minimum of 7 days and a maximum of 14 days as presented in Figure 1.

All participants will be treated with IV study intervention for a minimum of 3 days (6 doses).

Figure 1 Overview of Treatment Duration



IV = intravenous; Rx = treatment

Note: The duration of the treatment period (IV or IV plus oral switch, if applicable) is a minimum of 7 days and a maximum of 14 days. Participants will be treated with IV study intervention for a minimum of 3 days (6 doses). Upon meeting protocol-specified switching criteria (Section 6.2), participants will continue treatment of ABSSSI with a commercially-available, open-label, oral antibiotic selected by the investigator.

Upon meeting protocol-specified switching criteria (Section 6.2), participants will continue treatment of ABSSSI with a commercially-available, open-label, oral antibiotic selected by the investigator. An overview of the study design is presented in Section 4 and the Schedule of Activities is presented in Section 1.3.

Eligible participants will be randomized (2:1) to 1 of 2 treatment arms: TNP-2092 300 mg IV q12h or vancomycin 1 g IV q12h. Randomization will be stratified by ABSSSI types to ensure proper balance between treatment arms. The types of eligible ABSSSI include cellulitis/erysipelas, wound infections, and major cutaneous abscesses; however, participants with major cutaneous abscess should not comprise >30% of randomized population. Participants with a minimum ABSSSI lesion surface area of 75 cm^2 will be enrolled. No prior systemic antibiotic treatment is permitted before enrollment in the study, and no other concomitant systemic or topical antibiotics are permitted during the study. If a participant enrolls and is subsequently found to have a gram-negative bacterial infection, they will remain in the study but may be switched to another antibiotic as appropriate. Participants will not be replaced.

An adequate local ABSSSI site specimen must be collected from all participants with non-cellulitis ABSSSI for microbiologic evaluation at baseline. Local ABSSSI site specimens and blood cultures from 2 separate venipuncture sites, will be collected from all participants before administration of study intervention, whenever possible. All local ABSSSI site specimens will undergo Gram-stain and culture at the local laboratory and all blood cultures will be processed at the local laboratory. Specimens should be

processed according to standard recognized methods. All bacteria isolated from an adequate local ABSSSI site specimen or blood culture at the local laboratory will be sent to a designated central laboratory for confirmation of species identification and antimicrobial susceptibility testing. Microbiologic methods are described in Section 8.4.2 and more details are presented in the laboratory manual.

If local antimicrobial susceptibility testing of a baseline pathogen indicates possible non-susceptibility to study intervention (eg, intermediate susceptibility or resistance to a fluoroquinolone, rifamycin, and/or glycopeptide) but the participant is stable or clinically improving, the participant should remain on study intervention at the investigator's discretion. In these cases, the investigator should discuss each situation with the medical monitor before discontinuation from study intervention.

Screening assessments to determine study eligibility will be performed within 1 day before the first dose of study intervention is administered. Intravenous study intervention may be administered in a hospital or outpatient infusion center; outpatient administration of IV study intervention is limited to participants who are clinically stable and have adequate home support with reliable transportation to and from the hospital or clinic, as described in the Pharmacy Manual.

Day 1 is the first day of study intervention; subsequent study days are consecutive calendar days. For purposes of analysis, study assessments will be performed during the treatment period on Day 1, Day 2, at early assessment (EA) 48 to 72 hours after IV treatment is started, at end of IV (EOIV, 3 to 14 days after IV treatment is started) at end of treatment (EOT, after a minimum of 7 days up to 14 days of intervention, IV or IV plus oral switch, if applicable), at posttreatment evaluation (PTE, 7 to 14 days after EOT), and at long-term follow-up (LTFU, 20 to 25 days after EOT) (Figure 2).

The primary endpoint is assessment of safety and tolerability: incidence of adverse events (AEs), vital signs laboratory data, and ECG findings, and a qualitative assessment of local tolerability (including local infusion site reaction and thrombotic events) measured throughout the study. Secondary endpoints comprise PK (first dose and at EOIV treatment) and efficacy assessments (programmatic clinical response at EA aligns with the current FDA guidance [2013]). Secondary efficacy endpoints also include the investigator assessments of clinical response at designated timepoints and microbiological responses at PTE.

Number of Participants:

This protocol plans to enroll 120 participants who meet study entry criteria who will be randomly assigned to 1 of 2 treatment arms in a 2:1 ratio as presented in Table 2. A sample size of 80 participants who receive TNP-2092 is deemed sufficient to provide an initial assessment of safety and PK data to inform the future development of TNP-2092.

Intervention Arms and Duration:

The total duration of the study is up to 40 days from the screening visit to the LTFU. The screening period will be up to 1 day in duration before intervention, followed by a

treatment period of up to 14 days with at least 3 days (6 doses) of IV intervention and a minimum of 7 days and up to 14 days of treatment, a PTE visit 7 to 14 days after the EOT, and a LTFU visit comprising a telephone call, 20 to 25 days after the EOT to monitor continuing AEs and concomitant medications (Figure 2).

The 2 treatment arms are presented in Table 2.

Table 2 Treatment Arms

Arm	Study Intervention, Dose, Duration	Assigned Treatment Intervention Concentration	Planned Number of Participants
A	TNP-2092 300 mg IV q12h Day 1 up to Day 14 (at least 3 days [6 doses] required)	TNP-2092 (lyophilized red orange powder) 300 mg in 200 mL D5W (1.5 mg/mL) for IV infusion	80
B	Vancomycin 1 g IV q12h, Day 1 up to Day 14 (at least 3 days [6 doses] required)	Vancomycin 1 g in 200 mL D5W (5 mg/mL) for IV infusion	40

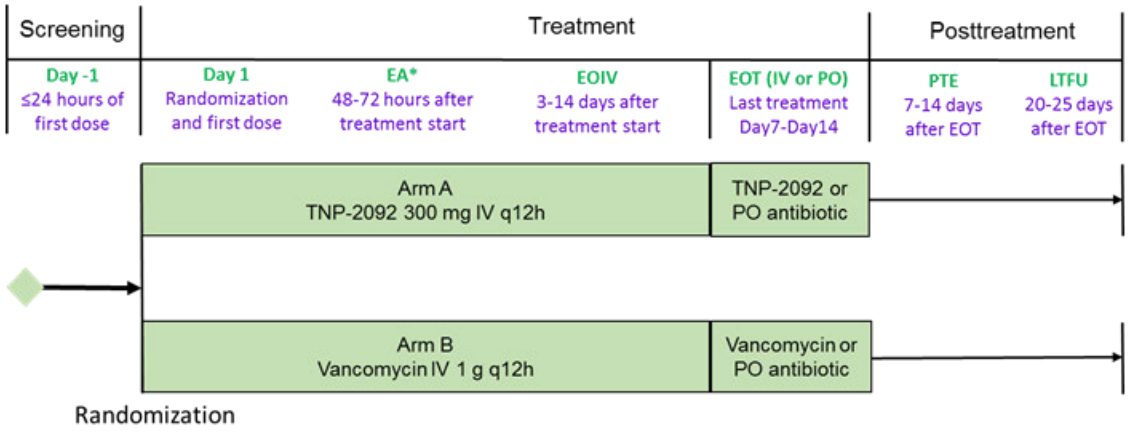
IV = intravenous; q12h = every 12 hours

The treatment period can comprise IV treatment exclusively or a combination of IV plus oral switch treatment for a minimum of 7 days and up to 14 days of treatment. A switch from IV to oral open-label antibiotic treatment is permitted after at least 3 days (6 doses) of IV study intervention provided oral switch criteria and procedures are met (Section 6.2).

1.2 Schema

An overview of the study design is presented in Figure 2.

Figure 2 Overview of Study Design



EA = early assessment; EOIV = end of IV treatment; EOT = end of treatment; IV = intravenous; LTFU = long-term follow-up; PO = oral; PTE = posttreatment evaluation; q12h = every 12 hours
Note: Participants receive a minimum of 3 days (72 hours, 6 doses) of IV study intervention. After 72 hours, participants may begin oral antibiotic treatment upon meeting protocol-specified criteria (Section 6.2).
*EA (48 to 72 hours after start of first dose of IV intervention) and EOIV (at least 72 hours, 6 doses after start of first dose of IV intervention) may occur simultaneously. EOT may be any day after at least 7 days of treatment initiation up to 14 days after treatment initiation.

1.3 Schedule of Activities

A Schedule of Activities is presented in Table 3.

Table 3 Schedule of Activities

Study Visit	Screening [a]	Intravenous plus Oral Treatment Period [b]					PTE [d]	LTFU [e]
	Day -1	Day 1[b]	Day 2	EA [c] After 48 to 72 h	EOIV (+ 1) After 72 h up to Day 14	EOT [c] (+ 1) ≥ Day 7 up to Day 14	7 to 14 Days after EOT	20 to 25 Days after EOT
Informed consent, demographics, medical/surgical history, inclusion/exclusion criteria, CrCl [f,g]	X							
Randomization [h]		X						
Prior/concomitant medications [i]	X	X	X	X	X	X	X	X
Physical exam/focused physical exam [j]	X		X	X	X	X	X	
Vital signs [k]	X	X	X	X	X	X	X	
12-lead ECG [l]	X			X		X	X	
Serum or urine pregnancy test [m]	X					X		
Assess primary ABSSSI site [n]	X	X	X	X	X	X	X	
Investigator assessment of clinical response [o]					X	X	X	
Hematology/chemistry/urinalysis [p]	X	X	X	X	X	X	X	
Administer study intervention up to 14 days [q]		X						
ABSSSI specimen, Gram-stain and culture, blood cultures [r,s]	X	(X)	(X)	(X)	(X)	(X)	(X)	
Record procedures (I&D) [t]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
PK sample collection [u]		X			X			
Thrombotic and local infusion site reaction AE assessments		X	X	X	X			
Adverse Events	X	X	X	X	X	X	X	X

AEs = adverse events,β-HCG = beta-human chorionic gonadotropin; BP = blood pressure; CrCl = creatinine clearance; EA = early assessment; ECG = electrocardiogram; EOIV = end of IV assessment; EOT = end of treatment; HR = heart rate; I&D = incision and drainage; IV = intravenous; IWRS = interactive web response system; LTFU = long-term follow-up; PK = pharmacokinetic: PTE = posttreatment evaluation; SAE = serious adverse event

a Screening assessments for study eligibility will occur within 1 day of the administration of the first dose of study intervention.

b Day 1 is the first day for administration of IV study intervention and subsequent days are calendar days. Participants will receive IV infusion at the hospital or clinic for a minimum of 3 days (6 doses) based on the investigator's clinical judgment and after switching criteria are met (Section 6.2). The duration of the treatment period (IV or IV plus oral switch, if applicable) is a minimum of 7 days and a maximum of 14 days.

c EA assessments will be performed 48 to 72 hours after the start of the first dose of IV study intervention. EOT assessments will be performed on the last calendar day of study intervention (IV or IV plus oral switch, if applicable). Participants who prematurely discontinue study intervention or withdraw from the study before EOT should have all EOT assessments performed on the day of withdrawal (+ 1 day).

d Participants will attend the PTE 7 to 14 days after the EOT for collection of safety and efficacy data (clinical and microbiological response [Section 8.4.1 and Section 8.4.2]) .

e Telephone contact will be made between 20 to 25 days after the EOT for participants who do not have symptoms of clinical relapse, ongoing AEs, new or ongoing SAEs, or laboratory abnormalities that require the attention of a healthcare provider at the clinic or hospital. Participants who fit into any of these listed categories will go to the clinic or hospital.

