Statistical Analysis Plan: 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

NCT03964493

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STATISTICAL ANALYSIS PLAN

# 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

Study: PJI001-02

**CONFIDENTIAL**

**August 19, 2019**

# STATISTICAL ANALYSIS PLAN APPROVAL
# Study: PJI001-02
# Version 1.0

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# 1 Abbreviations and Definitions

## 1.1 Abbreviations:

| | |
|---|---|
| ABSSSI | Acute bacterial skin and skin structure infection |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical class |
| BMI | Body Mass Index |
| CE | Clinically evaluable |
| CI | Confidence interval |
| CM | Compartmental modeling |
| CSR | Clinical Study Report |
| CRO | Contract Research Organization |
| CV | Coefficient of Variation |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| GGT | Gamma-glutamyl transferase |
| H | High |
| ITT | Intent-to-treat |
| IV | Intravenous (ly) |
| IWRS | Interactive web response system |
| L | Low |
| LDH | Lactate dehydrogenase |
| LLN | Lower Limit of Normal |
| ME | Microbiologically evaluable |
| MedDRA | Medical Dictionary of Regulatory Activities |

| | |
|---|---|
| MIC | Minimum Inhibitory Concentration |
| $MIC_{50}$ | Minimum Inhibitory Concentration to inhibit 50% of the isolates |
| $MIC_{90}$ | Minimum Inhibitory Concentration to inhibit 90% of the isolates |
| MIN | Minimum |
| MITT | Modified intent-to-treat |
| Micro-ITT | Microbiological intent-to-treat |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| MSSA | Methicillin-sensitive *Staphylococcus aureus* |
| NCA | Non-compartmental analysis |
| PK | Pharmacokinetic |
| PO | Oral |
| q12h | Every 12 hours |
| QTcF | Corrected QT interval using the Fridericia correction formula |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard Deviation |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| WBC | White blood cell count |

## 1.2 Definitions of Terms:

| **Term** | **Definition** |
|---|---|
| Day 1 | Day of administration of first IV dose |
| Dose | Any amount of study drug (IV or PO) taken at the time of dosing. |
| EA | Early assessment (48 - 72 hours after the start of the first dose of IV study drug) |
| EOT | End of Treatment (last day of study drug; Day 7 - Day 14) |
| EOIV | End of IV Treatment (3 - 14 days after treatment start) |

| Term | Definition |
|---|---|
| Lesion Response | Percent reduction in lesion size ≥20% compared with baseline |
| LTFU | Long-Term follow-up (20 - 25 days after EOT) |
| PTE | Post treatment evaluation (7 - 14 days after EOT) |
| Subject | An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control |
| TNP-2092 | The investigational medicinal product in this study which will be administered intravenously every 12 hours at dose equivalent of 300 mg. |
| Vancomycin | The comparator antibiotic which will be administered intravenously every 12 hours at dose equivalent of 1 g. |

## 2 Introduction

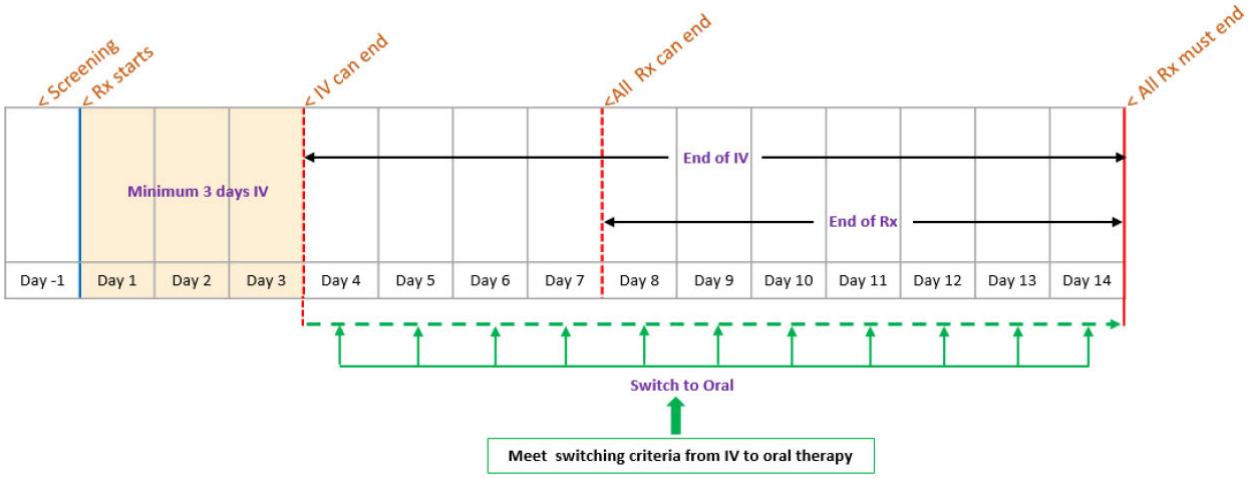
This document presents the Statistical Analysis Plan (SAP) for the protocol PJI001-02, “A Phase 2, Double-Blind, Randomized, Multicenter, Parallel, Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Tnp-2092 to Treat Acute Bacterial Skin and Skin Structure Infection in Adults”. The statistical plan described is an a priori plan and no analyses have been conducted prior to the preparation of this plan. This SAP summarizes the study design and objectives and provides details of the outcome definitions and statistical methods that will be used to analyze the data from protocol PJI001-02. Changes made to the SAP after it has been signed but prior to study unblinding will be documented in an amendment. Any important changes made to the analyses will be described in the clinical study report (CSR). This SAP is based on the original protocol version dated September 16, 2018 and protocol amendment 1 dated February 14, 2019.

## 3 Study Design

This Phase 2, double-blind, randomized, multicenter, parallel, controlled study will be conducted to evaluate safety, tolerability, pharmacokinetic (PK) and efficacy of TNP-2092 300 mg IV q12h and vancomycin 1 g IV q12h in adults with acute bacterial skin and skin structure infection (ABSSSI) suspected or confirmed to be caused by gram-positive pathogens.

The screening period will be up to 1 day in duration before intervention, followed by a treatment period (IV or IV plus oral switch, if applicable) of between 7 to 14 days in duration as presented in Figure 1.

**Figure 1: Overview of Treatment Duration**




IV = intravenous; Rx = treatment

All subjects will be treated with IV study intervention for a minimum of 6 doses and upon meeting protocol-specified switching criteria, subjects may switch and continue treatment of ABSSSI with a commercially-available, open-label, oral antibiotic selected by the investigator. The post treatment evaluation (PTE) visit is 7 to 14 days after the end of treatment (EOT) and a long-term follow-up (LTFU) visit to monitor continuing adverse events (AEs) and concomitant medications is comprised of a telephone call at 20 to 25 days after the EOT visit. Hence the total duration of the study can be up to 40 days from the screening visit to the LTFU visit.

Subjects who meet the entry criteria 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 type to ensure proper balance between treatment arms (Planned N = 120, n = 80 for TNP-2092 arm A and n = 40 for vancomycin arm B). Subjects who are randomized will not be replaced.

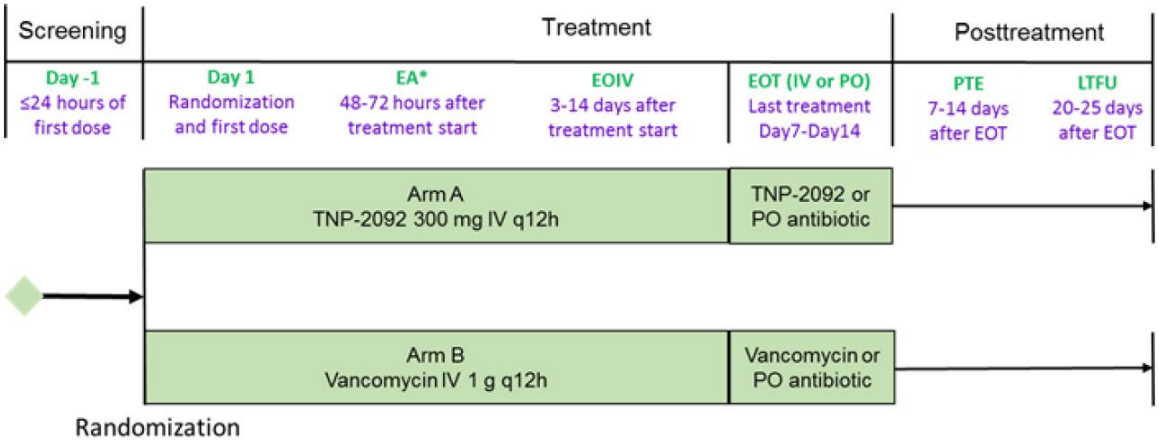
The types of eligible ABSSSI include cellulitis/erysipelas, wound infections, and major cutaneous abscesses; however, participants with major cutaneous abscess should not comprise > 30% of the randomized population. Participants with ABSSSI with a minimal lesion surface area of 75 $cm^2$ will be enrolled. 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 which excludes all participants with gram-negative pathogens.

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. If local antimicrobial susceptibility testing of a baseline pathogen indicates possible non-susceptibility to study intervention (e.g., intermediate susceptibility or resistance to a fluoroquinolone, rifamycin, and/or glycopeptide) but the participant is stable or clinically improving, the participant can 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.

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).

**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. *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.

The primary endpoint is the 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 time points and microbiological responses at PTE.

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. 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.

# 4 Study Objectives

## 4.1 Primary Objectives

The primary objective is as follows:

- Evaluate safety and tolerability of TNP-2092 300 mg q12 formulation compared with vancomycin 1g q12h

## 4.2 Secondary Objectives

- To determine the PK of TNP-2092 300 mg q12h
- To evaluate the efficacy of TNP-2092 300 mg q12h and vancomycin 1 g q12h

## 4.3 Endpoints

The primary endpoints are as follows:

- Incidence, causality, and severity of AEs
- Investigator assessment of thrombotic events and local infusion site reactions and tolerability
- Assessment of vital signs, laboratory data, and ECG findings

The secondary endpoints are as follows:

- Characterize the PK of TNP-2092 300 mg q12h in adult subjects with ABSSSI. PK parameters will be calculated from the concentration versus time data using either non-compartmental analysis (NCA) or compartmental modeling (CM). Although the final decision will be made once the data are available, based on the sampling schedule in Table 21 of the study protocol, CM is more likely to be the applicable method.
- Evaluate early clinical response at:
  - EA in the intent-to-treat (ITT) population
  - EA in the modified intent-to-treat (MITT) population

  - EA in the microbiological intent-to-treat (micro-ITT) population
- Evaluate per-subject microbiological response at:
  - PTE in the in the microbiological intent-to-treat (micro-ITT) population
  - PTE in the in the microbiologically evaluable (ME-PTE) population
- Evaluate per-pathogen microbiological response at:
  - PTE in the in the microbiological intent-to-treat (micro-ITT) population
  - PTE in the in the microbiologically evaluable (ME-PTE) population
- Evaluate the Investigator's assessment of clinical response at each time point:
  - End of IV (EOIV; last day of IV infusion) in the MITT, micro-ITT and CE-EOIV populations
  - End of treatment (EOT; last day of study drug) in the MITT, micro-ITT and CE-EOT populations
  - Post treatment evaluation (PTE; 7 to 14 days after EOT) in the MITT, micro-ITT and CE-PTE populations

## 5 Data Management

Data management procedures, including database design, development of the data dictionary, and coding of medical history, adverse events and medications, will be performed at a Contract Research Organization (CRO). Data will be entered into an electronic case report form (eCRF) at the study sites. A series of logic and consistency checks will be conducted to ensure accuracy and completeness of the clinical database. Safety laboratory results, microbiology data, and pharmacokinetic data will be electronically transmitted from external vendors. After database lock and after the evaluability and pathogen review process has been completed, randomization data will be provided electronically from RTMS, interactive web response system (IWRS) vendor. Refer to the Data Management Plan for further Data Management details.

