B. Braun Medical Inc.
STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of a Single 3 Gram Dose of Cefazolin in Adult Subjects Weighing ≥120 kg Scheduled for Surgery

Protocol Number: US-G-H-2101

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Final Statistical Analysis Plan

Version 1.0

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0.1	15FEB2022		Draft
0.2	07MAR2022	8.3.2, 8.3.3, 8.3.4	Text related to missing of relationship and severity of adverse events, are removed.
		12.2	The figure related to mean plasma concentration vs time profile is removed and figure with individual plasma concentration and mean plasma concentration vs time profile will be presented together..
1.0	15MAR2022		Finalized version

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
IV	Intravenous
ICF	Informed Consent Form
ICH	International Conference On Harmonisation
MedDRA	Medical Dictionary For Regulatory Activities
MIC	Minimum Inhibitory Concentration
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
USP	United States Pharmacopeia
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations to be used by PPD Biostatistics in the analysis and presentation of data for the B. Braun Medical Inc. study US-G-H-2101, entitled "A Phase 1, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of a Single 3 Grams Dose of Cefazolin in Adult Subjects Weighing ≥120 kg Scheduled for Surgery".

1.1 Background Information

Cefazolin is an antibacterial agent that in in vitro testing has been shown to act by inhibition of bacterial cell wall synthesis. Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP is a sterile, nonpyrogenic, single-use, packaged combination of Cefazolin Sodium USP (lyophilized) and sterile iso-osmotic diluent (i.e., Dextrose Injection USP) in the DUPLEX® sterile container.

Cefazolin Sodium USP and Dextrose Hydrous USP are supplied as a lyophilized form equivalent to either 1 gram or 2 grams of cefazolin (i.e., contains approximately 2 grams dextrose [4.0% weight to volume ratio (w/v)] and 1.5 g dextrose [3.0% w/v] for the 1 gram and 2 grams dosages, respectively).

For the Investigational 3grams Cefazolin dosage utilized in this study, the concentration of dextrose in the diluent is 2.0% w/v, as dextrose monohydrate.

The pharmacokinetic/pharmacodynamic (PK/PD) relationship for cefazolin has not been evaluated in patients. However, it is commonly accepted that β-lactam antibiotics exhibit time-dependent killing of bacteria. Thus, the percentage of time that drug concentrations remain above the minimum inhibitory concentration (MIC) of the bacterial pathogen is the relevant PK-PD index for cefazolin.

Patients weighing ≥ 120 kg may not achieve a similar or therapeutic level of exposure to 2 grams of Cefazolin as patients weighing ≤ 120 kg. In order to ensure a therapeutic exposure to cefazolin from a single dose in this heaver population of patients, B. Braun Medical Inc. is developing a 3 grams Cefazolin DUPLEX® bag for use in individuals who weigh at least 120 kg. To support this dosing recommendation, a thorough literature search was performed to obtain information regarding Cefazolin use in patients weighing at least 120 kg. Monte Carlo simulations were then performed using the previously developed population PK model constructed from one study in healthy adults and 2 studies in pediatric patients (ICPD 2019). This population PK model was used to perform model-based simulations of a 2-grams or 3-grams dose of Cefazolin in 2 simulated populations of obese (≥ 120 kg) adult patients.

This Phase 1 study was based on the above population PK model and is designed to evaluate the pharmacokinetics (PK) of a single 3 grams dose of Cefazolin from a DUPLEX container, in adult subjects (weighing ≥ 120 kg) scheduled for surgery. Cefazolin will be administered as a 30-minute intravenous (IV), per cefazolin Package Insert for surgical prophylaxis. These data are planned to be assessed by a validated Cefazolin PK Model (Schmitz ML 2020) to

verify there are no significant PK changes within this study population. The results of this modelling analyses will be reported separately from the Clinical Study Report.

2. Objectives

2.1 Primary Objective

The primary objective of this study is to determine the PK of a single IV 3 grams dose of Cefazolin administered to adult subjects (weighing ≥ 120 kg) scheduled for surgery. Safety in this population will also be assessed.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 1, open-label, single-dose, multiple-center, study to determine the pharmacokinetics of a single 3 grams dose of Cefazolin administered as a 30-minute IV infusion in adult subjects (weighing ≥ 120 kg) scheduled for surgery. Adult subjects will be enrolled in order to ensure at least 12 subjects complete the study. Enrolment will be competitive across the study sites.

The Screening Period is up to 30 days before administration of study drug on Day 1. All subjects will have screening and baseline evaluations to ensure their eligibility for the study.