f Written, informed consent must be obtained before any nonstandard of care screening assessments are performed.(Section 10.1.4)

g CrCl will be calculated according to Cockcroft-Gault (Section 10.1.12). Participants with CrCl < 30 mL/minute will be excluded from the study.

h All inclusion and exclusion criteria need to be met before randomization on Day 1. All participants will be centrally assigned to randomized study intervention via IWRS (Section 6.4)

i All prior medications taken within 2 weeks before randomization will be recorded. All concomitant medications taken between Day 1 and EOT will be recorded to LTFU (Section 6.6).

j A complete physical examination (ie, general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest [heart, lungs], abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, lymph nodes) and height (screening only) and weight will be performed at screening, EOIV, EOT, and PTE (Section 8.2.1). Focused physical examinations (chest [heart, lungs], abdomen, skin, neurological and musculoskeletal examinations) are performed on Day 2, EA, and each subsequent day that IV treatment is administered but not including EOIV.

k Vital signs comprises temperature [oral], pulse rate, respiratory rate, and blood pressure performed at all visits except LTFU (Section 8.2.2).

l ECGs will be performed in triplicate within a 15-minute period at screening, EA, EOT, and PTE (Section 8.2.3).

m Female participants of childbearing potential (< 2 years after menopause and not permanently sterile) must have a β-HCG pregnancy test at baseline and EOT (Section 8.3.5)

n Direct evaluation of the primary ABSSSI site includes an assessment of the extent of infection as measured with a ruler (longest length by greatest perpendicular width) and an assessment of local signs and symptoms (Section 8.4.1).

o The investigator's assessment of clinical response is defined in Table 6.

p Laboratory assessments including hematology, coagulation, serum chemistry, and urinalysis testing will be performed to collect safety data at all visits except LTFU. Screening/baseline test samples will be collected and sent to local laboratory (to confirm eligibility) and central laboratory (screening and subsequent testing) (Section 8.2.4, Section 10.2, and Table 11).

q On Day 1, the first dose of study intervention should be administered as quickly as possible after eligibility criteria are met. Participants receive an IV infusion over 60 minutes q12h for a minimum of 3 days (6 doses) followed by a switch to a commercially-available, oral antibiotic (criteria described in Section 6.2) for the remainder of the intervention, minimum 7 to 14 days total.

r Obtain appropriate ABSSSI site specimens from all subjects at screening and perform gram-stain and culture at the local laboratory The ABSSSI site specimen should be obtained before administration of antibacterial therapy, whenever possible. Repeat testing is only required (X) if a previous culture was reported as positive, if clinically indicated, or if the participant is deemed a clinical failure (Section 8.4.1 and Section 8.4.2).

s. Two sets of blood cultures (each set comprises 1 aerobic and 1 anaerobic tube from 2 separate venipuncture sites, for a total of 4 tubes) will be collected from all participants at screening. The blood cultures should be obtained before administration of antibacterial therapy, whenever possible. Repeat testing is only required (X) if a previous blood culture was reported as positive, if clinically indicated, or if the participant is deemed a clinical failure (Section 8.4.1 and Section 8.4.2).

t If required, surgical procedures to treat ABSSSI (eg, I&D) should be performed, before the first dose of study intervention up to 24 hours (Day 2) after the first dose of study intervention. After Day 2, surgical intervention will be captured (X); however, subject evaluability in analysis populations may be affected (Section 6.6.3).

u Blood samples will be collected for PK analysis on Day 1 and at EOIV as described in Section 10.5

2 INTRODUCTION

2.1 Study Rationale

Antibiotic resistance poses a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared toward discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains. Additional novel antibiotic choices are needed to treat bacterial infections suspected or confirmed to be caused by antibiotic-resistant gram--positive pathogens, the leading cause of bacterial infections in humans (Van Hal, 2011). The Center for Disease Control estimates that greater than 80,000 invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections and greater than 11,000 related deaths occur annually in the United States. Moreover, an unknown but much higher number of less severe infections require treatment in community and healthcare settings (CDC, 2013).

TNP-2092 is being developed for the treatment of serious or life-threatening bacterial infections suspected or confirmed to be caused by gram-positive pathogens that have developed or acquired resistance to commonly used antibiotics. CCI

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TNP-2092 is predicted to be efficacious against ABSSSI suspected or confirmed to be caused by antibiotic resistant gram-positive pathogens, and biofilm-associated foreign body infections, including those medicated by multidrug-resistant pathogens.

2.2 Background

TenNor Therapeutics Limited (TenNor) is developing TNP-2092 for the treatment of gram-positive serious or life-threatening bacterial infections including pathogens that have developed or acquired resistance to commonly used antibiotics. Key target pathogens for TNP-2092 include staphylococci, streptococci, and pneumococci that exhibit resistance or reduced susceptibility to currently marketed antibacterial agents. Potential uses in the hospital setting include treatment of ABSSSI and other acute infectious disease syndromes, including those mediated by multidrug resistant pathogens.

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3 OBJECTIVES AND ENDPOINTS

This is the first study in which TNP-2092 is administered to participants with ABSSSI suspected or confirmed to be caused by gram-positive pathogens. Safety and tolerability comprise the primary objectives, and PK and efficacy comprise the secondary objectives. The objectives and endpoints are presented in Table 1.

4 STUDY DESIGN

4.1 Overall Design

This Phase 2, double-blind, randomized, multicenter, parallel, controlled study will be conducted to evaluate safety, tolerability, and PK of TNP-2092 300 mg IV q12h, and vancomycin 1 g IV q12h in adults with ABSSSI suspected or confirmed to be caused by gram-positive pathogens. The duration of the treatment period (IV or IV plus oral switch, if applicable) is a minimum of 7 days and a maximum of 14 days as presented in Figure 1.

All participants will be treated with IV study intervention for a minimum of 3 days (6 doses).

Upon meeting protocol-specified switching criteria (Section 6.2), participants will continue treatment with a commercially-available, open-label, oral antibiotic selected by the investigator. The Schedule of Activities is presented in Table 3 (Section 1.3).

Participants who meet the entry criteria (Section 5.1and Section 5.2) will be randomized (2:1) to 1 of 2 treatment arms: TNP-2092 300 mg IV q12h or vancomycin 1 g IV q12h (Table 2). Randomization will be stratified by ABSSSI types to ensure proper balance between treatment arms (Planned N = 120, n = 80 for TNP-2092 arm A and n = 40 for vancomycin arm B). The types of eligible ABSSSI include cellulitis/erysipelas, wound infections, and major cutaneous abscesses; however, participants with major cutaneous abscess should not comprise > 30% of randomized population. Participants with ABSSSI with a minimal lesion surface area of 75 cm^2 will be enrolled (FDA Guidance, 2013). No prior antibiotic treatment for the current ABSSSI is permitted before enrollment in the study, and no other concomitant systemic or topical antibiotics are permitted during the study. If a participant enrolls and is subsequently found to have a gram-negative or anaerobic bacterial infection, they may remain in the study but may be switched to an appropriate antibiotic and will not be included in the modified intent-to-treat (mITT) population (excludes all participants with gram-negative pathogens) as described in Table 9.

An adequate local ABSSSI site specimen must be collected from all participants with non-cellulitis ABSSSI for microbiologic evaluation at baseline. Blood samples from local ABSSSI site specimens, and blood cultures from 2 separate venipuncture sites, will be collected from all participants before administration of study interventions, whenever possible. All local ABSSSI site specimens will undergo Gram-stain and culture at the local laboratory and all blood cultures will be processed at the local laboratory. Specimens should be processed according to standard recognized methods. All bacteria isolated from an adequate local ABSSSI site specimen or blood culture at the local laboratory will be sent to a designated central laboratory for confirmation of species identification and antimicrobial susceptibility testing. Microbiologic methods are described in Section 8.4.2 and more details are presented the laboratory manual.

Screening assessments to determine study eligibility will be performed within 1 day before the first dose of study intervention is administered. Intravenous study intervention may be administered in a hospital or outpatient infusion center; outpatient administration of IV study intervention is limited to participants who are clinically stable and have adequate home support with reliable transportation to and from the hospital or clinic, as described in the Pharmacy Manual.

Day 1 is the first day of study intervention; subsequent study days are consecutive calendar days. For purposes of analysis, study assessments will be performed during the treatment period on Day 1, Day 2, at early assessment (EA) 48 to 72 hours after IV treatment is started, at EOIV (any calendar day up to Day 14) at the end of treatment (EOT, after a minimum of 7 days and up to 14 days of treatment, IV or IV plus oral switch, if applicable), at posttreatment evaluation (PTE, 7 to 14 days after EOT), and at long-term follow-up (LTFU, 20 to 25 days after EOT).

Safety assessments will be performed at each visit from screening to LTFU as indicated in the Schedule of Activities (Section 1.3). Safety will be assessed by AEs, physical examinations, vital signs, laboratory evaluations (hematology, chemistry, coagulation, urinalysis), and ECG parameters. Primary PK parameters are secondary endpoints and blood samples will be obtained for analysis on Day 1 and EOIV visits at designated times (Section 10.4).

Clinical assessments of the primary ABSSSI site (measurement of extent of infection and signs and symptoms) will occur at each visit from the screening visit to PTE, when clinically indicated, or if the participant is deemed a clinical failure (Section 8.4.1). ABSSSI site specimen cultures will be assessed at screening, when clinically indicated, or if the participant is deemed a clinical failure. Blood cultures will be assessed at screening with repeat testing if the previous blood culture was reported as positive, when clinically indicated or if the participant is deemed a clinical failure (Section 8.4.1).

4.2 Scientific Rationale for Study Design

Antibiotic resistance poses a serious threat to public health worldwide. Research efforts in recent years have become increasingly geared toward discovering and developing new classes of antibiotics with modes of action distinct from those of established agents and activity against resistant strains. Additional antibiotic choices are needed to treat gram-positive bacterial infections suspected or confirmed to be caused by antibiotic-resistant gram-positive pathogens.

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CCI [redacted] lthy subjects, treatment with TNP-2092 was evaluated between 10 mg and 600 mg per day.

CCI [redacted]

Based on the prescribing information, vancomycin is contraindicated in patients with known hypersensitivity to vancomycin. Warnings and precautions after rapid bolus administration over several minutes include exaggerated hypotension, including shock and rarely cardiac arrest. Infusions should be administered over a period of not less than 60 minutes to avoid rapid infusion-related reactions, and dosage should be adjusted for patients with renal dysfunction. Transient or permanent ototoxicity has occurred after vancomycin infusion usually in patients who receive excessive doses, have underlying hearing loss, or are receiving concomitant medications with another ototoxic agent. Vancomycin should be used with caution in patients with renal insufficiency to avoid the risk of toxicity which increases with high, prolonged blood concentrations. *Clostridium difficile* associated diarrhea has been reported with nearly all antibacterial agents, including vancomycin.

The current study is a Phase 2, double-blind, randomized, multicenter, parallel, controlled study designed to evaluate the safety, tolerability, PK, and efficacy of IV administered TNP-2092 (300 mg q12h) and IV administered vancomycin (1 g q12h) in adult participants with ABSSSI. The study design incorporates recommendations from the US Food and Drug Administration 2013 Guidance for Industry (ABSSSI: Developing Drugs for Treatment) (FDA, 2013). The safety and tolerability parameters monitored during the study are well-established measures of safety in clinical study participants. Blood samples will be collected to determine the PK parameters of TNP-2092 after the first dose and EOIV in this study population. The secondary endpoints of programmatic clinical response at EA aligns with the current FDA guidance (2013). Secondary efficacy endpoints also include the investigator assessments of clinical response at designated timepoints and microbiological responses at PTE.