## 6 Pathogen Determination

Pathogens will be identified based on the genus and species identification from the central laboratory. If the local laboratory grows an acceptable pathogen but the central laboratory is not able to grow the isolate, if isolates are lost during transportation or storage, or if there are any other major discrepancies between the local and central laboratory in the identification of species, the central laboratory or other Sponsor designee will request that the local laboratory resend the isolate. If the central laboratory cannot determine the genus

and species of the isolate for any reason, the local laboratory determination of genus and species will be used for pathogen identification.

Screening/baseline samples are collected within 24 hours of the first dose of study drug on either Day 1 or Day -1. If more than one baseline ABSSSI site sample was obtained using an acceptable ABSSSI specimen or more than one baseline blood sample was obtained, isolates from all samples will be reviewed for pathogen determination. For subjects with cellulitis/erysipelas, if no acceptable baseline infectious material has been obtained, or if no pathogens have been identified from the baseline sample, then a Day 2 or 3 ABSSSI site sample can be used as baseline if the sample is considered acceptable.

The organisms identified in Table 1 will always be considered an ABSSSI pathogen when isolated from an acceptable ABSSSI specimen. Additional pathogens will be identified during pathogen review prior to unblinding of the study.

**Table 1: ABSSSI Pathogens**

| | |
|---|---|
| • Methicillin-resistant *Staphylococcus aureus* (MRSA) | • Methicillin-susceptible *Staphylococcus aureus (*MSSA) |
| • *Streptococcus pyogenes (*Group A *streptococci)* | • *Streptococcus anginosus* |
| • *Streptococcus intermedius* | • *Streptococcus constellatus* |
| • *Streptococcus agalactiae* | • *Streptococcus dysglactiae* |
| • *Staphylococcus haemolyticus* | • *Staphylococcus lugdunensis* |
| • *Escherichia coli* | • *Enterococcus faecalis* |
| • *Enterococcus faecium* | • *Proteus mirabilis* |
| • *Pseudomonas aeruginosa* | • *Klebsiella pneumoniae* |
| • *Group C β-hemolytic streptococci* | • *Streptococcus viridans* group |

The following organisms in Table 2 will never be considered an ABSSSI pathogen when isolated from an ABSSSI specimen:

**Table 2: Not ABSSSI Pathogens**

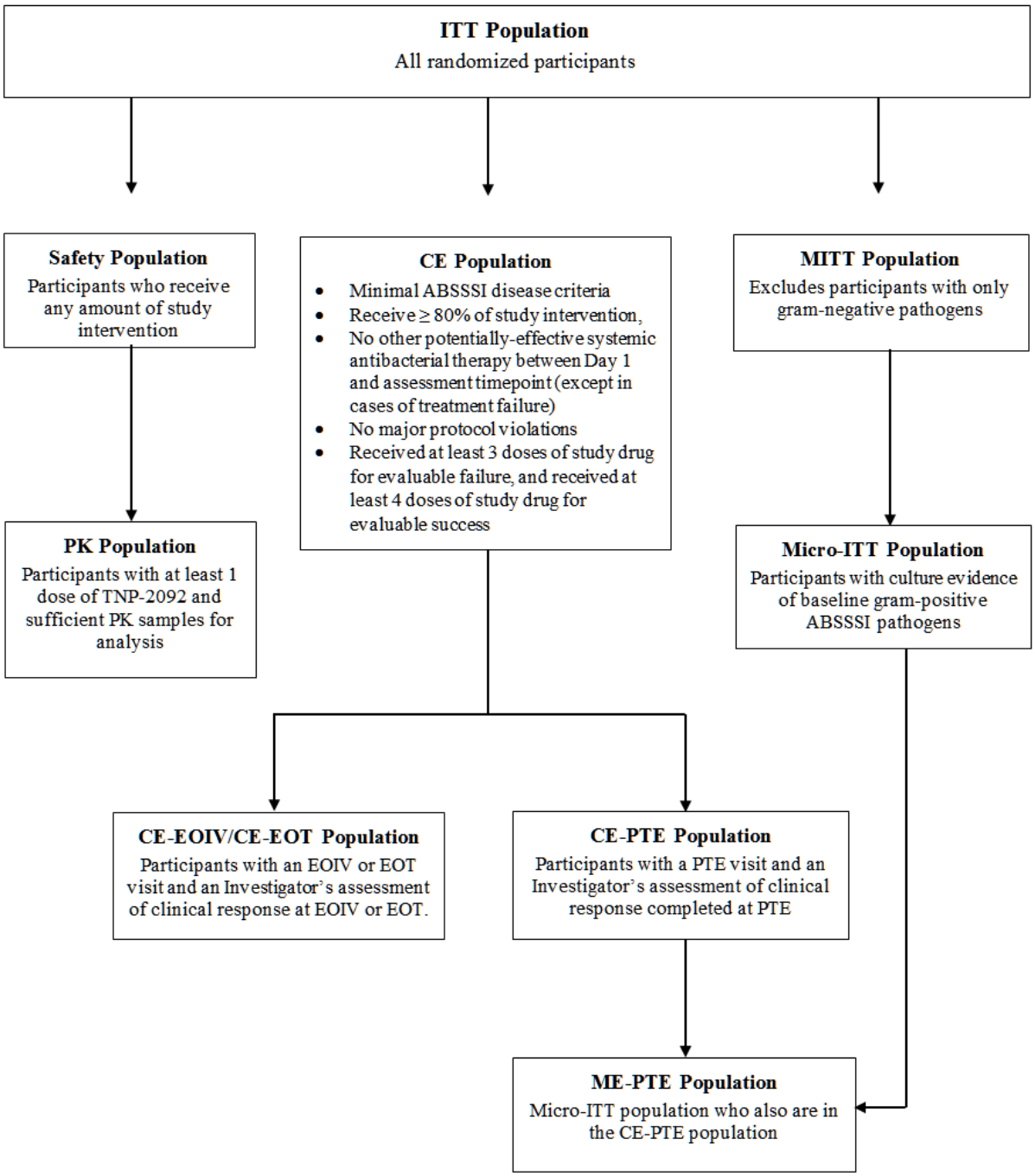
| | |
|---|---|
| • *Staphylococcus saprophyticus* | • *Corynebacterium* spp. |
| • *Staphylococcus epidermidis* | • *Staphylococcus hominis* |
| • *Staphylococcus warneri* | • *Bacillus* spp. |
| • *Micrococcus* spp. | • *Candida* spp. or other fungi |

All other organisms not listed above will be assessed on a case-by-case basis via manual review by the Sponsor (e.g., Gram-negative organisms, anaerobes). If needed, subject clinical (e.g., type of infection, type of specimen, subject underlying conditions, etc.) and microbiological information (e.g., Gram stain, etc.) will be used to assist in determining if the isolate is a pathogen. In addition, all polymicrobial infections (i.e., ABSSSI caused by more than 1 pathogen) and all cases of bacteremia will be reviewed manually.

## 7 Definition of Analysis Populations

The relationship between the analysis sets is shown in Figure 3 below.

**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.

### 7.1 Intent-to-Treat (ITT) Population

The ITT population will consist of all randomized subjects regardless of whether or not the subject received study drug. A subject is considered randomized when the Investigator or Investigator's designee receives the IWRS-generated randomization number.

### 7.2 Modified Intent-to-Treat (MITT) Population

All randomized subjects in the ITT population, excluding subjects with only a Gram-negative pathogen(s) at baseline.

### 7.3 Safety Population

The Safety population will consist of all randomized subjects who receive any amount of study drug. All safety analyses will be conducted in this population and will be presented in the summary tables by the treatment that the subject actually received. In the event that a subject received both TNP-2092 and vancomycin then that subject will be included in the TNP-2092 arm.

### 7.4 Microbiological Intent-to-Treat (Micro-ITT) Population

The Micro-ITT population will consist of all subjects in the ITT population who have culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI. Analyses in this population will be presented in summary tables by the treatment arm to which the subject was randomized.

### 7.5 Clinically Evaluable Population at End-of-IV (EOIV), End-of-Treatment (CE-EOT) and the Post-Treatment Evaluation (CE-PTE)

The CE-EOIV, CE-EOT and CE-PTE populations will consist of all subjects in the ITT population who:

- meet the minimal clinical disease criteria for ABSSSI described in the study Inclusion Criteria (Inclusion Criteria 2a, 2b, 2c, 3, 4a-4f, 5a-5d),
- receive at least 80% of expected IV doses based on length of therapy,
- did not receive any potentially-effective systemic or topical antibacterial therapies other than protocol specified study drug(s) for an indication other than ABSSSI between Day 1 and timepoint for assessment, where the timepoint for assessment is EOIV for the CE-EOIV population, EOT for the CE-EOT population, and PTE for the CE-PTE population.

- Did not have any major protocol violation, including but not limited to:
    - Prior administration of systemic antibacterial therapy within 96 hours before randomization
    - Received the wrong study drug or were unblinded before the timepoint of assessment for reasons other than safety

In addition, to be included in the CE-EOIV population, the following conditions must be met:

- Have an Investigator's assessment of clinical response at EOIV (i.e., response cannot be indeterminate)
- Had an EOIV visit within 1 calendar day of last dose of IV study drug (+1 day) [i.e., within 48 hours of the last dose of IV study drug]

In addition, to be included in the CE-EOT population, the following conditions must be met:

- Have an Investigator's assessment of clinical response at EOT (i.e., response cannot be indeterminate)
- Had an EOT visit within 1 calendar day of last dose of study drug and/or follow up open-label oral antibiotic (+1 day) [i.e., within 48 hours of the last dose of study drug]

To be included in the CE-PTE population, the following conditions must be met:

- Have an Investigator's assessment of clinical response at PTE (i.e., response can't be indeterminate unless the subject is deemed a clinical failure at the EOT visit)
- Had a PTE visit within 7-14 days after the EOT visit. If the EOT visit is out of the study window, then the PTE visit must still be within 7-14 days of the EOT visit. If the EOT visit is missed, then the PTE visit must be within 7-14 days of the last dose of study drug and/or follow up open-label oral antibiotic.

Additional minimal dose requirements for clinical failure or success at EOIV, EOT or PTE:

- Subjects who are defined as clinical failures at EOIV, EOT or PTE with fewer than 3 doses of study drug are not included in the CE-EOIV, CE-EOT or CE-PTE populations, respectively.
- Subjects who are defined as clinical successes at EOIV, EOT or PTE with fewer than 4 doses of study drug are not included in the CE-EOIV, CE-EOT or CE-PTE populations, respectively.

### 7.6 Microbiologically Evaluable Population (ME-PTE)

The ME-PTE Population includes all subjects in the CE-PTE Population with culture evidence of a baseline Gram-positive bacterial pathogen known to cause ABSSSI (i.e., meets both CE-PTE and Micro-ITT Population definitions).