Study drug will be administrated as an infusion over 30 minutes starting approximately 0.5 hours before surgery begins and following institutional guidelines on Day 1 (day of surgery). Planned surgical procedures may be performed outpatient or inpatient and are expected to last no longer than 3 hours.

If the surgery is extended unexpectedly beyond the 3-hours limit, additional doses of study drug are permitted according to institutional guidelines. PK blood sampling will not be halted due to this 2nd dose of study drug. The amount of study drug administered and the start and stop time of this 2nd dose of study medication must be recorded. PK blood sample collection will continue after the administration of an additional dose of Cefazolin. Safety in this population will also be assessed.

All subjects will have five (5) individual whole blood samples (4 mL each) collected for the estimation of cefazolin concentration in plasma at the following times after the start of the infusion: 0.5 (±10 min) end of infusion, 1 h (±15 min), 2 h (±15 min), 4 h (±15 min) and 8 h (±15 min).

Safety will be assessed by monitoring adverse events (AEs), physical examination, vital signs, and clinical laboratory tests. A follow-up visit or phone call will be performed on Day 8 (±1 day) for safety assessments.

A subject is considered a study completer if he/she has completed all study related procedures through the end of surgery and the required PK sample collections. It is highly preferred that the subjects also participate in the Day 8 (±1 day) Safety Follow-up. For

subjects who withdraw or are withdrawn before study completion of the study, every effort will be made to perform all Safety Follow up procedures.

Any subject who withdraws or is withdrawn before collection of at least 4 of the 5 PK samples will not be consider as a PK completer. If necessary, additional subjects must be enrolled to ensure that there are at least 12 PK completers.

On Day 8 (±1 day), a safety follow-up will be conducted. If this is an in-person visit, the following will be performed: vital signs, clinical laboratory tests, examination of the infusion site, review of AEs and concomitant medication. If an in-person visit is not possible, every effort will be made to contact the subject by phone and the subjects will be asked about any AEs and concomitant medication they may have taken.

3.2. Treatments

Cefazolin for Injection USP and Dextrose Injection USP is a sterile, non-pyrogenic, single-use, packaged combination of Cefazolin Sodium USP (lyophilized) and iso-osmotic diluent (i.e., Dextrose Injection USP) in the DUPLEX container. The DUPLEX container is a flexible dual-chamber container. Cefazolin Sodium USP (active ingredient) is currently supplied in the drug chamber as a lyophilized form equivalent to 1 gram or 2 grams of Cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.

For the Investigational 3grams Cefazolin dosage utilized in this study, the concentration of dextrose in the diluent is 2.0% w/v, as dextrose monohydrate. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.

In pre-reconstituted form, the Cefazolin appears as a white or almost white powder and the dextrose is a clear fluid. When reconstituted, the prepared solution is clear.

A peripheral venous catheter will be placed for all subjects before the start of the study drug administration for the IV infusion of the Cefazolin and dextrose solution. After reconstitution, the solution will be administered over 30 minutes through an infusion line by using an infusion pump on Day1 (day of surgery) for surgery prophylaxis and following institution guidelines. The study drug administration will begin approximately 0.5 hours prior to the start of surgery and following institution guidelines. If the surgery is unexpectedly extended beyond the 3 hours limit, additional doses of study drug are permitted according to institutional guidelines. However, dose administered and the start and stop time of the infusion must be recorded.

3.3. Dose Adjustment/Modifications

If the surgery is unexpectedly extended beyond the 3 hours limit, additional doses of study drug are permitted according to institutional guidelines. However, dose administered and the start and stop time of the infusion must be recorded.

It is necessary that a separate venous catheter for PK sample collection be placed in the contralateral arm to the catheter used for study drug infusion.

NOTE: The catheter that is used for study drug infusion and the arm it is inserted in cannot be used for collection of the PK samples.

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation, median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. All data will be displayed in listings sorted by subject number and visit/time, if applicable. Listings will be included all visits including unscheduled visits.

For summaries by visit (/time), if multiple records fall on the same visit (/time), then the record which is closest to the target visit (/time) will be considered. In case of a tie, the record with the latest date (/time) will be chosen. If multiple records on same day (/time), will consider the latest record. Unless otherwise specified, unscheduled will not be summarized but will be listed.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in treatment within the analysis set of interest, unless otherwise specified. Percentage will be presented to one decimal place.

“No data available for this report” will be presented when there are no data available to report.

Baseline is defined as the last non missing values obtained before surgery on Day 1.