4.3 Justification for Dose

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

4.4 End of Study Definition

A participant is considered to have completed treatment after receiving a minimum of 7 days and up to 14 days of the study intervention. Moreover, a participant is considered to have completed the study when the LTFU visit has been completed as shown in the Schedule of Activities (Section 1.3). The end of the study is defined as the date of the last visit for the last participant in the study.

5 STUDY POPULATION

The population of adult participants enrolled in this study require medical care to treat their ABSSSI suspected or confirmed to be caused by gram-positive pathogens.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study if all criteria apply as follows:

Age

1. Adult males or females, 18 years of age or older

Type of Participant and Disease Characteristics

2. ABSSSI suspected or confirmed to be caused by gram-positive pathogens that requires initial IV antibiotic treatment, which participants are willing to receive for at least 3 days (6 doses). Participants with 3 infection types will be enrolled:
   a. Cellulitis/erysipelas - a diffuse skin infection characterized by a spreading area of redness, edema, and/or induration
   b. Wound infection (traumatic or postsurgical) - an infection involving skin and subcutaneous tissue, characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration
   c. Major cutaneous abscess: an infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

3. Skin infection with a lesion surface area at least 75 cm^2 (longest length and widest width perpendicular to the length manually measurement with ruler). The surface area will be calculated by multiplying the length x width. The lesion size will be measured by area of redness, edema, or induration, whichever is greatest.

For participants with more than 1 type of eligible lesion/wound or with multiple lesions of the same type, the investigator must clearly identify the lesion to be evaluated for study purposes. Surgical procedures to treat ABSSSI (eg, incision and drainage [I&D]) are permitted before the first dose of study intervention up to 24 hours after the start of the first dose of study intervention.

4. At least 2 of the following local signs at the ABSSSI site:
   a. Purulent or seropurulent drainage/discharge
   b. Erythema
   c. Fluctuance
   d. Heat/localized warmth
   e. Pain/tenderness to palpation
   f. Swelling/induration
5. At least 1 marker of systemic inflammation:
   a. Fever or hypothermia (oral temperature ≥ 38.0ºC or ≤ 36.0ºC)
   b. White blood cell (WBC) count ≥10,000/mm^3 or ≤4,000/mm^3
   c. Immature neutrophils (bands) ≥15% irrespective of WBC count
   d. Presence of lymphangitis or lymphadenopathy proximal to the ABSSSI

Note that there is no requirement for at least 1 marker of systemic inflammation in participants ≥ 70 years old or in participants with diabetes.

Sex

6. Females of childbearing potential, < 2 years postmenopausal who are not permanently sterile, must have a negative serum or urine pregnancy test (beta-human chorionic gonadotropin [β-HCG]) at baseline, and agree to use 2 highly effective methods of birth control (eg, abstinence, oral contraceptive, intrauterine device, barrier contraception [condom]) to PTE. Females who are not of childbearing potential (have had a tubal ligation, hysterectomy, or bilateral oophorectomy, or are ≥ 2 years postmenopausal) or have a partner who has had a vasectomy do not need to use any contraception. Males must use a highly effective method of birth control if female partner(s) is of childbearing potential and must not donate sperm from baseline through PTE. Contraception guidance is described further in Section 10.7.

Informed Consent

7. Capable of giving signed informed consent as described in Section 10.1.4 which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Body mass index ≥30 kg/m^2 (obese)
2. History or hypersensitivity or intolerability to any fluoroquinolone, rifamycin or glycopeptide class
3. ABSSSI suspected or confirmed to be caused by pathogens that are resistant to the glycopeptide class
4. Prior administration of systemic antibacterial therapy within 96 hours before randomization
5. Pregnant or breastfeeding
6. Evidence of significant hepatic, hematologic, or immunologic disease determined by the following:
    a. Acute hepatitis from any cause within the past year; participants with stable chronic hepatitis B and/or hepatitis C may be eligible provided they do not meet exclusion criteria
    b. Serum ALT, AST, or bilirubin greater than 2 times upper limit of normal
    c. Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy
    d. Current or anticipated neutropenia defined as < 500 neutrophils/mm^3
    e. Known infection with human immunodeficiency virus (HIV) and a cluster of differentiation 4 (CD4) count that is unknown or documented to be < 200 cells/mm^3 within the last year, or an Acquired Immune Deficiency Syndrome (AIDS)-defining illness
    f. The receipt of cancer chemotherapy, radiotherapy, or potent noncorticosteroid immunosuppressant drugs (eg, cyclosporine, azathioprine, tacrolimus, immune-modulating monoclonal antibody therapy, etc.) within the past 3 months, or the receipt of corticosteroids equivalent to or greater than 40 mg of prednisone/day or for more than 14 days in the prior 30 days
7. QT interval corrected with Fridericia's formula (QTcF) > 450 msec based on the average of screening ECGs in triplicate; or history of QT prolongation, clinically significant hypokalemia, or other proarrhythmic conditions
8. Has other contraindications to receive a systemic fluoroquinolone antibiotic, including confirmed or suspected peripheral neuropathy, tendon disorder, myasthenia gravis, cirrhosis, aortic aneurysm, or central nervous system disorder that may predispose the participant to seizures or lower the seizure threshold
9. History of *Clostridium difficile* infection
10. ABSSSI with any of the following characteristics:

a. Suspected or confirmed infection caused by gram-negative or anaerobic organisms (eg, perineal wound infection, gluteal decubitus ulcer, wound infection associated with surgery on gastrointestinal tract or female genital tract, infection caused by a human or animal bite)
b. Suspected or confirmed fungal, mycobacterial, parasitic, or viral pathogens
c. Involving an ischemic ulcer due to peripheral vascular disease
d. Involving a decubitus ulcer or perirectal abscess
e. Involving a diabetic foot ulcer
f. Involving a burn
g. Involving an underlying inflammatory skin disease that may obscure determination of response (eg, chronic dermatitis) where inflammation may be prominent for an extended period, even after successful bacterial eradication has been achieved
h. Involving a bite other than an arthropod bite (ie, human or animal bite)
i. Involving a rapidly necrotizing process, such as necrotizing fasciitis
j. Involving gangrene of any etiology
k. Complicated by an immune deficiency (eg, development of ecthyma gangrenosum in neutropenic subject)
l. Anatomically associated with prosthetic materials (eg, central venous catheters, permanent cardiac pacemaker battery packs, or joint replacement prostheses), even if the device is removed
m. Requiring amputation
n. Requiring significant surgical intervention (ie, procedures that would not normally be performed at the bedside) that cannot be performed within 24 h after initiating study intervention treatment (Inclusion Criterion 3)
o. Minor cutaneous abscess or furuncle or any other condition with an estimated high cure rate after surgical incision alone or after aggressive local skin care
p. Associated with infection at other anatomic sites or spaces, such as endocarditis or other endovascular infection, thrombophlebitis, osteomyelitis, or septic arthritis
q. Anticipated need for antibacterial therapy for longer than 14 days

11. History or evidence of severe renal disease or has a calculated creatinine clearance of < 30 mL/min, according to the Cockcroft-Gault equation (Section 10.2, Table 11)
12. Presence of any other surgical or medical condition (including a clinically significant laboratory abnormality) as determined by the investigator and/or the sponsor's medical monitor, that could interfere with the participant's ability to participate in the study, the administration of study intervention, and/or the interpretation of study results.
13. Anticipated need for concomitant use of medications from randomization to EOT: HIV protease inhibitors (eg, ritonavir-boosted or non-boosted saquinavir, atazanavir, darunavir, fosamprenavir, or tipranavir); praziquantel, halothane, and Class IA and III

anti-arrhythmics (eg, disopyramide, procainamide, quinidine, amiodarone, dofetilide, dronedarone, ibutilide, and sotalol) (Table 20).

Prior/Concurrent Clinical Study Experience

14. Previous enrollment in this study or previous treatment with TNP-2092
15. Received an investigational medication within 30 days or 5 half-lives (whichever is longer) before the first dose of study intervention.

5.3 Lifestyle Considerations

After switching to oral antibiotic treatment, food or drug restrictions (Section 6.6.2) may be necessary, depending on the antibiotic chosen. The investigator will inform the participants of any restrictions after reviewing the prescribing information for each antibiotic.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

A minimal set of screen failure information is required and will be collected to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention or marketed product, intended to be administered to a participant according to the protocol. During the first part of this study, each participant will receive an IV infusion q12h of study intervention for a minimum of 3 days (6 doses). Intervention comprising IV or IV plus oral medications switch (if applicable) will be administered for a minimum of 7 days up to 14 days. After the IV infusion part of the study is completed and participants meet switching criteria, they will be switched to a commercially-available, oral, open-label antibiotic selected by the investigator.

6.1 Study Interventions Administered

One-hundred twenty participants who meet study entry criteria will be randomly assigned to treatment in 1 of 2 treatment arms in a 2:1 ratio as presented in Table 2. A sample size of 80 participants who receive TNP-2092 is deemed sufficient to provide an initial assessment of safety and PK data to inform the future development of TNP-2092.

The study intervention refers to supplied IV TNP-2092 and IV vancomycin and the commercially available, open-label, oral antibiotic. Infusions of study intervention will be administered as follows:

- TNP-2092–300 mg IV q12h infusion will be administered over 60 minutes (treatment arm A) for a minimum of 3 days (6 doses) and a maximum of 14 days

- Vancomycin - 1 g IV q12h infusion will be administered over 60 minutes (treatment arm B) for a minimum of 3 days (6 doses) and a maximum of 14 days

For all study interventions used in this study, the clinical label will identify the product by name, lot number, manufacturer, storage conditions, and expiry date. Administration of the IV study intervention is limited to investigational use only. Refer to the Pharmacy Manual for additional information. All supplies packed and labeled will be formally released in accordance with both Good Manufacturing Practice and Good Clinical Practice (GCP) guidelines.

- Lyophilized TNP-2092 for IV administration will be provided in clear, glass vials (10 mL capacity) containing 100 mg TNP-2092. The vials should be kept frozen (-20ºC) until reconstitution. One vial of lyophilized TNP-2092 will be reconstituted in 5 mL of sterile Water for Injection, USP, for a final concentration of 20 mg/mL. Reconstituted TNP-2092 solution is injected into prepared IV bag at ambient temperature and diluted in 5% dextrose solution as presented in Table 4. Once the drug product is reconstituted, it will be stored for no longer than 4 hours at ambient temperature.
- Commercially-available, lyophilized vancomycin for IV administration will be provided in clear, glass vials containing 1 g vancomycin. The vials should be kept at ambient temperature until reconstitution. One vial of lyophilized vancomycin will be reconstituted in 20 mL of Sterile Water for Injection, USP, for a final concentration of 50 mg/mL. Reconstituted vancomycin solution is injected into the prepared IV bag, at ambient temperature, and diluted with 5% dextrose solution as presented in in Table 4. Once the drug product is reconstituted, it will be stored for no longer than 4 hours at ambient temperature.

Table 4 Preparation of Reconstituted TNP-2092 and Vancomycin

Intervention	Dose	D5W Volume Added to IV Bag	No. of Vials Needed	Total Volume Withdrawn from Vial	Total Volume	Volume Infused	Duration of Infusion
TNP-2092	300 mg	185 mL	3	15 mL	200 mL	200 mL	60 min
Vancomycin	1 g	180 mL	1	20 mL	200 mL	200 mL	60 min

Packaging for the final ready-to-infuse infusion for TNP-2092 and vancomycin will not be identical in appearance. To maintain the blind, the unblinded pharmacist will cover the IV bag with an ultraviolet light impermeable overwrap to facilitate blinding of the parenteral drug product. The tubing used for the infusion will be impenetrable to light, so the color will not be seen.