### 7.7 Pharmacokinetic Population (PK)

All subjects who receive at least 1 dose of TNP-2092 and had a sufficient number of plasma samples for TNP-2092 PK analysis.

### 7.8 Pathogen and Evaluability Determination

The Medical Monitor will review both clinical and microbiological data for determination of criteria used to assess inclusion in the analysis populations and for determination of baseline and post-baseline pathogens. The Medical Monitor will be blinded to treatment assignment and will review the data concurrent with the conduct of the study.

Inclusion into the ITT, Safety, and PK Populations will be determined programmatically from the eCRF data. Inclusion into the CE-EOIV, CE-EOT, and CE- PTE Populations will be determined programmatically from the eCRF data and evaluability review conducted by the Medical Monitors. The Medical Monitor may review subject data to confirm that population criteria are satisfied.

Inclusion into the MITT and ME-PTE Populations will be determined programmatically by incorporating the outcome of the pathogen review by the Medical Monitor. The Medical Monitor will determine whether each isolate (baseline and post-baseline) is considered an ABSSSI pathogen based on a review of information from samples including infection type, type of specimen, and local and central laboratory genus and species identification. In the event that a local culture is completed, but the reading from the central lab culture is not available, then the local lab result will be used.

Additional details can be found in the Evaluability and Pathogen review process document and Section 7.8 of this document.

# 8 Definition of Outcome Measures

## 8.1 Clinical Outcome Definitions

### 8.1.1 Programmatic Clinical Response at Early Assessment (EA)

Clinical response at EA will be determined programmatically based on data recorded on the eCRF. Note that the protocol EA visit window is 48-72 hours after the first dose of study drug.

A subject will be classified programmatically as a 'responder at EA' if the percent reduction in the primary ABSSSI lesion area at EA is greater than or equal to 20% compared to baseline and the subject did not die of any cause within 72 hours of the first dose of study drug.

- A subject will be classified programmatically as a 'non-responder at EA' if the percent reduction in the primary ABSSSI lesion size is less than 20% compared to baseline, or the subject received a potentially-effective non-study antibacterial agent with activity against gram-positive organisms for the treatment of ABSSSI through 72 hours, or died of any cause within 72 hours of the first dose of study drug.
- A subject will be classified programmatically as 'indeterminate at EA' if study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up, did not attend the EA clinic appointment, or if the EA visit is out of the 48-72 hour window).

If there is more than one ABSSSI measurement within the 48-72 hour window, the last measurement will be used to assess the clinical response at EA. If the baseline lesion measurement is missing and there is one within 6 hours of the first dose of study drug, this measurement may be considered the baseline measurement.

### 8.1.2 Investigator Assessment of Clinical Response at End-of-IV (EOIV)

Investigator-determined 'clinical improvement at EOIV' is defined by all of the following:

- ABSSSI sufficiently improved such that further IV antibacterial therapy is not needed
- These subjects may have some residual clinical signs and symptoms related to ABSSSI requiring continued oral antibiotic stepdown therapy (provided the subject

meets oral switch criteria, or ancillary (i.e., non-antibiotic) treatment, e.g., bandages on a healing wound, debridement of uninfected tissue.

Investigator-determined 'clinical failure at EOIV' is defined by any of the following:

- Investigator discontinued study intervention and indicated that the ABSSSI had responded inadequately such that alternative (rescue) non-study IV antibacterial therapy was needed,
- The subject received potentially-effective non-study 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 IV regimen,
- Unplanned major surgical intervention (i.e., procedures that would not normally be performed at the bedside) for the ABSSSI under study, or
- Died of any cause up to the EOIV visit.

Investigator-determined 'Indeterminate at EOIV' is defined as:

- Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up).

### 8.1.3 Investigator Assessment of Clinical Response at End-of-Treatment (EOT)

Investigator-determined 'clinical success at EOT' is defined by all of the following:

- ABSSSI sufficiently resolved such that further antibacterial therapy is not needed
- These subjects may have some residual changes related to infection requiring ancillary (i.e., non-antibiotic) treatment; e.g., bandages on a healing wound, debridement of uninfected tissue (i.e., necrotic)
- Did not die of any cause up to the EOT visit.

Investigator-determined 'clinical failure at EOT' is defined by any of the following:

- 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 potentially-effective non-study 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 (i.e., procedures that would not normally be performed at the bedside) for the ABSSSI under study, or
- Died of any cause up to the EOT visit.

Investigator-determined 'Indeterminate at EOT' is defined as:

- Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up).

#### 8.1.4 Investigator-Assessment of Clinical Response at Post-Treatment Evaluation (PTE)

Investigator-determined 'clinical success at PTE' is defined by all of the following:

- ABSSSI sufficiently resolved such that further antibacterial therapy is not needed
- These subjects may have some residual changes related to infection requiring ancillary (i.e., non-antibiotic) treatment, e.g., bandages on a healing wound, debridement of uninfected tissue (i.e., necrotic)
- Did not die of any cause up to the PTE visit.

Investigator-determined 'clinical failure at PTE' is defined by any of the following:

- 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 potentially-effective non-study 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 (i.e., procedures that would not normally be performed at the bedside) for the ABSSSI under study, or

- Died of any cause up to the PTE visit.

Investigator-determined 'Indeterminate at PTE' is defined as:

- Study data are unavailable for evaluation of efficacy for any reason (e.g., missing data, lost to follow-up).

The following overall assessment of clinical response based on the Investigator's Assessment will be determined at the PTE Visit based on the following rules. The Overall Assessment of Clinical Response at PTE will be summarized in all tables and the Investigator's assessment of clinical response at the PTE as reported in the eCRF visit will only be listed.

**Table 3: Overall Assessment of Clinical Response**

| EOT Visit | PTE Visit | Overall Assessment of Clinical Response |
|---|---|---|
| Success | Success | Success |
| Success | Failure | Failure |
| Success | Indeterminate | Indeterminate |
| Failure | Success | Failure |
| Failure | Failure | Failure |
| Failure | Indeterminate | Failure |
| Indeterminate | Success | Indeterminate |
| Indeterminate | Failure | Failure |
| Indeterminate | Indeterminate | Indeterminate |

## 8.2 Microbiologic Response

### 8.2.1 Per-Pathogen Microbiological Response at EOT and PTE Visits

Pathogen microbiological outcome categories are: eradication, presumed eradication, persistence, presumed persistence, and indeterminate and these as defined in the following table. Favorable microbiological outcomes include eradication or presumed eradication. Unfavorable microbiological outcomes include persistence or presumed persistence and are defined in Table 4.

**Table 4: Pathogen Microbiological Response at EOT and PTE Visits**

| | |
|---|---|
| **Eradication** | An adequate source specimen (from ABSSSI site and/or blood) demonstrates absence of the original screening/baseline pathogen(s). If there is a positive blood sample at screening/baseline, the last blood sample on or prior to the referenced visit (*) must be a negative. |
| **Presumed eradication** | An adequate source specimen was not available to culture and the subject was assessed as a clinical success by the Investigator at the referenced visit (*). If there is a positive blood sample at screening/baseline but there is no post-baseline blood sample available and the subject was assessed a clinical success by the Investigator at the referenced visit (*), then categorize as presumed eradication. |
| **Persistence** | An adequate source specimen demonstrates continued presence of the original baseline pathogen(s) (i.e., presence of original baseline pathogen cultured from the site of ABSSSI or blood) at the referenced visit (*). |
| **Presumed persistence** | An adequate source specimen was not available to culture from site of ABSSSI or blood and the subject was assessed as a clinical failure by the Investigator at the referenced visit (*). |
| **Indeterminate** | An adequate source specimen was not available to culture from site of ABSSSI or blood and the subject's clinical response was assessed as indeterminate at the referenced visit (*) |

Notes: Should EA or EOIV pathogen show results of 'no growth' for a subject, but no subsequent pathogens captured for the same subject, then the 'no growth' (i.e. eradication) results will be carried forward to EOT and PTE.

(*) the term 'referenced visit' is 'EOT' when defining the Pathogen Microbiological Response at EOT, and is 'PTE' when defining the Pathogen Microbiological Response at PTE.

### 8.2.2 Per-Subject Overall Microbiological Response at PTE

In order for a subject to have a favorable per-subject microbiological response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). In order for a subject to have an unfavorable per-subject microbiological response, the outcome for any baseline pathogen must be unfavorable (persistence, presumed persistence).

The proportion of subjects with a favorable microbiological response is defined as:

$$P_{Micro\ Fav\ Resp} = \frac{(\#\ subjects\ wih\ eradication\ or\ presumed\ eradication)}{All\ subjects\ (including\ indeterminates)}$$

The overall assessment of microbiological response will be implemented using responses at the EOT and PTE visits as identified in Table 5. Unless otherwise specified, all summaries of microbiological response are based on the overall microbiologic response at PTE.

**Table 5: Overall Assessment of Microbiological Response**

| Microbiologic Response | | |
|---|---|---|
| **EOT Visit** | **PTE Visit** | **Overall Microbiologic Response at PTE** |
| Favorable | Favorable | Favorable |
| Favorable | Unfavorable | Unfavorable |
| Favorable | Indeterminate | Indeterminate |
| Unfavorable | Favorable | Unfavorable |
| Unfavorable | Unfavorable | Unfavorable |
| Unfavorable | Indeterminate | Unfavorable |
| Indeterminate | Favorable | Indeterminate |
| Indeterminate | Unfavorable | Unfavorable |
| Indeterminate | Indeterminate | Indeterminate |
| Favorable is defined as eradication or presumed eradication. | | |

### 8.3 Emergent Infections

Microbiological definitions of superinfections or new infections are defined in Table 6.

**Table 6: Superinfections and New Infections**

| Category | Definition |
|---|---|
| Superinfection | Isolation of a new pathogen(s) (other than the original screening/baseline pathogen[s]) from the primary ABSSSI site (culture) which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy during the period up to and including EOT, based on the Investigator's assessment of clinical response. |
| New infection | Isolation of a new pathogen(s) (other than the original screening/baseline pathogen[s]) from the primary ABSSSI site (culture) which is accompanied by signs and symptoms of infection requiring alternative systemic antimicrobial therapy after EOT, based on the Investigator's assessment of clinical response. |

### 8.4 Safety Outcomes

Safety will be assessed through the determination and recording of the occurrence of adverse events (AEs) and AEs of special interest (Thrombotic and infusion site AEs), as well as by changes in vital signs, ECG parameters, and laboratory data. Additional safety events that occur after PTE will be assessed at LTFU. Adverse events will be evaluated by relationship to study drug and severity. Serious adverse events (SAEs) will be identified.

### 8.5 Pharmacokinetic Outcomes

Sampling for pharmacokinetic analysis (with evaluation of TNP-2092 levels) will occur at the time points shown in "Pharmacokinetic Sample Schedule" of Appendix G. Details of the analysis of this data will be provided separately by the pharmacokineticist in the CSR.

# 9 Statistical Methods and General Considerations

## 9.1 Sample Size

This study is not powered for inferential statistical analysis. With N=80, 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% confidence interval (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. Hence 120 (80 TNP-2092: 40 vancomycin) adult subjects with ABSSSI will be enrolled in this study.

## 9.2 Randomization and Masking

Fixed block randomization using an interactive response system (IWRS) will be used to assign subjects (2:1) to TNP-2092 or vancomycin. Randomization will be stratified by infection type (cellulitis/erysipelas, wound infection, or major cutaneous abscess). After informed consent has been obtained and study eligibility established, the study site's Pharmacist or Pharmacist's designee will obtain the subject number and the study drug assignment from a computer-generated randomization code via IWRS. A subject is considered randomized when the Pharmacist or Pharmacist's designee receives the randomization number or study drug assignment.