Study day is defined as:

- Visit/examination date – date of first study drug administration when date is prior to the date of first study drug administration (day 1).
- Visit/examination date – date of first study drug administration + 1 when date is after day 1

For the purpose of inclusion in tables, incomplete start and stop dates (e.g. AEs and prior/concomitant medication) will be imputed as follows:

Missing start dates (where UK and UKN indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year and the stop date (after any

imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month and year and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date;

- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year and the stop date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug and the stop date (after any imputation) is prior to the first dose of study drug, then assume the stop date for the start date.

Missing stop dates (where UK and UKN indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

If a subject die during the study, the stop date will be imputed as the date of death if the imputed stop date is after date of death.

All analyses will be conducted using SAS Version 9.4 or higher.

4.1. Sample Size

A range of sample sizes and PK sampling schemes were evaluated utilizing a previously approved PK model. The results of the model-based simulation analyses indicated that a sample size of 12 subjects, each of which provides 5 blood samples for cefazolin assay at times of 0.5 (±10 min) end of infusion, 1 h (±15 min), 2 h (±15 min), and 4 h (±15 min), and, 8 h (±15 min) after the start of the cefazolin infusion, would be expected to provide adequate power to determine the PK in adult subjects weighing ≥ 120 kg.

Thus, subjects will be enrolled to ensure at least 12 subjects will complete the study.

4.2. Randomization, Stratification, and Blinding

This is an open-label study. No randomization or blinding will be performed.

4.3. Analysis Set

The following analysis sets will be used: Enrolled Set, Safety analysis Set and PK analysis Set.

4.3.1. Enrolled Set

The enrolled set will include all subjects who were signed informed consent.

4.3.2. Safety Analysis Set

The safety analysis set will consist of all subjects who received any study drug. Safety will be assessed by monitoring AEs, physical examinations, vital signs, ECGs, and clinical laboratory results.

4.3.3. PK Analysis Set

The PK analysis set will consist of all subjects from whom at least 4 of the 5 PK samples are obtained.

5. Subject Disposition

5.3. Disposition

A summary of the analysis sets includes the number and percentage of subjects for the following categories: enrolled set, safety analysis set, and PK analysis set. All percentages will be based on the number of enrolled subjects. A listing will be presented by subjects for showing each subject in which analysis population set they are included.

Subject disposition will be summarized using enrolled set. A disposition of subjects includes the number and percentage of subjects who completed the study and subjects who discontinued from the study.

The reasons for study discontinuation will also be summarized in this table. The reason for study discontinuation includes the following:

- Does not meet the protocol inclusion or exclusion criteria
- Noncompliance with the protocol
- A Serious or Intolerable Adverse Event
- Lost to Follow-up
- Pregnancy
- Investigator Decision
- Withdrawal of Informed Consent
- Other

Subject disposition data will be presented in a listing.

5.4. Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study.

The number and percentage of subjects with protocol deviation will be summarized by category (major, minor). Protocol deviations will be listed with date of occurrence, deviation category, deviation description from which subject is excluded. All summaries and listings will be performed using the safety analysis set.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented. The demographic characteristics consist of age (year), sex, race, ethnicity, child bearing potential and menopause status. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2. Body mass index is calculated as (body weight in kilograms) / (height in meters)^2.

Age (year), baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of subjects by sex (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other), ethnicity (Hispanic or Latino, Not Hispanic or Latino), child bearing potential (Yes, No) and menopause status (Prior bilateral oophorectomy, Age >= 60 years, Age <60 years and amenorrhoeic for at least 12 months) will also be reported. Percentages will be based on the total number of subjects in the safety analysis set. Percentages for the child bearing potential and menopause status summary will be based on the number of female subjects from the safety analysis set.

Subject demographic and baseline characteristics will be presented in a listing. All listings will be performed using the safety analysis set.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher. Body systems will be included as recorded on the eCRF. Subject medical history data including specific details will be presented in a listing using the safety analysis set.

6.3. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in sections 4.2 and 4.3 of the protocol. The status of eligibility criteria met, inclusion criteria not met, or exclusion criteria met details will be listed using the enrolled set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

A prior medication is defined as any medication where the start date and stop date are before the date of first dose of study drug. A concomitant medication is defined as one where the start or stop date is either on or after the date of first dose of study drug. All medications will be coded according to the World Health Organization drug dictionary (WHODRUG 2020 March or later). Incomplete dates will be imputed following rules in Section 4. All medications will be listed.