Treatment with study intervention will begin with the infusion of the IV formulation of study intervention on Day 1 as soon as possible after eligibility criteria are met. Treatment with the IV formulation will continue for at least 3 days (ie, 6 doses), after which participants may be

switched to the oral antibiotic only (Section 6.2). Participants will be hospitalized or will come to the clinic twice daily to receive study intervention.

Study intervention will be dispensed to the sites as summarized in Schedule of Activities (Section 1.3). Returned study intervention must not be reused and must be disposed of according to instructions provided in the pharmacy manual. Upon completion of the IV infusion part of the study, the commercially-available, oral antibiotic treatment will be administered in an open-label manner after participants meet the switching criteria described in Section 6.2. The prescribing information provided by the manufacturer will be followed to ensure that it is administered appropriately.

6.2 Criteria for Intravenous to Oral Treatment Switch

Following at least 3 days of study intervention (ie, 6 doses of TNP-2092 or vancomycin), participants may be switched from the twice daily IV study intervention to commercially-available, open-label, oral antibiotic therapy, if all of the following conditions are met:

- In the previous 24 hours, the participant has had 4 temperature measurements, each separated by approximately 6 hours, and all 4 measurements are ≤ 37.6°C / 99.7°F.
- Peripheral WBC count and immature neutrophils returning or have returned to normal range according to the local laboratory reference range
- No increase from baseline or the previous visit in ABSSSI lesion area compared to the screening visit or a previous visit
- No increase in severity of inflammatory findings at the primary site of infection (erythema, edema, induration) from baseline or a previous visit; in general, the severity of these findings should be mild
- Unequivocal improvement in some or all clinical signs of ABSSSI under study; if some signs have not improved, none should have worsened (ie, stability for that sign is observed).
- Ability to maintain oral intake

Participants in any treatment arm may be switched to oral therapy, once the investigator's assessment of clinical response is improvement, as described in Section 8.4.1. When the participant is switched to oral therapy, treatment will continue in an open-label manner with no attempt to blind the oral treatment. The IV antibiotic treatment will remain blinded until the database is unlocked. The oral antibiotic will be selected by the investigator and that part of the study will be conducted in an open-label manner.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 IV Antibiotic

All unit doses of study intervention, TNP-2092 IV and vancomycin IV, will be prepared at the study site by an unblinded pharmacist or by designated members of the clinical pharmacy staff. They will be responsible for maintaining the blind from other study personnel.

Preparation and administration of study intervention will be performed in accordance with the treatment schedule.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a locked, secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions (-20ºC) with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3.2 Oral Antibiotic

The investigator will select the type and dosage of commercially-available, antibiotic used. The oral antibiotic choice will not be blinded.

6.4 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomly assigned in a 2:1 ratio of the study interventions (TNP-2092: vancomycin). Randomization will be stratified by ABSSSI type (cellulitis/erysipelas, wound infection, or major cutaneous abscess); however, participants with major cutaneous abscess should not comprise > 30% of randomized population. All participants will be centrally assigned to randomized study intervention with an Interactive Web Response System (IWRS). Before the study is initiated, login information and directions for the IWRS will be provided to each site.

Investigators will remain blinded to each participant's assigned study intervention throughout the study. After informed consent has been obtained and study eligibility established, the study site's pharmacist or designee will obtain the randomization number and the study intervention assignment from the IWRS and the participant is considered randomized. To maintain the blind, the study pharmacist will be responsible for the reconstitution and dispensation of all study intervention. The participant or legally authorized representative will also be instructed to avoid discussing the IV treatment or packaging of the study intervention with the investigator.

This is a double-blind study. Those blinded to study intervention assignment include the sponsor, investigator, study statistician, clinical study personnel participating in direct participant care and those involved in all clinical evaluations. Those unblinded to study intervention assignment include the pharmacy personnel, the unblinded study monitor, and the bioanalytical laboratory. To minimize the potential for bias, treatment randomization

information will be kept confidential by and from the sponsor personnel and will not be released to the investigator, blinded investigator site personnel, or the blinded study monitor until the conclusion of the study. Procedures to ensure that the blind is maintained are detailed in the Study Blinding Manual.

Unblinding Study Intervention

If study intervention is determined not to be safe and/or not tolerated, the study intervention assignment for those participants with a significant safety concern may be unblinded. The investigator and medical monitor will review the participant's data, discuss the findings, and jointly decide to unblind the treatment assignment, continue or terminate enrollment in the study.
The blind may also be broken in the case of a medical emergency that requires the investigator to know the identity of the study intervention to appropriately guide the participant's medical management. Before unblinding the treatment, 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 sponsor before unblinding the treatment, the investigator must notify the sponsor as soon as possible, without revealing the participant's study intervention assignment (unless important to the safety of participants remaining in the study). All instances of treatment unblinding will be thoroughly investigated and documented by the unblinded study monitor.

In the event of a quality assurance audit, the auditor will be allowed access to unblinded study intervention records at the sites to verify that randomization/dispensing has been done accurately.

6.5 Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Each dose of IV study intervention will be administered by study staff, under direct medical supervision of the investigator, and recorded on the electronic case report form (eCRF). Participants who are not hospitalized during IV treatment will have to return to the clinic or hospital for each IV infusion. The following compliance information will be documented and reported in the eCRF:

- The dates and times of administration of each IV study intervention.
- For IV infusion, the time when infusion starts and when it ends is recorded along with the total volume of solution administered (if infusion is halted or interrupted for any reason, the time of premature discontinuation and re-initiation of infusion is recorded).

Participants managed as outpatients who receive oral antibiotics will self-administer study intervention. At the EOT, unused study medication and used/empty bottles will be collected and used to determine compliance to treatment. Compliance will be calculated on the number of doses of study intervention administered, divided by the total number of expected doses from information obtained from the eCRF. Deviations from the prescribed dosage regimen will be recorded on the eCRF.

A further check of compliance will be the determination of blood concentrations of TNP-2092 during the analytical phase of the study (Section 10.4).

6.6 Concomitant Therapy

6.6.1 Other Medication Therapy

All prescription medications and over-the-counter medications, including herbal, nutritional, and dietary supplements (eg, any antacid, iron supplement, or multivitamin) administered within 2 weeks (14 days) before randomization and during the study between Day 1 and LTFU will be documented in the eCRF. Any changes in prior or concomitant medications will also be recorded.

In addition to the name of the medication, the following information will be collected and documented:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.2 Prohibited Medications and Medications Requiring Special Consideration

Participants who received prior administration of systemic antibacterial therapy within 96 hours before randomization are excluded from the study. No other concomitant systemic or topical antibacterial agents are permitted during the study. A list of prohibited medications is presented in Table 20 and Section 5.2, Exclusion Criterion 13.

Caution is advised with concomitant use of medications that may have drug-drug interactions with rifamycin or fluoroquinolones. The investigators will receive the prescribing information for rifampin (2019) and moxifloxacin (2016). The investigators should review this information about these agents as representative examples from these drug classes. In addition, training sessions will be provided to the investigators regarding these drug classes.

6.6.3 Adjunctive Therapy

The following non-drug adjunctive therapies are permitted:

a. Local bedside wound care as per hospital protocol
b. Lesion debridement at the bedside
c. If required, surgical procedures to treat ABSSSI (eg, I&D) should be performed before the first dose of study intervention up to 24 hours (Day 2) after the first dose of study intervention. After Day 2, if performed, any surgical intervention will be captured; however, subject evaluability in analysis populations may be affected.

6.6.4 Rescue Medication

Concomitant or rescue antimicrobial medications are not permitted in this study, except in cases of failure of the study intervention and need for open-label antimicrobial therapy to continue treatment of the ABSSSI. If rescue medication is needed, study intervention should be prematurely discontinued and all EOT visit assessments should be completed, if possible, before rescue therapy is initiated.

6.7 Dose Modification

No dose modifications will be permitted in this study.

6.8 Intervention After the End of the Study

Continuation of study intervention beyond the 14-day treatment period is not permitted following the end of the study because participants with ABSSSI should be cured. For participants who withdraw from treatment because of lack of efficacy, all safety assessments from the EOT visit should be completed before rescue therapy with another antibiotic is initiated.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants who prematurely discontinue treatment will remain in the study. Before premature discontinuation, the study site personnel should notify the medical monitor, time permitting. Efforts will be made by the site to complete all protocol-specified assessments listed for the EOT visit as appropriate, and to perform follow-up safety assessments as specified at the PTE visit and LTFU visit as scheduled. Ongoing AEs should be following to resolution or to a satisfactory outcome, as determined by the investigator. Participants who withdraw will not be replaced. See the Schedule of Activities for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed (Section 1.3).

7.2 Participant Discontinuation/Withdrawal from the Study

Participants have the right to withdraw from the study without prejudice by request or may be withdrawn at any time at the discretion of the investigator. All participants should be encouraged to complete all study assessments before withdrawal, as shown in the Schedule of Activities (Section 1.3). Study assessments should be completed before any rescue therapy is initiated. After the study assessments are completed the participant will be permanently discontinued from the study. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before consent is withdrawn. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document the request and destruction in the site study records.

Data for all participants will be reviewed to ensure that 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.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Section 10.1.9.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Protocol Adherence

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 Institutional Review Board (IRB). Each investigator will be responsible for enrolling only those participants who have met the protocol inclusion and exclusion criteria.

- Study procedures and their timing are summarized in Section 1.3. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized

for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

- Blood samples will be collected from each participant over the duration of the study, and extra assessments will be collected as required. The sponsor anticipates that the total amount of blood will not exceed 200 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files and will not constitute a protocol amendment. The IRB, IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical Examinations

Physical examinations, both complete and focused, will be performed as follows:

- A complete physical examination comprises weight, height (screening only), general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin/soft tissues, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.
- A focused physical examination comprises chest (heart, lungs), abdomen, skin, neurological and musculoskeletal systems.

Complete physical examinations will be performed at the screening, EOIV, EOT, and PTE visits. Focused physical examinations will be performed on Day 2, EA, and every subsequent day of IV treatment (minus EOIV).

8.2.2 Vital Signs

Vital signs will be assessed preferably by the same observer and with the same instruments per participant at each visit from screening to PTE as follows:

- Temperature (oral), pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is unavailable.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (taken before blood collection for laboratory and PK assessments) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.

8.2.3 Electrocardiograms

Triplicate 12-lead ECG recordings will be obtained within a 15-minute period, separated by at least 1 minute, before collection of blood for laboratory and PK assessments, and within 4 hours (± 30 minutes) of study intervention administration. These assessments will be performed at screening, EA, EOT, and PTE.

8.2.4 Clinical Safety Laboratory Assessments

Central laboratory safety assessments for hematology, coagulation, serum chemistry, and urinalysis will be performed at each visit from screening through PTE according to the

Schedule of Activities (Table 3). Specifically, central laboratory assessments include β-HCG pregnancy test at baseline and EOT, and hematology, coagulation, serum chemistry, and urinalysis testing at each visit from screening through PTE. Given the duration of time required to ship, receive, and analyze the central laboratory tests, the central laboratory results will not be available to immediately affect participant management in real-time. Therefore, local laboratory testing should be performed as needed according to local standards of care to appropriately manage participants.