This is a double-blind study. Those blinded to study drug assignment include the Sponsor, Investigator, study statistician, clinical study personnel participating in subjects' care or clinical evaluations, and the subjects. Those unblinded to study drug assignment include the pharmacy personnel, the unblinded study monitor, and the bioanalytical laboratory. Blinded personnel must not make any effort to determine which study drug therapy is being administered. Blinded personnel will remain blinded to study drug assignment until all subjects have completed the study and the database is locked. Procedures to ensure that the blind is maintained are detailed in the Sponsor, CRO and Vendor Blinding plan, the Blinded Clinical Monitoring Plan, and the Site-Specific Blinding Plans.

If study drug is determined not to be safe and tolerated, the study drug assignment for those subjects with a safety concern may be unblinded after discussion between the Investigator and Sponsor. The blind may also be broken in the case of a medical emergency requiring

the Investigator to know the identity of the study drug to appropriately guide the subject's medical management. Prior to any unblinding, the Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. If the blind is broken for any reason and the Investigator was unable to contact the Sponsor before unblinding, the Investigator must notify the Sponsor as soon as possible, without revealing the subject's study drug treatment assignment (unless important to the safety of subjects remaining in the study). All instances of unblinding will be thoroughly investigated and documented by the unblinded study monitor.

After the database is locked and the SAP is final, and all analysis populations have been determined, the study will be unblinded.

### 9.3 Interim Analysis

There is no formal interim analysis of efficacy or safety for this study and a Data Monitoring Committee will not be utilized.

### 9.4 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- Baseline - A baseline value is the last non-missing value recorded prior to the first dose of study drug. For subjects who never get dosed, the screening measurements will be considered the baseline assessment. If an assessment has both a date and time that exactly match the date and time of first dose of study drug, the assessment will be counted as baseline.
    - Baseline pathogens however will include any pathogens identified from samples during the baseline/screening visit. For subjects with cellulitis/erysipelas, if no acceptable baseline infectious material has been obtained, or if no pathogens have been identified from the baseline sample, then a Day 2 or 3 ABSSSI site sample can be used as baseline if the sample is considered acceptable.
    - In the event of missing baseline lesion measurements, a lesion size baseline measurement may include a measurement up to 6 hours after the first dose.
- Change from baseline - Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus that subject's baseline value.

- Study day – For a given date (date), the study day is calculated as days since the date of first dose of study drug (firstdose).

  Study day = date – firstdose + 1, where date ≥ firstdose

  Study day = date – firstdose, where date < firstdose
- Days – Durations, expressed in days, between one date (date1) and another later date (date2) are calculated using the following formula: duration in days = (date2-date1+1).
- Body Mass Index (BMI) - BMI ($kg/m^2$) = weight (kg) / [[height (cm)/100]$^2$].
- Age, in years, will be computed from the date of birth to the date of informed consent.

### 9.5 Handling of Missing Data

All missing data and missing and partial dates for events occurring after randomization or for medications received after randomization will be queried for a value. If no value can be obtained missing data will be handled as outlined below:

- All AEs with partial or missing dates and times will be considered treatment emergent unless a partial start date and/or time indicates the AE began prior to the start of study medication or a stop date indicates the AE ended prior to the start of study medication.
- The severity and causality assessment for adverse events must not be missing and will be queried for a value. Should there be missing data, adverse events with missing severity will be considered severe and adverse events with missing relationship to study drug will be considered related to study drug.
- Missing start and stop times for antibiotics will be queried for a value. The actual value (blank) will be recorded on the eCRF and will be used in the listings.
- All other (non-antibiotic) medications with partial or missing dates and times recorded on the concomitant medication eCRF will be considered concomitant unless a partial stop date and time clearly indicates it was stopped before the first dose of study treatment.

For clinical and microbiological response, missing data will be handled as follows:

- For the primary efficacy outcome measure (early clinical response at 48 to 72 hours):
  - The subject will have missing data if there is no lesion size measurement (either length or width) at the EA visit and will be defined as an indeterminate response.

- If the time of administration of the first dose of study drug is missing, the subject will also be defined as an indeterminate response.

- For the Investigator's assessment of clinical response:
  - Subjects will be defined as an indeterminate if the Investigator cannot determine whether the subject is a clinical success/improvement or failure or if any data is missing to make a determination of failure or success. By definition, subjects with an indeterminate response are included in the denominator for analyses in the ITT, MITT, and micro-ITT analysis sets, and thus, are considered failures; however subjects with an indeterminate response are excluded from the CE-EOIV, CE-EOT, CE-PTE, and ME-PTE Populations.

- For microbiologic response:
  - If no source specimen is obtained and the subject has an Investigator's assessment of clinical response, the per-pathogen microbiological response is based on the Investigator's assessment of clinical response; hence a per-pathogen microbiological response will be considered missing or indeterminate only if the clinical response is also missing or indeterminate.

- Missing values for other individual data points will remain as missing. Missing values will not be imputed and only observed values will be used in data analyses and presentations.

- Where individual data points are missing, categorical data will be summarized based on reduced denominators (i.e., only subjects with available data will be included in the denominators).

### 9.6 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

- All listings will be sorted by subject number in ascending order. All relevant data captured on the case report forms (eCRFs) and external data sources, including specific descriptions of 'other' and comments fields will be included on the listings.

- All summary tables will be presented by study drug. Summary tables presenting results by study visit will include all scheduled study visits using informative visit labels.

- Continuous variables will be summarized using number (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries of blood concentration will also include the geometric mean (GM) and coefficient of variation (CV).
- Frequency counts and percentages will be reported for all categorical data.
- Duration variables will be calculated using the general formula (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤ 5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.
- For all "by visit" safety tables (e.g., laboratory values, vital signs, electrocardiograms (ECGs)), nominal visits will be summarized. In addition within tables that summarize changes from baseline, the minimum and maximum post-baseline values will be summarized to take unscheduled visits into account.
- Version 9.4 of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

- The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to this will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

# 10 Statistical Analyses

## 10.1 Subject Disposition

The number and percentage of subjects included in each of the analysis populations (ITT, MITT, Safety, Micro-ITT, CE-EOIV, CE-EOT, CE-PTE, ME-PTE) will be summarized by treatment group and the number of subjects screened and the reasons for screen failures will also be summarized. A table will summarize the reasons for exclusion from each

population and a listing will be provided that indicates each subject's inclusion/exclusion from the CE populations and the reason for exclusion from each CE population.

The number and percentage of subjects completing the study, prematurely discontinuing from study drug, and prematurely withdrawing from the study will be presented for each treatment group for the ITT, Safety, and CE- PTE populations. Reasons for premature discontinuation of study drug and/or premature withdrawal from the study as recorded on the eCRF will be summarized (number and percentage) by treatment group.

A listing of all subjects who prematurely discontinued from study drug or prematurely withdrew from the study will be presented, and the primary reason for discontinuation of study drug or withdrawal from the study will be provided.

### 10.2 Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be presented by treatment group in the ITT, Safety, Micro-ITT, CE-EOIV, CE-EOT, and CE-PTE analysis populations. A table will present the subject demographics (e.g., gender, age, ethnicity and race) and baseline characteristics (height, weight, and BMI) collected before the start of study drug.

A demographic data listing, which includes the date the informed consent was signed, will also be provided.

### 10.3 Medical and Surgical History

Medical history will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) classification, version 21.1. Medical history (skin infection related) and all other medical history and surgical history will be summarized separately for the ITT Population and Safety population by system organ class, preferred term, and treatment group. Subjects reporting the same system organ class or preferred term more than once will be counted only once for that system organ class and preferred term.

Relevant medical and surgical history for all prior and concurrent skin infections, previous history of ABSSSI (within 10 years), current or recent IV drug use, chronic hepatic disease, concurrent secondary infection, history of diabetes mellitus, peripheral vascular disease or alcohol abuse will be identified if possible from the medical history terms and will be summarized treatment group for the ITT and Safety populations.

A listing of medical and surgical history will be provided.

### 10.4 Baseline Disease Characteristics

The primary disease diagnosis at baseline (cellulitis/erysipelas, wound infection, or major cutaneous abscess), location of infection, symptoms of infection, and size of infection (<=300 $cm^2$, >300-600 $cm^2$, >600-1000 $cm^2$ and >1000 $cm^2$) will be summarized by treatment group for the ITT, Micro-ITT, CE-EOIV, CE-EOT, and CE-PTE Populations. The location of infection will be categorized as follows: head or face or neck, chest or shoulder or back or abdomen, groin or buttock, arm or hand (upper extremities), and leg or thigh or knee or lower leg or ankle or foot (lower extremities).

Baseline information about each ABSSSI including mean infection area, mean infection area by disease diagnosis, and the signs and symptoms of disease will be summarized by treatment group for the ITT, Micro-ITT, CE-EOIV, CE-EOT, and CE-PTE populations.

### 10.5 Baseline Microbiology

The number and percentage of subjects with each type of ABSSSI site specimen obtained, whether or not there was Gram stain, whether there was growth, whether there was culture grown, the type of bacteria (Gram-positive cocci, Gram-negative cocci, Gram-positive bacilli, Gram-negative bacilli), and the presence of white blood cells from the local laboratory will be provided by treatment group in the Micro-ITT and ME-PTE populations. Baseline blood specimen results from the local laboratory will be summarized similarly for the Micro-ITT and ME-PTE populations. All ABSSSI site specimen and blood specimen Gram stain results will be listed.

The pathogenic organisms identified by the central or local laboratory from the baseline blood culture or culture of the ABSSSI specimen will be presented. If there is disagreement between the central and local organism, the pathogen will be identified as described in the Evaluability and Pathogen Review process document. The number and percentage of subjects with Gram positive and Gram negative organisms will be presented by genus and species for the Micro-ITT and ME-PTE populations overall and by infection type; additionally for the Staphylococcus aureus genus and species, the resistance phenotype will also be presented for Methicillin, Rifampin and Ciprofloxacin. The same pathogen identified from both the blood and the ABSSSI culture will be counted only once in the summary. The pathogenic organisms identified at baseline from blood sample(s) will also be presented for the Micro-ITT and ME-PTE populations.

The number and percentage of subjects with monomicrobial Gram-positive, polymicrobial Gram-positive, mixed (Gram positive and Gram negative) infections, will be presented by treatment group, and provided for specimens from blood or ABSSSI culture for both the Micro-ITT and ME-PTE populations. When per-subject counts of *S. aureus* are presented, subjects with both MRSA and MSSA are counted only once.

A listing will be provided that includes all baseline and post-baseline isolates obtained from the blood and primary ABSSSI site specimen and will indicate the type of specimen and pathogenic organism identified from both the local and central laboratories. Gram stain results will also be listed.