The total number of prior and/or concomitant medications and the number and percentages of subjects with at least one prior and/or concomitant medication will be summarized. The number and percentages of all prior and/or concomitant medication will be summarized and listed by ATC (Anatomical Therapeutic Chemical) level 4 and preferred term. At each level of summarization, a subject is counted once if the subject reported one or more medication at that level. Any medications and treatments taken prior to and not stopped prior to the infusion of study drug will be counted in concomitant medication.

All prior/concomitant medication summaries and listing will be presented using safety analysis set.

7.2.Study Treatments

Study treatment and modification is detailed in section 3.2 and 3.3.

7.2.1 Duration of Infusion

Duration of infusion will be calculated in hours as end time of study drug infusion – start time of study drug infusion. Interruption of study drug infusion may also occur during the study, in such case, the duration of the infusion will be computed after adjusting the interrupted duration.

Duration of infusion (hours) and infusion rate (mL/h or mL/min) will be summarized using descriptive statistics along with number and percentage of subjects who had infusion interruptions and additional study drug infusion will also be presented in table for safety analysis set.

A summary of each subject's study drug infusion will be presented in a listing.

7. Efficacy Analysis

Not applicable.

8. Safety Analysis

All analyses of safety will be conducted using safety analysis set.

8.1.Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug.

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions, based on the actual AE dates or imputed dates:

- begins on or after the start of study drug infusion;
- begins before the start of study drug infusion and worsens in either intensity or frequency on or after the first dose of study drug.;
- is completely missing a start date and the stop date;
- is completely missing a start date and the stop date is on or after the study drug infusion.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as explained in section 4.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (Version 24.0 or higher).

Number and percentage of subjects with any AE, SAE, TEAE, serious TEAEs, study drug-related TEAEs, study drug-related serious TEAEs, TEAE leading to treatment discontinuation, TEAE leading to study discontinuation, and AE leading to death will be summarized. Percentages will be calculated using number of subjects in the safety analysis set.

All AEs will be presented in a listing using the safety analysis set.

8.3.1. Incidence of Adverse Events

Number and percentage of subjects with at least one TEAE and the total number of TEAEs will be summarized. TEAEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated using number of subjects in the safety analysis set.

TEAEs will be sorted in descending order of frequency of SOC. Within each SOC, PTs will be sorted in alphabetical order of preferred terms.

8.3.2. Relationship of Adverse Events to Study Drug

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Unrelated”, “Possibly Related”, “Probably Related” and “Definitely Related”.

A summary of TEAEs related to Cefazolin will be presented in a table same as mentioned in section 8.3.1. TEAEs that with a relationship other than “Unrelated” will be considered as “Related”. Percentages will be calculated out of the number of subjects in the safety analysis set.

8.3.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are "Mild", "Moderate", and "Severe". In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Percentages will be calculated out of the number of subjects in the Safety analysis set.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in section 8.3.1.

8.3.4. Serious Adverse Events

A serious AE (SAE) is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious treatment-emergent adverse events (Serious TEAEs) will be presented in a table. Serious TEAEs which are related to study drug will also be presented in a table.

At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety analysis set.

The serious TEAEs data will be categorized and presented by SOC and PT in a manner similar to that described in section 8.3.1.

8.3.5. Adverse Events Leading to Treatment Discontinuation

A summary of TEAEs where the answer to "Action Taken" are "Drug Withdrawn" will be presented in a table by SOC and PT in a manner similar to that described in section 8.3.1. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated using number of subjects in the safety analysis set.

8.3.6. Adverse Events Leading to Study Discontinuation

A summary of TEAEs where the answer to "Caused Study Discontinuation" is "Yes" will be presented in a table by SOC and PT in a manner similar to that describe in section 8.3.1. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated using number of subjects in the safety analysis set.

8.3.7. Death

A summary of AEs where the answer to "Outcome" is "Death Related to Adverse Event" will be presented in a table by SOC and PT in a manner similar to that describe in section 8.3.1. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety analysis set.

All subjects who have an AE with an outcome of "Death Related to Adverse Event" will be presented in a listing.

8.4. Clinical Laboratory Evaluations

Laboratory assessments will be performed by the local or central laboratory. All summaries and listings will be presented in SI units.

Summary tables presenting observed values and changes from baseline will be presented for clinical laboratory tests (Hematology and Clinical Chemistry) with numeric values for subjects in the safety analysis set. All hematology, clinical chemistry and pregnancy test will be listed in separate listings using safety analysis set.