Local laboratory tests are required to ensure eligibility at screening (Section 5.1 and Section 5.2). Specifically, local laboratory testing for eligibility includes plasma WBC count and immature neutrophil percentage (potentially required to meet Inclusion Criterion 5); β-HCG pregnancy testing (Inclusion Criteria 6); serum ALT, AST, total bilirubin, and absolute neutrophil count (Exclusion Criterion 6); and serum creatinine for creatinine clearance calculation (Exclusion Criterion 11). Any other local laboratory samples may be collected as part of site-specific routine management of participants per local standards of care, whether at baseline or postbaseline.

All laboratory tests with values considered clinically significantly abnormal during participation in the study, including any value beyond PTE, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. Additional details of clinical laboratory testing are presented in the Laboratory Manual.

A complete list of tests to be performed is presented in Section 10.2 (Table 11).

The investigator duties regarding laboratory test results are as follows:

- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study, including any value beyond PTE, should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).
- If values from laboratory assessments not specified in the protocol performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE (Table 12), SAE (Table 14), and the types of events meeting the definition of AE (Table 13) are presented in Section 10.3. Adverse events will be reported by the participant during the study visits either in person or by telephone. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE as presented in Table 15. They remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study.

Thrombotic and infusion site AEs will be considered events of special interest and will be collected and documented separately from AEs from the screening to EOIV visits (Section 1.3).

8.3.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the time the ICF is signed to the LTFU visit, 20 to 25 days after the EOT, at the time points specified in the Schedule of Activities (Section 1.3). Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not within the AE section. All SAEs will be recorded and reported to the sponsor or designee immediately within 24 hours of awareness, as presented in Table 19. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the conclusion of the study (LTFU), investigators are not obligated to actively seek AE or SAE information. However, the investigator must promptly notify the sponsor if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation.

8.3.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing the intensity and causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are presented in Table 16 and Table 17, respectively.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, AEs that lead to discontinuation, and AEs of special interest Section 10.3, will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB /Independent Ethics Committee (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRBs/IECs, if appropriate according to local requirements.

8.3.5 Pregnancy

A serum or urine β-HCG test will be performed at screening and at the EOT for all women of childbearing potential.

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention until the outcome of the pregnancy is determined.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures described in Section 10.7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported following the SAE reporting process (Section 10.3.5).

The risks of treatment with TNP-2092 during pregnancy have not been fully evaluated. Therefore, females of childbearing potential, < 2 years postmenopausal who are not permanently sterile, must have a negative baseline serum or urine pregnancy test (β-HCG) at baseline, and agree to use 2 highly effective methods of birth control (eg, abstinence, oral contraceptive, intrauterine device, barrier contraception [condom]) to PTE. Females who are not of childbearing potential (have had a tubal ligation, hysterectomy, or bilateral oophorectomy, or are ≥ 2 years postmenopausal) or have a partner who has had a vasectomy do not need to use any contraception. Males must use a highly effective method of birth control if female partner(s) is of childbearing potential and must not donate sperm from baseline through PTE. Contraception guidance is described further in Section 10.7.

Female and male participants must be instructed to inform the investigator immediately if they or their female partner become pregnant during the study and follow the procedures described in Section 10.7.

8.3.6 Death Events

Death is an outcome of an AE, but not an AE itself. All deaths from the start of the screening visit to the LTFU visit after the last dose of study medication must be reported, regardless of the cause or relationship to study medication. If a death occurs greater after the LTFU visit and is considered possibly related to study intervention, the investigator should report the death and associated event on the SAE Report Form.

8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Worsening of the primary ABSSSI for which the participant was enrolled is not considered an AE. All events that do not quality as an AE or SAE are presented in Table 12.

8.4 Efficacy Assessments

Clinical response and microbiologic assessments of ABSSSI will be performed from the screening visit to the PTE visit as described below.

8.4.1 Clinical Response

All participants must have their primary ABSSSI site evaluated by the investigator, including ABSSSI site measurements described below. At the screening visit, the primary anatomical site and predisposing cause for infection, if known (eg, trauma, arthropod bite, fungal dermatosis, surgery, spontaneous, etc.) should be recorded.

When conducting a clinical examination of the primary ABSSSI site, the investigator will perform and record the following assessments:

- Extent of the infection (area in cm^2) as measured with a ruler provided by the sponsor. The area of redness, edema, or induration will be measured from the longest length multiplied by the greatest perpendicular width. Instructions for primary ABSSSI measurements are described in the Site Infection Assessment and Measurement Manual.
- Local signs and symptoms of erythema (and any distant extension of erythema), swelling/edema, localized warmth, tenderness on palpation, drainage, fluctuance, and induration as described in the Site Infection Assessment and Measurement Manual.

Programmatic Determination of Clinical Response

Objective evaluation of clinical response as determined programmatically will be made at the EA visit 48 to 72 hours after the study intervention begins. The lesion size will be a component of the clinical response and instructions for measuring lesions are provided in the Site Infection Assessment and Measurement Manual. Participants will be considered as responders, nonresponders, or indeterminate as defined in Table 5.

Table 5 Clinical Response Definitions – Programmatic Determination

Timepoint Classification	Definition
At Early Assessment (48 to 72 hours after IV Treatment Starts)	
Responder	Percent reduction in primary ABSSSI lesion size is ≥ 20% compared with baseline Did not die of any cause up to the specified visit
Nonresponder	Percent reduction in primary ABSSSI lesion size is < 20% compared with baseline Intercurrent antibacterial therapy administered for the treatment of the primary ABSSSI lesion that might have potential antibiotic activity directed toward the gram-positive pathogens implicated in the ABSSSI Did not die of any cause up to the specified visit
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (eg, missing data, lost to follow-up, did not attend the EA clinic appointment)

ABSSSI = acute bacterial skin and skin structure infection; EA = early assessment; IV = intravenous

Investigator's Assessment of Clinical Response

The investigator's assessment of clinical response at EOIV, EOT, and PTE visits will be classified as defined in Table 6. Investigator assessed clinical failures at EOT will be carried forward as the clinical response at PTE.

Table 6 Clinical Response Definitions – Investigator's Assessment

Timepoint Classification	Definition
At EOIV	
Improvement	The ABSSSI sufficiently improved such that further IV antibacterial therapy is not needed. These participants may have some residual clinical signs and symptoms related to ABSSSI requiring continued oral antibiotic stepdown therapy (provided the subject meets oral switch criteria, Section 6.2) or ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue.
Failure	Investigator discontinued study intervention and indicated that the ABSSSI had responded inadequately such that alternative (rescue) nonstudy IV antibacterial therapy was needed The participant received antibacterial therapy for a different infection that may be effective for the ABSSSI under study The participant developed an AE that required discontinuation of study intervention before completion of the planned IV regimen Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the ABSSSI under study Died of any cause up to the specified visit
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (eg, missing data, lost to follow-up).
EOT and PTE	
Success	The ABSSSI sufficiently resolved such that further antibacterial therapy is not needed. These participants may have some residual changes related to infection requiring ancillary (ie, non-antibiotic) treatment, eg, bandages on a healing wound, debridement of uninfected tissue (ie, necrotic) Did not die of any cause up to the specified visit
Failure	Investigator discontinued study intervention and indicated that the ABSSSI had responded inadequately such that alternative (rescue) non-study antibacterial therapy was needed The subject received antibacterial therapy for a different infection that may be effective for the ABSSSI under study The subject developed an AE that required discontinuation of study intervention before completion of the planned treatment regimen Unplanned major surgical intervention (ie, procedures that would not normally be performed at the bedside) for the ABSSSI under study Died of any cause up to the specified visit
Indeterminate	Study data are unavailable for evaluation of efficacy for any reason (eg, missing data, lost to follow-up).

ABSSSI = acute bacterial skin and skin structure infection; EOIV = end of IV treatment; EOT = end of treatment; PTE = posttreatment evaluation

8.4.2 Microbiologic Evaluation

All participants enrolled with ABSSSI in this study must undergo microbiological assessments at screening, bacterial culture and Gram-stain, except microbiological

assessments from cellulitis lesions are optional (eg, invasive tissue samples are encouraged but not required from cellulitis lesions). Samples from local ABSSSI site specimens, and blood cultures from 2 separate venipuncture sites, will be collected from all participants before administration of study interventions, whenever possible. All ABSSSI site specimens will undergo Gram-stain and culture at the local laboratory and all blood cultures will be processed at the local laboratory. The screening microbiological assessments are critical, in that microbiological response against pathogens responsible for ABSSSI is an important secondary outcome of the study (Table 1). Similarly, participants with an infection suspected or confirmed to be caused by gram-negative bacteria (eg, *Pseudomonas aeruginosa* in burn patients), and anaerobic pathogens, mycobacteria, or fungi should not be enrolled, and participants with ABSSSI suspected or confirmed to be caused by gram-positive bacteria will be analyzed in the microbiological populations. If an enrolled participant is subsequently found to have a confirmed infection with gram-negative or anaerobic organisms, they may remain in the study but may be switched to the appropriate antibiotic.

The ABSSSI site specimens are collected at screening, when clinically indicated, or if the participant is deemed a clinical failure. The following types of specimens are considered acceptable, in order of preference:

- Biopsy of involved cutaneous or subcutaneous tissue, preferably from the advancing margin of the lesion
- Debrided tissue
- Tissue scraping (with curette or scalpel)
- Needle aspirate of involved, nonpurulent cutaneous or subcutaneous tissue
- Pus or infected tissue collected during an I&D procedure
- Pus aspirated into a syringe
- Deep swab of purulent material (only if collected from infected tissue that has been incised or is draining)

Deep swabs of infected areas taken during significant surgical interventions are acceptable specimens. Superficial swabs of infected areas are not acceptable, due to the high probability that such specimens could be contaminated with clinically insignificant, and potentially misleading isolates.

Two sets of blood cultures comprising 1 aerobic and 1 anaerobic culture bottle from 2 separate venipuncture sites will be collected from all participants. When possible, the blood cultures should be obtained before administration of antibacterial treatment. Blood cultures must be repeated at the time that any previous blood culture was reported as positive, any time if clinically indicated, or if the participant is deemed a clinical failure. If repeat blood cultures remain positive with the causative bacteria initially isolated, the investigator must consider modifying the antibiotic treatment administered to the participant and discuss the case with the medical monitor.

All blood cultures and ABSSSI site specimens will be processed for Gram-stain and culture at the local laboratory. Laboratory reports on Gram-stain should include a semiquantitative description of the number of polymorphonuclear leukocytes per low power field (ie, 100×) and a description of bacterial morphologies. All bacterial isolates that are identified from an ABSSSI site specimen or blood culture at the local facilities collaborating laboratory will be sent to a designated central laboratory for confirmation of species identification and antimicrobial susceptibility testing. All microbiological specimen and processing details methods are described in the laboratory manual.

Antimicrobial susceptibility testing should be performed at the local laboratory according to local standards of care; all clinically significant gram-positive pathogens should be tested locally for rifamycin, fluoroquinolone, and vancomycin susceptibility, as appropriate. Susceptibility testing for TNP-2092 will not be available at the local laboratory. Instead, the central laboratory will confirm and test all gram-positive isolates for both TNP-2092 and vancomycin susceptibilities. After the cultured isolates are sent to the central laboratory, the central laboratory will confirm and retest all gram-positive isolates for rifamycin, fluoroquinolone, and vancomycin susceptibilities. The local laboratory should retain all isolates until confirmation of a viable organism is received from the central laboratory. Back-up 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. All necessary procedures for antimicrobial susceptibility testing are described in the laboratory manual.