The minimum inhibitory concentration (MIC) of TNP-2092 to baseline pathogens from the primary ABSSSI site or blood culture will be summarized by genus, species and treatment group in the Micro-ITT and ME-PTE populations. The MIC of vancomycin will be summarized similarly. If available, the baseline MIC of other available antibacterial medications (e.g., Rifampin, Ciprofloxacin and Methicillin) will be summarized for the all pathogen genus and species by treatment group in the Micro-ITT population. Summary Statistics (range, $MIC_{50}$, $MIC_{90}$) will be presented for the study drug received to baseline pathogens from the primary ABSSSI site or blood culture will be summarized by treatment group in the Micro-ITT and ME-PTE populations. $MIC_{50}$ and $MIC_{90}$ values will only be presented for a particular pathogen if there are >=10 pathogens identified within a treatment arm. The $MIC_{50}$ and $MIC_{90}$ are the MICs required to inhibit the growth of 50% and 90% of organisms, respectively. For subjects with more than one baseline pathogen of the same genus and species, the one with the highest MIC to study drug received will be selected for analysis; thus subjects are counted only once for that pathogen. If there is a tie, the MIC with the lowest disk diffusion (if applicable) to study drug received will be chosen. Otherwise, the highest accession number is chosen.

### 10.6 Prior and Concomitant Medications

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

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Generic Drug Names using the World Health Organization (WHODrug

Global B3, March 2019) dictionary. Anatomical Therapeutic Chemical Classification (ATC) level 4 (fourth level indicates the chemical/therapeutic/pharmacologic subgroup) and 3 (third level indicates the therapeutic/pharmacologic subgroup).

Prior medications are those medications taken before the first dose of study drug. Concomitant medications are those medications taken at the start of study drug or initiated after the initial dose of study drug, or medications that were initiated prior to the start of study drug and continue to be taken after study drug is administered. (See the "Handling of Missing Data" section for details on handling in the event of missing medication dates.)

The proportion of subjects who receive the following prior and concomitant medications will be summarized by ATC level 3 class, preferred term, and treatment group:

- Concomitant systemic or topical antibacterial medications (excluding study drug) taken between time of the first administration of study drug on Day 1, the EOIV visit (ITT, MITT, CE-EOIV populations), the EOT Visit (ITT, MITT, CE-EOT populations) and the PTE Visit (ITT, MITT, CE-PTE populations)
- Prior medications (including antibacterial) taken (ITT, Safety populations)
- Concomitant non-antibacterial medications (ITT, Safety Population)

Subjects will be counted only once for an ATC class and preferred term.

All prior and concomitant antibacterial medications will be listed. All prior and concomitant non-antibacterials will also be listed

### 10.7 Study Drug Exposure and Compliance

The active study drugs TNP-2092 (300 mg IV q12h infusion) and vancomycin (1 g IV q12h infusion), will be administered for at least 6 doses up to a maximum of 14 days. The maximum of 14 days would result when subjects receive the IV formulations for the entire treatment duration. Alternatively, subjects may be switched to a commercially-available, open-label, oral antibiotic (as selected by the investigator) after 6 doses and will continue oral antibiotic treatment through the EOT visit. The Intervention comprising IV or IV plus oral medications switch (if applicable) will be administered for a minimum of 7 days up to 14 days.

By treatment group summaries will be provided for total number of IV doses in the ITT, MITT, Safety, CE-EOIV, CE-EOT and CE-PTE populations. The number of days and doses of IV dosing, until switch to PO, will also be summarized.

Duration of treatment is defined as the number of calendar days from when the subject first received study treatment until the day that they last received study treatment (IV or PO) and is calculated as (date of last dose – date of first dose +1). Duration of treatment will be looked at overall, and then also by route (IV or PO), where the duration of oral dosing is defined as the last day of oral dosing minus the first day of oral dosing + 1.

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

$$\boldsymbol{Compliance_{IV}} = 100 * \frac{(Number\ of\ doses\ received\ (IV))}{(Expected\ number\ of\ doses\ (IV))}$$

Descriptive statistics of percent compliance as well as the number and percentage of subjects at least 80% compliant by number of IV doses will be provided by treatment group for the ITT, MITT, Safety, CE-EOIV, CE-EOT, and CE-PTE populations.

Descriptive statistics of study drug exposure by route of administration will also summarized by treatment group, for the ITT, MITT, Safety, CE-EOIV, CE-EOT, and CE-PTE populations. This entails days of dosing for the IV and PO dosing regimens as well as IV doses for the intravenous portion.

### 10.8 Efficacy Analyses

For all efficacy analyses, subjects will be analyzed in the group to which they were randomized. By definition, subjects who receive the wrong study drug are not included in the CE and ME-PTE populations. The secondary efficacy endpoints are identified in Table 7.

All confidence intervals for responder rates or rates of success will be computed using the Exact (Clopper-Pearson) Confidence Limits. The differences in responder or success rates will be calculated and the confidence intervals for these differences will be computed using the method developed by Miettinen and Nurminen (Miettinen and Nurminen, 1985, Reference 2). Confidence intervals will not be calculated for by pathogen results.

**Table 7: Secondary Efficacy Endpoints**

| Efficacy Endpoints | Efficacy Population | | | | | | |
|---|---|---|---|---|---|---|---|
| | ITT | MITT | Micro-ITT | CE-EOIV | CE-EOT | CE-PTE | ME-PTE |
| Programmatic clinical response at EA | √ | √ | √ | | | | |
| Per-subject 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 | | √ | √ | | | √ | |

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 = post treatment evaluation

### 10.8.1 Efficacy Analysis

The efficacy analysis of interest is an examination of the percentage of subjects with early Clinical Response at the EA visit in the TNP-2092 treated group vs the percentage in the vancomycin group in the ITT population. This aligns with the FDA's primary efficacy endpoint of interest in ABSSSI studies (reference 1). The number and percentage of responders, non-responders and indeterminate responses will be summarized by treatment group and an exact 95% CI will be provided for the responder rates in each treatment group. The difference between the responder rates will be calculated and the difference between rates will be calculated. A summary of reasons for programmatic non-responder and indeterminate response at the EA Visit will also be summarized in the ITT population. Additional secondary efficacy analyses will also be included for the early clinical response at EA for the MITT and Micro-ITT populations. Similarly the reasons for programmatic non-responder and indeterminate response at the EA Visit will also be provided.

The Investigator's assessment of clinical response will be classified as described in the "Clinical Outcome Definitions" section of this SAP. The number of subjects with an

Investigator's assessment of 'clinical improvement', 'clinical failure', and 'indeterminate' at EOIV will be summarized for both treatment groups in the MITT, Micro-ITT and CE-EOIV populations. The number of subjects with an Investigator's assessment of 'clinical success', 'clinical failure', and 'indeterminate' at EOT will be summarized for both treatment groups in the MITT, Micro-ITT and CE-EOT populations. The Overall Assessment of Clinical Response based on the Investigator's assessment at PTE will be summarized for both treatment groups in the MITT, Micro-ITT and CE-PTE populations.

Note that subjects with an indeterminate response will be excluded from summaries in the CE-EOIV, CE-EOT and CE-PTE populations. The 95% CI will be provided for the rate of clinical success or improvement for each treatment group. The 95% CI will also be provided for the difference in rates of improvement at EOIV in the MITT, Micro-ITT and the CE-EOIV populations. The 95% CI will also be provided for the difference in rates of success at EOT in the MITT, Micro-ITT and the CE-EOT populations. Similarly the 95% CI will be provided for the difference in rates of success at PTE in the MITT, Micro-ITT and the CE-PTE populations. The reasons for 'failure' and 'indeterminate' will be summarized as well for the clinical responses at EOIV, EOT and PTE for the indicated populations as well as for the MITT and Micro-ITT populations.

The Overall Assessment of Clinical Response based on the Investigator's assessment at PTE will also be summarized by baseline pathogen in the Micro-ITT and ME-PTE populations. The Overall Assessment of Clinical response at PTE will also be summarized by the MIC of TNP-2092 and MIC of Vancomycin by treatment group in the Micro-ITT and ME-PTE populations.

### 10.8.2 Additional Efficacy Analysis

Early clinical response will be summarized in the ITT, MITT, and Micro-ITT populations, excluding subjects who did not receive any study drug. Early clinical response at the EA visit will also be summarized by ABSSSI type in the ITT and MITT populations. Also early clinical response at EA will be summarized by pathogen and baseline MIC of TNP-2092 and vancomycin, by treatment group in the Micro-ITT and ME-PTE populations.

Clinical response at EOIV, EOT and overall assessment of clinical response at PTE will also be summarized by ABSSSI type in the MITT and CE-PTE populations. Also clinical response at EOIV, EOT and the overall assessment of clinical response at PTE will be summarized by pathogen and baseline MIC of TNP-2092 and vancomycin, by treatment in the Micro-ITT and ME-PTE populations.

### 10.8.3 Microbiological Outcomes

The number and percentage of subjects with favorable, unfavorable, and indeterminate microbiological responses will be summarized for the overall response at PTE in the micro-ITT and ME-PTE populations. A 2-sided exact 95% CI will be constructed for the percentage of subjects with favorable response and a 95% CI will be calculated for the difference in the per-subject favorable microbiological response.

Microbiologic response will be summarized by baseline pathogen and treatment randomized to, for each pathogen isolated at baseline from the primary ABSSSI site or from blood in the Micro-ITT and ME-PTE populations.

A listing will be provided that presents the subjects with a superinfection or a new infection.

## 10.9 Safety Analyses

All safety analyses will be conducted in the Safety population.

### 10.9.1 Adverse Events

Verbatim descriptions of AEs will be coded using Version 21.1 of MedDRA. Summary tables will be provided for all treatment-emergent adverse events (TEAEs). A treatment-emergent AE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug and up through the last study visit or evaluation, or an SAE that occurs during or after the first administration of study drug up through 30 days after the final administration of study drug.

An overall summary of AEs will include number and percentage of subjects in each treatment group who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE (defined as possibly, probably or definitely related to study drug), any severe or life-threatening TEAE, any serious TEAE (SAE), any drug-related

SAE, any SAE leading to death, and any TEAE leading to premature discontinuation of study drug and any SAE leading to premature study drug discontinuation.

All remaining adverse event tables will be summarized by treatment group and treatment type at start of adverse event: IV, oral, post-oral, and overall. Adverse events associated with IV administration, includes all AEs that started between the time of first IV dose and before the first oral dose (or last IV dose if subject never switched). Adverse events associated with oral administration, includes all AEs that started between the first oral dose to the last oral dose. Post-oral includes all AEs that started after the last oral dose. The number and percentage of subjects reporting a TEAE in each treatment group and treatment type will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (mild, moderate, and severe/life-threatening/death); and by system organ class, preferred term, and relationship (unrelated [defined as unrelated or unlikely related to study drug] or related to study drug).

Summary tables will be presented alphabetically by system organ class and preferred term within system organ class. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to study drug.

The number and percentage of subjects reporting a SAE and reporting a TEAE leading to premature discontinuation of study drug in each treatment group will be summarized by system organ class and preferred term.

The incidence of TEAEs that occur in at least 2% of subjects in either treatment group will be summarized by preferred term and treatment group, sorted by decreasing frequency in the TNP-2092 group.

Infusion related AEs (e.g., thrombosis, phlebitis) will be considered AEs of special interest and will be summarized by treatment groups over the period these are collected (D1 to EOIV visits).

In addition, all AEs (including non-TEAEs), serious AEs (SAEs), and TEAEs leading to study drug discontinuation will be provided in listings.

### 10.9.2 Laboratory Values

Summaries of laboratory data will include hematology, chemistry, coagulation and C-reactive protein laboratory parameters. Laboratory parameters will be presented in alphabetic order with the following exceptions: differentials of white blood cell (WBC) counts will be presented following the WBC results, and chemistry parameters will first be grouped by organ class (renal, liver, electrolytes, and other) and presented alphabetically within each of these classes, as shown in Table 8.

Several analyses of the laboratory data will be presented. Descriptive statistics (based on standard units) for chemistry, hematology, and coagulation values and the change from baseline will be summarized by treatment group at Day 1, Day 2, EA, EOIV, EOT, and PTE visits, and for the overall minimum and maximum post-baseline values (which includes unscheduled visits). Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value.

**Table 8: Laboratory Parameters**

| | |
|---|---|
| Renal | Blood urea nitrogen<br>Creatinine |
| Liver | Alkaline phosphatase<br>ALT<br>AST<br>Bilirubin direct<br>Bilirubin total<br>GGT<br>LDH |
| Electrolytes | Bicarbonate<br>Calcium<br>Chloride<br>Magnesium<br>Potassium<br>Sodium |
| Other | Albumin<br>Creatine kinase<br>Glucose, nonfasting<br>Phosphorus<br>Total protein |

Toxicity grade will be determined based on the modified DMID criteria (Appendix B). Shift tables will be presented to show the number of subjects with a chemistry or hematology laboratory value with a grade of 1, 2, 3 or 4 at baseline versus the worst post-baseline value.

Post-baseline substantially abnormal clinical laboratory values will also be summarized. For hematology, where substantially abnormal is defined as <75% of the lower limit of normal

(LLN) (<50% of ANC) for values normal at baseline, and <75% of the LLN (<50% for ANC) and of baseline for values abnormal at baseline. For chemistry substantially abnormal is defined as 2 x the upper limit of normal (ULN) for values normal at baseline and 2 x the ULN and 2 x the baseline.

The number and percentage of subjects with elevated liver function assessments will also be summarized by visit using the following categories: >3-5 xULN, >5-10 xULN, and >10 xULN, where ULN is the upper limit of normal.

A listing will be presented identifying all subject records meeting the substantially abnormal hematology, chemistry criteria. This same listing will also contain any abnormal liver function results that meet the laboratory criteria of Hy's law, which is: AST or ALT > 3xULN, alkaline phosphatase (ALP) < 2xULN, and total bilirubin > 2 ULN (reference 3).

A general detailed subject listing of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the clinically notable thresholds.

### 10.9.3 Vital Signs

Blood pressure (systolic and diastolic), respiration rate, heart rate, and temperature will be summarized using descriptive statistics by treatment group at each time point at which they were measured. Descriptive statistics of the change from baseline to each post-baseline time visit will also be provided.

The number and percentage of subject abnormal values, identified by the threshold levels provided in Table 9, will be summarized by treatment group. Only subjects with both baseline and post-baseline values will be summarized for diastolic blood pressure increases. All vital signs will also be provided in by-subject listings.

**Table 9: Abnormal Vital Threshold Values**

| Vital Sign | Threshold |
|---|---|
| Diastolic blood pressure | > 20 mmHg increase from baseline |
| Systolic blood pressure | ≥ 140 mmHg |
| Heart rate | < 60 beats/min |
| Heart rate | > 120 beats/min |
| Temperature | >102.3° F |

### 10.9.4 Electrocardiogram

ECGs will be recorded in triplicate at each visit, where all three measurements are taken within a 15 minute period. The mean of available triplicate values will be calculated and reported for each time point. If there are no triplicate values, the mean of the duplicate or single value will be used. ECGs are local only (no central ECGs) and the only parameter captured is the QT interval using the Fridericia correction formula (QTcF). Descriptive statistics for QTcF as well as the changes from baseline will be presented by treatment group at each scheduled visit.

A distribution showing counts and percentages for the maximum increase post-baseline to EOT, and then to PTE, will be provided for QTcF using the following categories: <0, ≥1 - <30 msec, ≥30 - <60 msec, ≥60 - <90 msec, >=90 msec. Actual QTcF visit values will also be summarized using counts and percentages for the following categories: ≤ 450, > 450 - ≤ 480, >480 - ≤ 500, and >500 msec).

The shift from baseline to each post-baseline visit will be summarized for the overall ECG interpretation. ECG interpretation categories include: normal, abnormal not clinically significant, and abnormal clinically significant. If there are differences in the interpretation for any of the triplicate values at a visit, the most severe interpretation will be summarized.

A listing of electrocardiogram data will also be provided.

### 10.9.5 Physical Examinations

Physical examination results will be presented in by-subject listings.

### 10.9.6 Pharmacokinetic Analyses

PK parameters will be calculated from the concentration versus time data using either NCA or CM. Although the final decision will be made once the data are available, based on the sampling schedule in Table 21 of the study protocol, CM is more likely to be the applicable method. If CM is used, then the estimated parameters will be: Central compartment clearance (CL), intercompartmental clearance (CLD2), volume of the central (V1) and peripheral (V2) compartments, distribution and elimination rate constants and their associated $t_{½}$s, steady-state maximum plasma drug concentration ($C_{max}$) and area under the curve (AUC), where AUC is over a dosing interval (12 hr). If NCA is used, then the estimated parameters will be: $C_{max}$, time to maximum observed plasma concentration ($t_{max}$), AUC versus time from time 0 to 12 hours [$AUC_{0-12}$], and CL [after last dose].

Summaries for TNP-2092 blood concentrations and PK parameters will include descriptive statistics (including the geometric mean and geometric CV% for all parameters except $t_{max}$)

If NCA is used, then figures for TNP-2092 plasma concentrations will display geometric mean concentrations versus time on linear and semi-logarithmic axes. Nominal blood sampling times will be used to calculate the geometric mean concentrations at each time point. Individual subject plasma concentrations versus time will be displayed on linear and semi-logarithmic axes. Boxplots comparing select PK parameters, for Day 1 (first dose) versus EOIV (last dose), will also be displayed.

If CM is used, then individual subjects observed and model-predicted plasma concentrations will be plotted on linear and semi-logarithmic axes.

Subject plasma concentrations for TNP-2092 and PK parameters values will be listed.

### 10.9.7 Protocol Deviations

A listing of all protocol deviations will be provided. Protocol deviations will also be reviewed by the Sponsor and categorized into general categories such as: randomization, at least one inclusion criterion not met, at least one exclusion criterion met, study procedures/visits not done, study visit outside window, noncompliance with dose, and use of prohibited medications or treatments. The number of subjects with at least one protocol deviation, the number of subjects with a minor protocol deviation, the number of subjects with a major (or

important) deviation, and the number of subjects with at least one deviation in each category will be presented by treatment group for the ITT Population. A major (or important) deviation is defined as one that potentially affects the efficacy and/or safety analyses and will be determined by a review by the Sponsor. The study Medical Responsibility Plan and the InClin standard operating procedure 02-06.03 (Review and Reporting of Deviations from Clinical Protocol) will be followed for the reporting, review, and management of protocol deviations.

## 11 Deviations from the Protocol

The SAP and the population definition sections of the protocol specify that the Clinically Evaluable populations include subjects who "did not receive any potentially-effective systemic antibacterial therapies other than protocol specified study drug(s) between Day 1 and timepoint for assessment"; however Figure 3 of the protocol incorrectly omits inclusion of the words "potentially-effective".

Table 10 of the protocol specified that the investigator's assessment of sustained clinical response would be summarized at LTFU. The investigator's assessment is not collected at LTFU and cannot be summarized.

## 12 Reference List

1. 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

2. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine. 1985;4(2):213-226.

3. Food and Drug Administration Guidance Document. Drug- Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at: https://www.fda.gov/media/116737/download

4. Qin Z. Protocol Clarification Letter. April 24, 2019

## Appendix A. Schedule of Events

**Note**: All table and section references in the appendices are referring to the protocol.
The calendar day on which the first dose of study drug is administered is Day 1.

| 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, **and** if repeat culture is clinically indicated, or **(b)** 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

## Appendix B. Division of Microbiology and Infectious Diseases Adult Toxicity Table

The DMID Adult Toxicity Table (November 21, 2007) was modified to exclude the clinical component of the toxicity grading because clinical signs and symptoms related to abnormal laboratory values are not collected in this study. In addition, Grade 0 was added to the table so that shifts from normal could be analyzed. For toxicity grades based on a multiple of the ULN, the normal range from the central laboratory will be applied. For toxicity grades based on fixed values, the grades will be assigned regardless of the normal actual range values from the central laboratory. For example, a hemoglobin value of 10.0 gm/dL will be assigned a grade of 1 toxicity, even if the lower limit of normal from the laboratory was 9.8 gm/dL.

| ENZYMES | | | | | |
|---|---|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| AST (SGOT) | <1.25xULN | 1.1-2.0xULN | 2.0-3.0xULN | 3.0-8.0xULN | >8.0xULN |
| ALT (SGPT) | <1.25xULN | 1.1-2.0xULN | 2.0-3.0xULN | 3.0-8.0xULN | >8.0xULN |
| GGT | <1.25xULN | 1.1-2.0xULN | 2.0-3.0xULN | 3.0-8.0xULN | >8.0xULN |
| Alkaline Phosphatase | <1.25xULN | 1.1-2.0xULN | 2.0-3.0xULN | 3.0-8.0xULN | >8.0xULN |

| HEMATOLOGY | | | | | |
|---|---|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hemoglobin (gm/dL) | >10.5 | 9.5-10.5 | 8.0-9.4 | 6.5-7.9 | <6.5 |
| Absolute Neutrophil Count (count/$mm^3$) | >1500 | 1000-1500 | 750-999 | 500-749 | <500 |
| Platelets (count/$mm^3$) | ≥100,000 | 75,000-99,999 | 50,000-74,999 | 20,000-49,999 | <20,000 |
| WBCs (count/$mm^3$) | 1000-10,999 | 11,000-12,999 | 13,000-14,999 | 15,000-30,000 | >30,000 |
| % Polymorphonuclear Leucocytes + Band Cells | ≤80% | >80%-90% | >90–95% | >95% | ---------- |

| CHEMISTRY | | | | | |
|---|---|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Hyponatremia (mEq/L) | >135 | 130-135 | 123-129 | 116-122 | <116 |
| Hypernatremia (mEq/L) | <146 | 146-150 | 151-157 | 158-165 | >165 |
| Hypokalemia (mEq/L) | >3.4 | 3.0-3.4 | 2.5-2.9 | 2.0-2.4 | <2.0 |
| Hyperkalemia (mEq/L) | <5.6 | 5.6-6.0 | 6.1-6.5 | 6.6-7.0 | >7.0 |
| Hypoglycemia (mg/dL) | ≥65 | 55-64 | 40-54 | 30-39 | <30 |
| Hyperglycemia (mg/dL) (nonfasting and no prior diabetes)* | <116 | 116-160 | 161-250 | 251-500 | >500 |
| Hypocalcemia (mg/dL) (corrected for albumin) | >8.4 | 8.4-7.8 | 7.7-7.0 | 6.9-6.1 | <6.1 |
| Hypercalcemia (mg/dL) (correct for albumin) | ≤10.5 | 10.6-11.5 | 11.6-1.5 | 12.6-13.5 | >13.5 |
| Hypomagnesemia (mEq/L) | >1.4 | 1.4- 1.2 | 1.1-0.9 | 0.8-0.6 | <0.6 |
| Hypophosphatemia (mg/dL) | ≥2.5 | 2.0-2.4 | 1.5-1.9 | 1.0-1.4 | <1.0 |
| | | | | | |
| Hyperbilirubinemia (when accompanied by any increase in other liver function test) | <1.1xULN | 1.1 - <1.25xULN | 1.25 - <1.5xULN | 1.5 – 1.75xULN | > 1.75xULN |
| Hyperbilirubinemia (when other liver function are in the normal range) | <1.1xULN | 1.1 - <1.5xULN | 1.5 - <2.0xULN | 2.0 – 3.0xULN | > 3.0xULN |
| BUN | <1.25xULN | 1.25-2.5xULN | 2.6-5xULN | 5.1-10xULN | >10xULN |
| Hyperuricemia (uric acid) (mg/dL) | <7.5 | 7.5–10.0 | 10.1–12.0 | 12.1–15.0 | >15.0 |
| Creatinine | <1.1xULN | 1.1-1.5xULN | 1.6-3.0xULN | 3.1-6xULN | >6xULN |

* The DMID toxicity table reports hyperglycemia detected in nonfasting specimens obtained from subjects with no prior diabetes.