Per-Pathogen Microbiological Response

A microbiological outcome at the PTE visit is determined for each pathogen isolated from the ABSSSI site or blood at screening from the categories defined in Table 7. Favorable microbiological outcomes include eradication or presumed eradication. Unfavorable microbiological outcomes include persistence or presumed persistence.

Table 7 Microbiologic Outcome Categories

Outcome Category	Definition
PTE	
Eradication	An adequate source specimen demonstrates absence of the original screening pathogens
Presumed Eradication	An adequate source specimen was not available to culture and the participant was assessed as a clinical success by the investigator at PTE
Persistence	An adequate source specimen demonstrates continued presence of the original screening pathogens
Presumed persistence	An adequate source specimen was not available to culture and the participant was assessed as a clinical failure by the investigator at PTE
Indeterminate	An adequate source specimen was not available to culture and the participant's clinical response was assessed as indeterminate

PTE = posttreatment evaluation

Per-Participant Microbiological Response

An overall microbiological response at the PTE visit will be determined in the micro-ITT and ME population for each participant based on individual outcomes for each-baseline pathogen. For a participant to have a favorable per-participant microbiological response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated, as defined in Table 7). For a participant to have an unfavorable per-participant microbiological response, the outcome for each baseline pathogen must be unfavorable (persistence, presumed persistence, as defined in Table 7). If the same pathogen is isolated from multiple sites (eg, blood and ABSSSI site culture), the worst response will be used to determine the per-participant microbiological response.

Emergent Infections

ABSSSI caused by pathogens first appearing after screening will be categorized as either superinfections or new infections as defined in Table 8.

Table 8 Emergent Infections

Category	Definition
End of Intravenous Treatment	
Superinfection	Isolation of a new pathogen other than the original screening pathogen from the primary ABSSSI site and from an appropriate ABSSSI specimen which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period up to and including EOT
New Infection	Isolation of a new pathogen other than the original screening pathogen from the primary ABSSSI site and from an appropriate ABSSSI specimen which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period after EOT

ABSSSI = acute bacterial skin and skin structure infection; EOT = end of treatment

8.5 Treatment of Overdose

At the time this protocol was written, no known incidents of overdose with TNP-2092 were known. The highest single dose administered to humans was 400 mg in the CBR-2092-001 Clinical Study, and the highest multiple-dose/day was 600 mg for 14 days in the CBR-2092-002 Clinical Study.

An overdose is defined as deliberate or accidental administration of TNP-2092 at a dose greater than twice the daily dose assigned to that participant according to the protocol. In the event of a suspected overdose, the investigator should take the following steps:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 30 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the CRO's medical monitor based on the clinical evaluation of the participant.

In case of overdose of vancomycin or commercially-available, open-label, oral antibiotic, the prescribing information (2018) should be consulted.

8.6 Pharmacokinetics

Pharmacokinetic samples will be obtained from whole blood on Day 1 and at EOIV visits according to Table 21. Primary PK parameters will be calculated from concentration versus time data with noncompartmental techniques (C_{max}, t_{max}, AUC versus time from time 0 to 12 hours [AUC_{0-12}], and CL [after last dose]).

All participants from each treatment arm will have whole blood samples collected but only samples collected from participants in treatment arm A (TNP-2092 arm) will be analyzed (Section 10.5). Some degree of inference may be possible to the influence of baseline participant characteristics (eg, age, gender, weight, body mass index, race) on the clearance of the drug.

The bioanalytical laboratory will measure plasma concentrations of TNP-2092 according to validated bioanalytical methods. Selected PK samples may be used in the identification of TNP-2092 metabolites. Specific instructions for the collection of plasma and urine drug concentration specimens will be described in the Laboratory Manual and should be reviewed before collection.

When multiple assessments are scheduled at any given timepoint, clinical assessments should precede all blood collection, including ECGs.

The actual date and time (24-hour clock time) of each sample will be recorded. Approximately 5 mL/sample will be collected for measurement of TNP-2092. Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until after the study treatment has been unblinded.

The PK population is defined in Section 9.8. Additional details regarding the collection and analysis of PK samples are described in the PK Analysis Plan.

8.7 Pharmacodynamics
Pharmacodynamic parameters are not evaluated in this study.

8.8 Genetics
Genetics are not evaluated in this study.

8.9 Biomarkers
Biomarkers are not evaluated in this study.

8.10 Health Economics/Medical Resource Utilization and Health Economics
Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS
All data will be summarized separately by study intervention (TNP-2092 300 mg q12h or vancomycin 1 g q12h). Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables for each study intervention. Frequency distributions (counts and percentages) will be presented for categorical variables. Listings will be provided for individual participant study data.

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before the database is locked.

9.1 Statistical Hypotheses
No formal hypotheses testing will be conducted.

9.2 Sample Size Determination
This study is not powered for inferential statistical analysis. If the responder rate in the TNP-2092 arm is 0.8 at EA (48 to 72 hours after start of study intervention) according to the programmatic clinical response, this results in a 95% CI of (0.7, 0.88) for the responder rate in the TNP-2092 arm at the EA visit (Clopper and Pearson, 1934). A sample size of 80 participants who receive TNP-2092 is deemed sufficient to provide an initial assessment of safety and PK data to inform the future development of TNP-2092.

9.3 Populations for Analyses
The analysis populations are defined as presented in Table 9 and Figure 3.

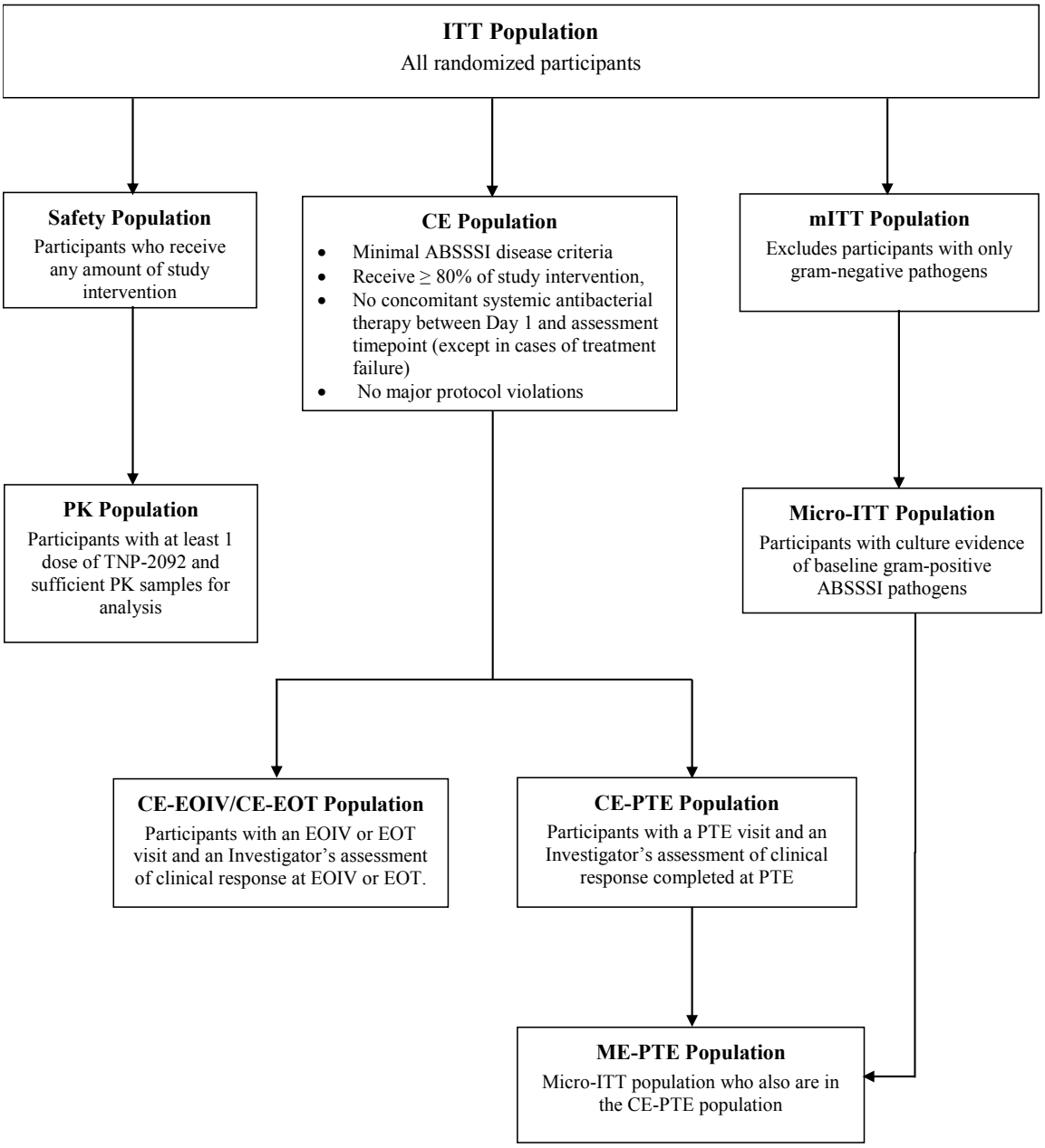
Inclusion in the ITT, safety, and PK populations will be determined programmatically from eCRF data. Inclusion in the mITT population will be determined by the medical monitor. The medical monitor will decide whether each isolate is considered a pathogen. All manual reviews and determinations of population inclusion/exclusion requirements will be done before the study is unblinded.

Table 9 Populations for Analysis

Population	Description
Intent-to-Treat (ITT)	All randomized participants will be included, regardless of whether study intervention is administered.
Safety	All randomized participants who receive any amount of study intervention will constitute the safety population. Participants in the safety population will be analyzed according to study intervention received.
Modified ITT (mITT)	All randomized participants in the ITT population excluding those participants who have gram-negative pathogens only.
Microbiologic ITT (micro-ITT)	All randomized participants in the mITT population with culture evidence of a baseline gram-positive ABSSSI pathogens (exclude sole gram-negative and culture-negative participants)
Clinically Evaluable (CE)	All participants in the ITT population who meet the minimal clinical disease criteria for ABSSSI; do not have any major protocol deviations, receive at least 80% of the expected doses of study intervention; do not receive any potentially-effective systemic antibacterial therapies other than protocol-specified study intervention (except in cases of treatment failure). Included in the CE-EOIV population, if the following conditions are met: • Have an investigator's assessment of clinical response at EOIV (ie, neither response can be indeterminate) • Have an EOIV visit (+ 1 day) • Included in the CE-EOT population, if the following conditions are met: • Have an investigator's assessment of clinical response at EOT (ie, neither response can be indeterminate) • Have an EOT visit (+ 1 day) • Included in the CE-PTE population, if the following conditions are met: • Have an investigator's assessment of clinical response at PTE (ie, neither response can be indeterminate) unless the participant was defined as a clinical failure based on the assessment at EOT • Have a PTE visit 7 to 14 days after EOT, unless the participant was defined as a clinical failure based on the assessment at EOT
Pharmacokinetic (PK)	All participants who receive at least 1 dose of TNP-2092 and have a sufficient number of plasma samples for TNP-2092 PK analysis.
Microbiologically Evaluable at PTE (ME-PTE)	All participants in the micro-ITT population who belong to the CE-PTE population.