## Appendix C. Safety Laboratory Tests

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

## Appendix D. Prohibited Medications

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

| 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).

## Appendix E. Local Signs and Symptoms of ABSSSI

Local signs and symptoms will be assessed for the primary ABSSSI site.

The Investigator is to provide a categorical assessment and comparison to baseline of the following parameters using the scale below:

| Parameter | Absent | Mild | Moderate | Severe |
|---|---|---|---|---|
| Erythema | None | Pink | Red | Fiery red |
| Swelling/edema | None | Swelling just apparent on casual inspection (up to 2 mm of pitting) | Marked swelling (≤ 4 mm of pitting) | Maximal swelling (> 4 mm of pitting) |
| Localized warmth | None | Slightly warm | Warm | Hot |
| Tenderness on palpation | None | Slight or mild tolerable discomfort on palpitation | Uncomfortable with light palpitation or pressure | Intolerable by even a mild stimulus such as sheet touching |
| Drainage | None | Serous | Seropurulent | Purulent |
| Fluctuance | None | Present | Not applicable | Not applicable |
| Induration | None | Present | Not applicable | Not applicable |

## Appendix F. 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.

## Appendix G. 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.

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: PJI001-02

# EVALUABILITY REVIEW PROCESS

**Version 1.0, 10September2019**

**Table of Contents**

## 1.0 INTRODUCTION

This document presents the Evaluability Review Process for protocol PJI001-02, "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." The evaluability review process and the detailed patient population definitions provided in the Statistical Analysis Plan (SAP) are finalized prior to determination of patient evaluability.

## 2.0 DEFINITIONS OF PATIENT POPULATIONS

Detailed definitions of the patient analysis populations are provided in the SAP.

## 3.0 REVIEW TEAM

One evaluability review team (ERT) will be organized and will consist at a minimum of the study Medical Monitors (Paul Eckburg and Zhijie Qin). A study biostatistician will be in charge of consolidating comments and will facilitate the review meetings. Other sponsor staff may participate in the review as required. The review team will review isolates for pathogen determination and patient inclusion in the micro-ITT population and also clinical data for inclusion in or exclusion from the CE-EOIV, CE-EOT, and CE-PTE populations, including a review of the programmatic assessment of patient inclusion in or exclusion from the CE-EOIV, CE-EOT, and CE-PTE populations.

Review of data and determination of evaluability will be performed in a blinded manner prior to database lock. All pathogens must be identified and finalized prior to unblinding. A subject's CE population classification will be considered locked at database unblinding and may only be changed programmatically for those subjects who did not receive the correct study drug (i.e., randomized study drug) or for those subjects who were unblinded during the study.

## 4.0 OVERVIEW OF PROCESS FOR DETERMINING EVALUABILITY

### 4.1 ITT and Safety Populations

Inclusion in the Intent-to-Treat (ITT), modified Intent-to-Treat (MITT), Pharmacokinetic (PK), Safety, and Microbiologically Evaluable (ME-PTE) populations is determined programmatically and does not require review by the ERT.

### 4.2 Micro-ITT Population

Inclusion in the Micro-ITT population will be determined programmatically using pathogen determinations provided by the review team. The review team will be provided with an EXCEL spreadsheet that will include the specimen source (ABSSSI site specimen, blood), the date, time, and study day (relative to the date of the first dose of study drug) of specimen collection, local laboratory specimen number, central laboratory isolate accession number, local laboratory genus

and species identification, central laboratory genus and species identification, final identification of genus and species, the programmed pathogen flag, and the programmed baseline pathogen flag.

- The programmed pathogen flag will have a value of "Yes" if any of the pathogens identified in Table 2 of the SAP are identified. When there is a central laboratory result, the central laboratory result will be used. When there is only a local laboratory result, the local result will be used. If there are discrepancies between the local and central laboratory, then a manual override can be used during the review process to specify the pathogen. The programmed baseline pathogen flag will be programmed similarly and will have a value of "Yes" if the pathogen was identified at baseline.

- The programmed pathogen flag will have a value of "No" if the organism is identified in Table 3 of the SAP or there is no organism identified (no growth). The programmed baseline pathogen flag will be programmed similarly.

- All other cases will be reviewed manually.

The review team will confirm the pathogen status of isolates whose pathogen status could not be programmatically determined according to the rules specified above and in Section 6 of the SAP and will confirm the final identification of genus and species for those cases where there is a discrepancy between the local and central laboratory identification of genus and species. Further details regarding the programming of the EXCEL spreadsheet are provided in Section 6.0 of this document.

### 4.3 CE Populations

The review team will be provided with an EXCEL spreadsheet that will include an indication of whether or not the patient met or did not meet each criterion for inclusion in or exclusion from the CE-EOIV, CE-EOT, and CE-PTE populations listed in the SAP and in Table 1, below, along with all systemic or topical antibacterial medications received on or after the date of the first dose of study drug through the PTE assessment date. For those patients who must be reviewed on a case-by-case basis, the review team will review the spreadsheet to determine whether the patient should be included in the CE-EOIV, CE-EOT, and CE-PTE populations. The decision will be noted on the EXCEL spreadsheet. If it is determined that a patient should be excluded from the CE populations, the reason(s) for exclusion from the CE populations will also be provided. Further details regarding the programming of the EXCEL spreadsheet are provided in Section 6.0 of this document.

Table 1 summarizes the eligibility criteria for the CE populations. Inclusion in or exclusion from the CE populations will be determined programmatically for those criteria that always result in inclusion in or exclusion from the CE populations.

| **Table 1: Eligibility Criteria for CE Populations** | | | |
|---|---|---|---|
| **Criteria Number** | **Criteria** | **Determined Programmatically** | **Reviewed Manually** |
| 1 | Met the minimal clinical disease criteria for ABSSSI described in the study Inclusion Criteria (See Inclusion criteria in Protocol- Inclusion Criteria 2a- 2c, 3, 4a-4f, 5a-d). | X | |
| 2 | Receive at least 80% of expected IV doses based on length of IV therapy | X | |
| 3 | Did not have any major protocol deviation including but not limited to:<br>• Violated Exclusion 4 (prior administration of systemic antibacterial therapy within 96 hours before randomization)<br>• Received the wrong study drug or unblinded before the timepoint of assessment for reasons other than safety | X | X |
| 4 | Did not receive any potentially-effective systemic or topical antibacterial therapies other than protocol specified study drug(s) between Day 1 and EOIV (CE-EOIV), EOT (CE-EOT) or PTE (CE-PTE), except in cases of treatment failure. | X | X |
| 5 | For the CE-EOIV analysis population:<br>a. Completed the CE-EOIV Visit within 1 calendar day of the last dose of IV drug (+1 day) [i.e., within 48 hours of the last dose of study drug].<br>b. Must not have had a clinical response of indeterminate based | X | |

| **Table 1: Eligibility Criteria for CE Populations** | | | |
|---|---|---|---|
| **Criteria Number** | **Criteria** | **Determined Programmatically** | **Reviewed Manually** |
| | on the Investigator's assessment at EOIV.<br><br>For the CE-EOT analysis population:<br><br>c. Completed the EOT Visit within 1 calendar day of the last dose of study drug (+1 day) [i.e., within 48 hours of the last dose of study drug].<br><br>d. Must not have had a clinical response of indeterminate based on the Investigator's assessment at EOT<br><br>For the CE-PTE analysis population:<br><br>a. Completed the 7-14 after the EOT visit. If the EOT visit is out of the study window, then the PTE visit must still be within 7-14 days of the EOT visit. If the EOT visit is missed, then the PTE visit must be within 7-14 days of the last dose of study drug unless the patient was considered a failure at EOT.<br><br>b. Must not have had a clinical response of indeterminate based on the overall assessment of clinical response (based on the Investigator assessment at PTE) unless the subject was a failure at EOT. | | |

| **Table 1: Eligibility Criteria for CE Populations** | | | |
|---|---|---|---|
| **Criteria Number** | **Criteria** | **Determined Programmatically** | **Reviewed Manually** |
| 6 | Subjects who are clinical failures at EOIV, EOT or PTE (by overall assessment at PTE), but don't have at least 3 doses of IV study drug are not included in the CE-EOIV, CE-EOT or CE-PTE populations respectively. | X | |
| 7 | Subjects who are clinical successes at EOT or PTE (overall assessment at PTE) but have fewer than 4 doses of IV study drug are not included in the CE-EOT or CE-PTE, populations, respectively. Subjects who have clinical improvement at EOIV but have fewer than 4 doses of IV study drug are not included in the CE-EOIV population. | X | |

Some subjects may only receive IV study drug. For these subjects, their end of treatment (EOT) visit information is recorded in the EOT visit only and not the EOIV visit within study database. Efficacy data at EOT will be duplicated for EOIV and these subjects will be summarized at both visits within study tables and the evaluability spreadsheet. Similarly, these subjects will be considered for inclusion in both the CE-EOT and CE-EOIV populations.

## 5.0 DATA REVIEW

EXCEL spreadsheets will be provided to the review team prior to database soft-lock and once after database soft-lock. If a data query results in a change to any of the data fields used for either pathogen determination, inclusion in or exclusion from the patient populations, then re-determination (either programmatically or by the review teams) of the patient's population classifications and/or pathogen review will be conducted. The patient study population classification will not be locked or finalized until there are no outstanding queries that affect population determination for the patient.

The review process will result in two final spreadsheets, the first with final pathogen determinations and the second with final population determinations, including the reasons patients are not included in the CE-EOIV, CE-EOT, and CE-PTE populations. The pathogen determination, CE population flags, and reviewer comments from the spreadsheets will be included as part of the final clinical analysis datasets as detailed in Section 6.0. These spreadsheets will also be converted into datasets and will be merged with the study ADaM datasets, as appropriate.

## 6.0 PROGRAMMING AND REVIEW DETAILS

EXCEL spreadsheets will be generated by InClin for the following relevant data:

1. Isolates for pathogen determination
2. All of the relevant clinical evaluability criteria flags with final CE-EOIV, CE-EOT, and CE-PTE flags for inclusion in or exclusion from the CE populations

Each of these spreadsheets will be sent to the review team for review. The following details provide a description of each step of the evaluability process and the associated data spreadsheets (see Figure 1 for a detailed algorithm). All data spreadsheets, as well as associated SAS datasets, are saved on the InClin server.

Pathogen Determination

- The project programmer will generate an EXCEL spreadsheet that includes the patient ID, specimen source (ABSSSI site specimen or blood), nominal visit identifier (e.g., screening, the date, time, and study day (relative to the date of the first dose of study drug) of specimen collection, method of collection (e.g. needle aspiration, deep swab, etc), central laboratory isolate accession number, local laboratory genus and species identification, central laboratory genus and species identification, final identification of genus and species, a final genus and species override column, the programmed pathogen flag ("PATHPROG" heading), and the programmed baseline pathogen flag ("BPATHPRG" heading), and override columns for both the pathogen and baseline pathogen flags. In addition, placeholder columns will be provided in the spreadsheet for reviewer comments ("PATHCOMM" heading), reviewer initials ("PATHINIT" heading), and date of review ("PATHDATE" heading).
- The review team will independently confirm the pathogen status of isolates whose genus and species are not identified in the SAP and the final identification of genus and species for those cases where there is a discrepancy between the local and central laboratory identification of genus and species, and will indicate his/her agreement or disagreement in the following columns:
  - 'Final Genus & species - Override' (F_ORGREV)
  - 'Programmed Pathogen Flag - Override'(PATHREV)
  - 'Programmed Baseline Pathogen Flag - Override' (BPATHREV)

  The review team will also provide comments in the comment column ("PATHCOMM" )
- The manual pathogen determinations will then be sent to the project statistician.

The project statistician will consolidate the independent evaluations from each member of the ERT and will highlight any discrepancies. This consolidated list of discrepant pathogen determinations will be sent back to the ERT for reconciliation.

- The ERT will review and discuss the discrepancies and provide the project statistician with the resolved final pathogen determinations.
- The EXCEL spreadsheet with the final suitable specimen and pathogen determinations will be saved as a PDF and archived.
- The EXCEL spreadsheet with the final pathogen determinations will be sent to the project programmer and a new final pathogen flag ("PATHYN") will be generated taking into consideration the "PATHPROG" and "PATHREV" columns and saved as a SAS dataset. A new final baseline pathogen flag ("BPATHYN") will be generated taking into consideration the "BPATHPROG" and "BPATHREV" columns and saved as a SAS dataset. In cases where the programmatic pathogen determination ("PATHPROG"/ "BPATHPROG") flags are discrepant with the reviewer pathogen determination flags ("PATHREV"/ "BPATHREV"), the reviewer pathogen flags will be used for determination of the final pathogen flags ("PATHYN"/"BPATHYN"). The SAS dataset will also contain as variables final comments from the ERT.

CE Population Determinations

- The project programmer will generate another EXCEL spreadsheet that includes the patient ID with all the flags for each CE criterion from Table 1 and a programmatically-determined CE population flags ("CEEOIVPRG", "CEEOTPRG", and "CEPTEPRG" headings). In addition, placeholder columns with the following headings will be provided in the spreadsheet for ERT determinations of the CE population ("CEEOIVREV" ,"CEEOTREV", and "CEPTEREV" headings), confounding concomitant antibiotics ("CABXREV" heading), CABXPROG (confounding antibiotic override) and any comments regarding the yes/no determination of CE population ("CEEOIVCOM" ,"CEEOTCOM", and "CEPTECOM" headings), reviewer initials ("REVINIT" heading), and date of review ("REVDATE" heading).
- The above spreadsheet will be sent to ERT members for independent review. All of the CE criteria will be reviewed and each member of the ERT will independently review the programmatically-determined CE population flags ("CEEOIVPRG" ,"CEEOTPRG", and "CEPTEPRG" columns) and will indicate his/her agreement or disagreement with the programmatically-determined CE population flags in the "CEEOIVREV", "CEEOTREV", and "CEPTEREV" columns as well as provide comments in the "CECOMM" column. Each member of the ERT will also review concomitant systemic antibiotics and the programmatic determination of whether or not the concomitant antibiotics are considered potentially confounding of the clinical outcome (in the "CABXPROG" column) and will indicate his/her agreement with the programmatically determined confounding concomitant antibiotic flag in the "CABXREV" column.
- The project statistician will consolidate the independent evaluations from each member of the ERT and will highlight any discrepancies. This consolidated list of discrepant CE determinations will be sent back to the ERT for reconciliation.

- The ERT will review and discuss the discrepancies and provide the project statistician with the resolved final CE population determinations.
- The EXCEL spreadsheet with the final CE population determinations will be saved as a PDF and archived.
- The ERT-reviewed spreadsheet will be sent to the project programmer and new final CE population flags ("CEEOIVFL", "CEEOTFL" and "CEPTEFL") will be generated by the programmer taking into consideration the "CEEOIVPRG"/"CEEOTPRG"/ "CEPTEPRG" and "CEEOIVREV" /"CEEOTREV"/ "CEPTEREV" columns and saved as a SAS dataset. In cases where the programmatic CE population flags) and the reviewer CE population flags) are discrepant, the reviewer CE population flags will be used as the final CE population flags ("CEEOIVFL" ,"CEEOTFL", and "CEPTEFL"). The SAS dataset will also contain as variables within the dataset as well as final comments from the committee review of the discrepant CE determinations, along with the reviewers' initials and date of review. The final CE population flags ("CEEOIVFL", "CEEOTFL", and "CEPTEFL") will be used by the programmer for final implementation of inclusion or exclusion of patients into/from CE populations.
- A manual review of the final CE population determinations in the SAS dataset versus the PDF of the final CE population determinations will be conducted by the project statistician.

The pathogen review EXCEL spreadsheet will be created as specified, below:

1. Merge local specimen culture and serology information (mb1o.sas7bdat, mb2o.sas7bdat) with the central laboratory microbiology data (jmimicrodata.sas7bdat) by subject ID, date, and central laboratory accession number. Pathogens are then programmatically determined using Tables 2 and 3 of the Statistical Analysis Plan.

| | |
|---|---|
| **Program** | Pathogens.sas |
| **Input data** | SAS datasets: mb1o, mb2o, jmimicrodata and EXCEL spreadsheet: "organism list.xls" |
| **Output** | PJI001-02_PathReview_Date.xls |
| **Location** | F:\Biometrics\SASFiles\TenNor\ PJI001-02 \data\Excel |
| **Document type** | EXCEL spreadsheet |

2. Pathogen status and final pathogen identification reviewed and confirmed by the ERT.

| | |
|---|---|
| **Output** | PJI001-02_ PathReview_Date.xls, reviewed and completed by ERT. |
| **Location** | F:\Biometrics\SASFiles\TenNor\ PJI001-02 \data\excel |
| **Document type** | EXCEL spreadsheet |

The CE review EXCEL spreadsheet will be created as specified, below:

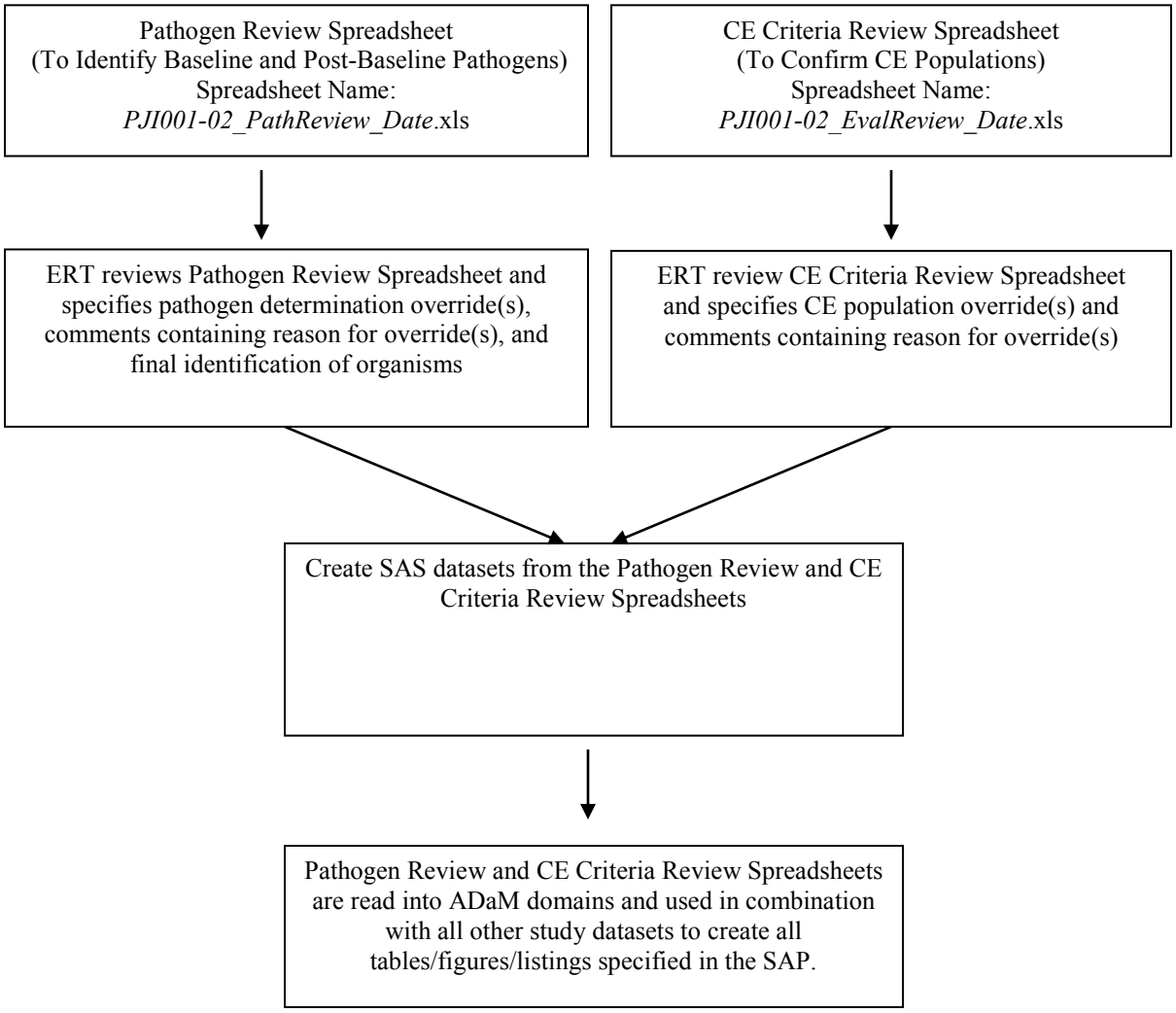
1. A SAS dataset will be generated that will include the programmed clinical evaluable (CE) population flags along with all CE population criteria. It is then converted to a spreadsheet for clinical review.

| | |
|---|---|
| **Program** | CE_Criteria.sas |
| **Input data** | RAW SAS datasets: IE, IEP<br>SDTM datasets: DM, SV, FA, EX, suppEX, DV, CM, suppCM |
| **Output** | PJ1001-02 _EvalReview_Date.xls |
| **Location** | F:\Biometrics\SASFiles\TenNor\ PJI001-02 \data\excel |
| **Document type** | EXCEL spreadsheet |

2. The reviewed spreadsheet with CE population overrides and comments will be sent back to InClin.

| | |
|---|---|
| **Output** | PJ1001-02 _EvalReview_Date.xls |
| **Location** | F:\Biometrics\SASFiles\TenNor\PJI001-02 \data\excel |
| **Document type** | EXCEL spreadsheet |

**Figure 1: Process and flow of spreadsheets used for pathogen and evaluability determinations.**



## 7.0 APPENDIX A

PJI001-02_PathReview_Date.xls

PJI001-02_EvalReview_Date.xls