ABSSSI = acute bacterial skin and skin structure infection; CE = clinically evaluable; EOIV = end of IV; EOT = end of treatment; ITT = intent-to-treat; mITT = modified ITT; micro-ITT = microbiological ITT; PTE = posttreatment evaluation

Figure 3 Overview of Analysis Populations



ABSSSI = acute bacterial skin and skin structure infection; CE = clinically evaluable; EOIV = end of IV; EOT = end of therapy; ITT = intent-to-treat; IV = intravenous; ME = microbiologically evaluable; mITT = modified intent-to-treat; micro-ITT = microbiological intent-to-treat; PK = pharmacokinetic; PTE = posttreatment evaluation; SAP = statistical analysis plan

9.4 Analysis of Study Populations and Participant Characteristics

Enrollment, study interventions administered, premature discontinuations from study interventions, withdrawals from the study, and protocol deviations will be summarized by treatment arm. A protocol deviation is defined as any variation from the protocol (eg, enrollment of a participant who did not meet all inclusion and exclusion criteria, failure to perform the assessments and procedures within the required time frame).

Demographics (age, race, sex), description of the baseline ABSSSI type, medical history, and baseline clinical signs and symptoms of ABSSSI will be summarized by treatment arm. Baseline pathogens identified at the primary ABSSSI site will also be summarized by treatment arm.

The number and percentage of participants in each population and reasons for exclusion from populations will be listed and summarized by treatment arm.

The SAP will be developed and finalized before the database is locked and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

9.5 Study Intervention Exposure

By treatment arm summaries will be provided for the total number of doses, the number of IV doses of antibiotic, and the number of commercially-available oral antibiotic doses. Compliance to study intervention will be calculated based on the total number of doses taken, divided by the total number of expected doses. A further check of compliance will be the determination of blood concentrations of TNP-2092 during the analytical phase of the study (Section 10.5).

9.6 Safety Analyses

Safety and tolerability of TNP-2092 IV, 300 mg q12h, will be assessed for a minimum of 3 days (6 doses) and a maximum of 14 days to treat ABSSSI is the primary endpoint and the primary objective of this Phase 2 study. Safety will be assessed by AEs, physical examinations, vital signs, laboratory evaluations (hematology, chemistry, coagulation, urinalysis), and ECG parameters. For each safety parameter, the last assessment before the first administration of study intervention will be used as the baseline for all analyses.

The incidence of treatment-emergent AEs (defined in Table 12) will be presented by system organ class and preferred terms according to Medical Dictionary of Regulatory Activities (MedDRA®); by system organ class, preferred term, and relationship to study intervention; and by system organ class, preferred term, and severity. In addition, the incidence of SAEs and treatment-emergent AEs leading to discontinuation of study intervention will be presented by system organ class, preferred term, and relationship to study intervention. If the incidence of SAEs and treatment-emergent AEs leading to discontinuation of study intervention is low, only a listing will be provided.

Descriptive statistics of vital signs at each timepoint measured, as well as the change from baseline and potentially clinically significant changes, will be presented by treatment arm. Potentially clinically significant changes will be defined in the SAP. Descriptive statistics for

ECGs will also be presented for each timepoint measured by treatment arm. Abnormal physical examination data will also be summarized. Descriptive statistics for clinical laboratory tests and for the change from baseline will be presented by study visit and treatment arm.

9.7 Efficacy Analyses – Secondary Endpoints

All secondary efficacy endpoints will be summarized by treatment arm by analysis populations presented in Table 10.

9.7.1 Clinical Outcomes

Programmatic clinical response will be assessed at EA in the ITT, mITT, and micro-ITT populations. The number and percentage of participants with each outcome will be summarized by treatment arm. Confidence intervals (95%) will be provided for the responder rates at EA for each treatment arm. The difference between the responder/clinical response rates in the TNP-2092 treatment arm and the vancomycin treatment arm will be calculated and 95% CI for the difference between rates will be calculated (Miettinen and Nurminen, 1985).

The investigator's assessment of clinical response at EOIV, EOT, and PTE will be summarized for the mITT, micro-ITT, CE-EOIV, CE-EOT, and CE-PTE populations, respectively. Success rates will be calculated for each analysis and differences in success rates between the TNP-2092 and vancomycin treatment arms will be calculated, along with corresponding 95% CI will be presented according to the same methods used for the programmatic response. The number and percentage of participants with sustained clinical response and clinical relapse will also be summarized at LTFU in the micro-ITT and CE-ME populations.

Table 10 Efficacy Evaluations by Analysis Population

Efficacy Endpoints	Efficacy Population						
	ITT	mITT	Micro-ITT	CE-EOIV	CE-EOT	CE-PTE	ME-PTE
Secondary:							
Programmatic clinical response at EA	√	√	√				
Per participant microbiological response at PTE			√				√
Microbiological response per baseline pathogen at PTE			√				√
Investigator's assessment of clinical response at EOIV		√	√	√			
Investigator's assessment of clinical response at EOT		√	√		√		
Investigator's assessment of clinical response at PTE		√	√			√	
Investigator's assessment of sustained clinical response at LTFU		√	√				

CE = clinically evaluable; EA = early assessment; EOIV = end of IV treatment; EOT = end of treatment; IV = intravenous; mITT = modified intent-to-treat; ME = microbiologically evaluable; micro--ITT = microbiological intent-to-treat; PTE = posttreatment evaluation

9.7.2 Microbiological Outcomes

The number and percentage of participants with favorable microbiological responses will be summarized at PTE in the micro-ITT and ME-PTE populations. Responses include eradication, presumed eradication, persistence, presumed persistence, and indeterminate (Table 7). 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. If a participant has > 1 baseline pathogen, all pathogens must have a favorable response to have overall favorable response.

The number and percentage of participants with a favorable outcome (eradication, presumed eradiation) will also be summarized for each baseline pathogen by treatment arm in the micro-ITT and ME-PTE populations.

Emergent infections (eg, superinfection, new infection) will not be considered in the microbiological response and will be listed separately (Table 8).

9.8 Pharmacokinetic Analyses

Characterization of the PK of TNP-2092 for a minimum of 3 days (6 doses) and a maximum of 14 days to treat ABSSSI is an important secondary objective for this study. Plasma samples from participants in the PK population (Section 10.5) will be analyzed for TNP-2092 concentrations with a validated bioanalytical method. Key basic PK parameters will be assessed on Day 1 and at EOIV visits. Only PK samples collected from participants randomized to TNP-2092 (treatment arm A) will be analyzed. Further details of the PK sample collection and analyses are provided the Statistical Analysis Plan and Laboratory Manual.

9.9 Handling of Dropouts, Missing, Unused and Spurious Data

Every effort will be made to collect all data at specified times. For secondary efficacy measures, the outcome will be classified as indeterminate if the data are unavailable for evaluation for any reason. A detailed description of the handling of dropouts and missing, unused, and spurious data will be provided in the SAP.

9.10 Interim Analyses

No interim analysis or data monitoring committee is planned for this study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences CIOMS International Ethical Guidelines
    - Applicable ICH GCP Guidelines

- Applicable laws and regulations

- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Information

10.1.2.1 Investigators and Subinvestigator Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.2.2 Finance and Insurance

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

10.1.3 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4 Informed Consent Process

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Participants will provide written consent to participate in the study at the first visit, before initiation of any study-related procedure after being informed of the purpose of the study as follows:

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of modifications, participants must reconsent to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant or the participant's legally authorized representative. If applicable, it will be provided in certified translation for non-English speaking participants.

Signed consent forms must remain in the participant's study file and be available for verification by the sponsor or representatives of a competent regulatory agency at any time. The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.5 Dissemination of Clinical Study Data

Publication planning and other activities related to nonpromotional, peer-reviewed publications, to ensure the scientific integrity of publication activities will be performed by or on behalf of the sponsor. Access may be granted to analyzable datasets from clinical studies through a secure system, following independent assessment of the scientific merit of a rigorously-defined research question from a third party.

10.1.6 Data Quality Assurance

Written standard operating procedures from InClin will be followed to ensure that the study is conducted, 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, standard operating procedures, GCP, and the applicable regulatory requirement(s)”, will be conducted throughout the conduct of the study.

Each investigator must adhere to the protocol as described in Section 8.1. The investigator will allow representatives of the sponsor or regulatory authorities to inspect facilities and records relevant to this study.

The sponsor or sponsor representative will conduct site visits to inspect study data, participants’ medical records, and eCRFs in accordance with current ICH E6 GCP guideline, and regulations and guidelines, as applicable. Data for all participants will be reviewed to ensure the investigators are following the protocol-criteria for clinical response and queries will be issued as needed to clarify any response that does not meet the protocol definition. The sponsor or sponsor representative will also be able to review 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 ICFs, and all other study-related documents. An unblinded monitor will be utilized for monitoring ongoing drug accountability and adherence to blinding procedures.

The purpose of monitoring is to verify that:

- Rights and well-being of the human participants are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is compliant with the currently approved protocol, 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 ensure the reliability and integrity of the QC systems for the study and recognized standards.

The purpose of an audit is to:

- Ensure participant safety
- Ensure compliance to study protocol procedures, regulatory requirements, and standard operating procedures
- Ensure data quality

Further instructions for the site and sponsor are presented below:

- All participant data relating to the study will be recorded on an eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, laboratory test results, and medication inventory records pertaining to the conduct of this study must be retained by the

investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7 Electronic Case Report Forms and Data Capture System

This study will be performed with an eCRF. 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 participant is treated with study intervention at an investigational site, the sponsor or sponsor representative will meet with the investigator and the study site's personnel to train them to record the data on the eCRFs from an electronic data capture system. The investigator or designee will be responsible for reviewing eCRFs, resolving data queries generated by the sponsor via the system, providing missing or corrected data, and approving all changes performed on the participant data. This approval method will include applying an electronic signature, a uniquely assigned user name, 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 will be answered electronically by that study site's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable) will be collected.

10.1.8 Source Data and Document Management

All data collected on the eCRFs must have a source record. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected and are filed at the investigator's site. Data reported or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. The definition of what constitutes source data can be found in the Monitoring Plan.

The investigator agrees that by his/her participation 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 site during the study on a regular basis, 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 as appropriate. At a participant's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from participants during the study is confidential and disclosure to third parties other than those noted above is prohibited.

10.1.9 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development
- Fabrication or alteration of data

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. The sponsor requires the availability of the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through LTFU for participants 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 and IRB approval and notification, if appropriate.
- A summary of the trial conduct and ethical considerations of the study prepared by the investigator (an IRB summary letter is acceptable).

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-required procedures.

10.1.10 Institutional Review Board Approval

This study will be conducted in compliance with the protocol approved by the IRB 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 except when it may be necessary to eliminate an immediate hazard to a research participant. In such case, the deviation will be reported to the IRB as soon as possible.

This protocol, the informed consent document, and all relevant supporting data must be submitted to the IRB for approval. Approval of the protocol, ICF, and any advertisement used to recruit study participants must be obtained before study initiation.

The investigator is responsible for informing the IRB of any changes made to the protocol, and to advise them, at least once a year, about the study progress. The investigator is also responsible for notifying the IRB of any SAEs and significant AEs that occur during the study.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments. All personal data relating to the identity of the participant will not be disclosed without prior written authorization from the sponsor and participant. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in-line with International Committee of Medical Journal Editors authorship requirements.

10.1.12 Data Management and Monitoring

Training sessions, regular monitoring of the investigative site by sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure quality of all study data.

It will be the responsibility of the investigator to ensure that essential documents are available in the investigator's files or at the institutional site. All documents may be subject to, and should be available for, monitoring by the sponsor or inspection by regulatory authorities.

10.2 Clinical Laboratory Tests

Protocol-required laboratory assessments are presented in Table 11.

Table 11 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count: Red blood cell (RBC) count Hemoglobin Hematocrit Haptoglobin	Coagulation: Partial thromboplastin time (PTT) Prothrombin time/International normalized ratio (PT/INR)	RBC Indices: Mean RBC volume (MCV) Mean RBC hemoglobin (MCH) % reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [a]	Blood urea nitrogen (BUN) Creatinine [b] Glucose	Potassium Sodium Calcium Magnesium Chloride Phosphorus Iron studies (iron, transferrin, transferrin saturation, ferritin) Bicarbonate	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma glutamyltransferase (GGT) Alkaline phosphatase Lactate dehydrogenase Creatine kinase Lipase	Total and direct bilirubin Total protein' Albumin
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if abnormal for WBC, RBC, casts, bacteria, crystals)			
Other screening tests	β-HCG pregnancy test (women of childbearing potential) The results must be entered in the eCRF.			

[a] All events of ALT ≥3 × ULN, bilirubin ≥2 × ULN (>35% direct bilirubin), or ALT ≥3 × ULN, and INR >1.5, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.

[b] According to Cockcroft-Gault Formula: Female = ([140-age] X weight)/(72 X serum creatinine) X 0.85; Male =([140-age] X weight)/(72 X serum creatinine)

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

The definition of an AEs and events that meet that definition are defined in Table 12 and Table 13, respectively.

Table 12 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. 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 intervention 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 (Section 8.2.4 and Section 8.2.3 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 intervention or concomitant medication without any signs or symptoms, unless the participant is hospitalized for observation. • Worsening of the primary ABSSSI for which the participant was enrolled.
Treatment-Emergent AE Definition
• An AE that occurs from the start of the study intervention through the LTFU

Table 13 Events Meeting the AE Definition

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition (not ABSSSI) including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease). Serious adverse events are defined in Table 14.

Table 14 Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:
1. **Results in death**
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

Information regarding the recording and follow-up of AEs and/or SAEs are presented in Table 15. The assessment of AE/SAE intensity is presented in Table 16. The causality is presented in Table 17.

Table 15 Recording and Follow-Up of AE and/or SAE and Assessment of Intensity

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the disposition/AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by health care providers or the participant. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to the health care providers. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Follow-Up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

Table 16 Assessment of Adverse Event/Serious Adverse Event Intensity

Assessment of Intensity
The investigator will assess the intensity for each AE and SAE reported during the study and assign it to a defined category with the following ratings: • None = 0 • Mild = 1: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate = 2: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe = 3: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Table 17 Assessment of Causality

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE according to the following scale: o Unrelated: The event is definitely not associated with administration of study intervention and is judged as clearly due to causes other than the study intervention. o Possibly related (Suspected Adverse Reaction [SAR]): a causal relationship between study intervention and the AE is at least a reasonable possibility, ie, the relationship cannot be ruled out. This implies a lesser degree of certainty about causality than a related AE. Additional evidence to suggest a SAR includes the following: ▪ Individual occurrences of uncommon AEs that are known to be strongly associated with exposure to study intervention (eg, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, Stevens-Johnson Syndrome) ▪ One or more occurrences of an AE that is uncommon in the study population, but not commonly associated with exposure to study intervention (eg, heart valve lesions in young adults, intussusception in healthy infants) o Related (Adverse Reaction): A causal relationship between the study intervention and the AE is definite. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality after receiving follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4 Adverse Events of Interest

Infusion site reactions including thrombotic events are AEs of interest and will be assessed as presented in Table 18.

Table 18 Assessment of Infusion Site Reactions

Assessment of Infusion Site Reactions
Study personnel will assess the occurrence of infusion site reactions, including thrombosis, from the start of IV treatment to EOIV according to the following phlebitis scale (Infusion Nurses Society): 0 = no symptoms 1 = erythema at access site with or without pain 2 = pain at access site with erythema and/or edema 3 = pain at access site with erythema and/or edema, streak formation, palpable venous cord up to 1 inch in length 4 = pain at access site with erythema and/or edema, streak formation, palpable venous cord greater than 1 inch in length, purulent drainage • Mild = 1: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate = 2: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe = 3: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Causality is defined in Table 17.

10.3.5 Reporting of SAEs

Reporting of SAEs to the sponsor is presented in Table 19.

Table 19 SAE Reporting to the Sponsor

SAE Reporting to the Sponsor via Paper CRF
• E-mail transmission of the InClin SAE Report Form is the preferred method to transmit this information to the InClin Drug Safety group • Notification by telephone is acceptable for urgent events and a completed InClin SAE Report will be sent as follow-up with documentation of the SAE information provided via telephone. • Initial notification via telephone does not replace the need for the investigator to complete and sign the InClin SAE Report Form within the designated reporting time frames. • Contacts for SAE reporting can be found in Project Management Plan.

10.4 Prohibited Medications

No concomitant systemic or topical antibacterial agents are permitted during the study. In addition, a list of prohibited concomitant medications is presented in Table 20.

Table 20 List of Prohibited Concomitant Medications

Drug Class	Subclass	Generic Name
Anti-arrhythmics	IA	Disopyramide
		Procainamide
		Quinidine
	III	Amiodarone
		Dofetilide
		Dronedarone
		Ibutilide
		Sotalol
Antimicrobials	Antiparasitics	Praziquantel
Anesthetics		Halothane
HIV-protease inhibitors		Ritonavir-boosted saquinavir
		Saquinavir
		Atazanavir
		Darunavir
		Fosamprenavir
		Tipranavir

HIV = human immunodeficiency virus

Note: Medication use is prohibited by study entry criteria (Section 5.2).

Source: Prescribing information for rifampin (2019) and moxifloxacin (2016).

10.5 Pharmacokinetic Sample Schedule for Pharmacokinetic Assessments

Primary PK parameters will be calculated from concentration versus time data with noncompartmental techniques. These parameters include C_{max}, t_{max}, AUC_{0-12}, and CL (after last dose).

All participants from each treatment arm will have whole blood samples collected on Day 1 and at the EOIV visit. Only PK samples collected from participants in treatment arm A (TNP-2092 arm) will be analyzed and is presented in Table 21. Bioanalytical testing will be performed by Bioanalytical Systems, Inc. 2701 Kent Avenue, West Lafayette, IN 47906 USA.

Table 21 Pharmacokinetic Sample Schedule

Collection Time	Day 1 – First Dose	EOIV – Last Dose a
Predose at 0 minutes	X	X
End of infusion, 57 to 60 minutes after infusion start	X	X
1.5 to 3 hours after infusion start	X	X
4 to 6 hours after infusion start	X	X
12 hours after infusion start	X	X
End of second infusion, 57 to 60 minutes after infusion start	X	Not Applicable

EOIV = end of intravenous

[a] Participants received an IV infusion for at least 3 days (6 doses) up to 14 days. The EOIV infusion will vary by participant from Day 4 to Day 14.

10.6 List of Abbreviations

ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{last}, AUC_{inf}	area under the curve vs. time from time 0 to last time point or to infinity
β-HCG	beta-human chorionic gonadotropin
bid	twice daily
CD4	cluster of differentiation 4
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
D5W	5% dextrose injection
ECG	electrocardiogram
eCRF	electronic case report form
EOIV	end of IV
EOT	end of treatment
GCP	good clinical practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I&D	incision and drainage
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	Interactive web response system
Lesion response	percent reduction in lesion size ≥20% compared with baseline
LTFU	long-term follow-up
MedDRA	Medical Dictionary of Regulatory Activities
mITT	modified intent-to-treat
micro-ITT	microbiologic intent-to-treat
MRSA	methicillin-resistant Staphylococcus aureus
PI	principal investigator
PK	pharmacokinetic
PTE	posttreatment evaluation
q12h	every 12 hours
q24h	every 24 hours
QTcF	QT interval calculated with Fridericia's correction formula
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal half-life
t_{max}	time to maximal concentration
V_z	volume of distribution

10.7 Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until she is postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

1. Documented hysterectomy

Documented bilateral salpingectomy

Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determine study entry. Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    i. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women who do not use hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one follicle stimulating hormone measurement is required.
    ii. Females on hormone replacement therapy and whose menopausal status is in doubt will be required to use 1 nonestrogen hormonal highly effective contraception methods if they wish to continue their hormone replacement therapy during the study. Otherwise, they must discontinue hormone replacement therapy to allow confirmation of postmenopausal status before study enrollment.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours after learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Report Form and submitted to the sponsor within 24 hours after learning of a participant's pregnancy.

- Study medication should be stopped immediately.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.
- The investigator should counsel the participant regarding the possible effects of prior study medication exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. The Pregnancy Report Form will be used to follow-up the outcome of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

11 REFERENCES

1. Arciola CR, Campoccia D, Montanaro L. Implant infections: adhesion, biofilm formation and immune evasion. Nature Reviews/Microbiology. 2018; https://doi.org/10.1038/s41579-018-0019-y.

2. Avelox® [prescribing information]. Wayne, NJ. Bayer Healthcare Pharmaceuticals Inc., September 2016.

3. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013 (report). US Department of Health and Human Services, 2013. Available at http://www.cdc.gov/drugresistance/threat-report-2013/. Accessed 22 August 2018.

4. Chaisson RE. Treatment of chronic infections with rifamycins: Is resistance likely to follow? Antimicrob Agents Chemther. 2003;47(10):3037–3039.

5. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26:404–413.

6. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry—Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Oct 2013. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071185.pdf

7. Infusion Nurses Society. Infusion nursing standards of practice, Phlebitis Scale. J Infus Nurs 2011;34(1S):S65.

8. Ma Z, Lynch AS. Development of a dual-acting antibacterial agent (TNP-2092) for the treatment of persistent bacterial infections. J Med Chem. 2016;59:6645–6657.

9. Miettinen OS, Nurminen MM. Comparative analysis of two rates. Statistics in Medicine. 1985;4 (2):213–226.

10. Pace JL, Rupp ME, Finch RG. *Biofilms, infection, and antimicrobial therapy*. Boca Raton, FL CRC Press; 2006.

11. Rifadin IV [prescribing information]. Bridgewater, NJ: Sanofi-Aventis, 2019.

12. Robertson GT, Bonventre EJ, Doyle TB et al. In vitro evaluation of CBR-2092, a novel rifamycin-quinolone hybrid antibiotic: Studies of the mode of action in Staphylococcus aureus. Antimicrob. Agents Chemother. 2008;52(7):2313–2323.

13. Robertson GT, Bonventre EJ, Doyle TB et al. In vitro evaluation of CBR-2092, a novel rifamycin-quinolone hybrid antibiotic: Studies of the mode of action in Staphylococcus aureus. Antimicrob. Agents Chemother. 2008;52(7):2324–2334.

14. Tande AJ, Patel R. Prosthetic Joint Infection. Clinical Microbiology Reviews. 2014;27(2):302–345.

15. TenNor Therapeutics Limited. Investigator's Brochure. TNP-2092. Edition 2.0. September 2018.

16. Vancomycin [prescribing information]. Lake Forest, IL: Hospira, 2018.

17. Van Hal SJ, Peterson DL. New gram-positive antibiotics: Better than vancomycin? Curr Opin Infect Dis. 2011;24:515–520.

18. Waldvogel, FA, Bisno, AL. Molecular basis of adherence of Staphylococcus aureus to biomaterials. In Waldvogel, FA, Bisno, AL eds. *Infections Associated with Indwelling Medical Devices.* 3rd ed. Washington, DC: ASM Press;2000:27–39.