Table 8.1: Clinical Laboratory Tests

Hematology	• Hemoglobin • Hematocrit • Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Platelets • Red blood cell • White blood cell with differential count
Clinical Chemistry	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen • Serum creatinine[1] • Total bilirubin • Sodium • Potassium • Chloride • Bicarbonate • Glucose • Uric acid • Calcium

	• Phosphate • Total protein • Creatine phosphokinase (CPK) • Lactic acid dehydrogenase (LDH)

[1]At Screening, serum creatinine performed within 3 months of the planned surgical procedure will be accepted if the subject was in stable medical condition at the time of the test and has remained in stable medical condition since the test was performed.

8.5. Vital Sign Measurements

Summary tables presenting observed values and changes from baseline to each scheduled post-baseline will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), respiration (breaths/minute), and temperature (°C) for subjects in the safety analysis set.

Number and percentage of subject's vital signs interpretation will be presented by each time point using safety analysis set.

All vital sign results and interpretation will be presented in a listing by visit/timepoint using the safety analysis set.

8.6. Physical Examination

A physical examination will be performed by the investigator or his/her qualified designee according to the schedule of events (Appendix 12.1). A complete physical examination will be performed and will include the following body systems general appearance and a review of systems (dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, and respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems).

Physical examination results for all subjects will be presented in a listing by visits using the safety analysis set.

8.7. Electrocardiogram

All subjects will have a standard electrocardiogram (ECG) performed at the time points as scheduled (Appendix 12.1), that will be recorded in single reading.

The summary tables of observed values and changes from baseline will be presented for electrocardiogram data, including Ventricular rate (beats per minute), PR-interval (msec), QRS-duration (msec), QT-interval (msec) and QTc interval (msec) for subjects in the safety analysis set. Normal sinus rhythm (yes/no) will be presented with number and percentage of subjects by visit using the safety analysis set.

A table will summarize ECG interpretations by visit for the safety analysis set. Interpretation results include Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Not Done.

All ECG results and interpretation will be presented in a listing for subjects by visit using the safety analysis set.

8.8. Other Safety Data

8.8.1. Infusion site reaction

The number and percentages of subjects having infusion site reaction will be summarize by severity and the diameter of redness (Erythema) and diameter of swelling hardness will be summarized using descriptive statistics by timepoints and visits. All summarizations will be done using the safety analysis set.

All infusion site reaction status and related data will be presented in a listing using the safety analysis set.

9. Pharmacokinetics

9.1 Pharmacokinetic Measurement

PK blood samples (4 mL each) will be obtained at 0.5 (±10 min) end of infusion 1 h (±15 min), 2 h (±15 min), 4 h (±15 min) and 8 h (±15 min) after the start of the study drug infusion. The total amount of blood obtained from each subject for the PK samples will be approximately 20 mL.

If the surgery is extended unexpectedly beyond the 3-hour limit, additional doses of study drug are permitted according to institutional guidelines. PK blood sampling will not be halted due to this 2nd dose of study drug. The amount of study drug administered and the start and stop time of this 2nd dose of study medication must be recorded. PK blood sample collection will continue after the administration of an additional dose of Cefazolin and remaining collection times will be based on the start time of the 1st dose of study drug.

9.2 Pharmacokinetic Analysis

Individual plasma concentrations of Cefazolin will be presented in data listings using the safety analysis set. Plasma concentrations will be summarized at scheduled timepoints using the PK analysis set and descriptive statistics (number of non-missing observations, mean, standard deviation (SD), mean coefficient of variation (CV), geometric mean, geometric coefficient of variation, median, minimum, and maximum). For the descriptive statistics, all plasma concentrations that are below the limit of quantification (BLQ) will be set to zero. Plasma concentration data will be analyzed with the same precision as the source data regardless of how many significant figures or decimals the data carry. After analysis, 3 significant digits will be used as the standard rounding for all statistics except for coefficient of variation. Coefficient of variation will always be reported to 1 decimal place.

Plasma concentrations over scheduled time will be provided which include a single line profile for each of the 12 subjects and a mean (± Standard deviation) profile of all the subjects. This will be plotted on both linear and semi-logarithmic scale for the PK analysis set.

10. Changes in the Planned Analysis

Enrolled set is added to section 4.3 to trace the screen failed subjects in Table or Listings.

As per section 12.1 of protocol, "baseline demographic and background variables will be summarized by arm and overall, for all subjects" but we have modified this statement in section 6.1. Since we have only one study treatment, we have designed the demographic summary table with a single column summary.

11. References

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Schmitz ML, Rubino CM,Onufrak NJ, et al. Pharmacokinetics and Optimal Dose Selection of Cefazolin for Surgical Prophylaxis of Pediatric Patients. 2020;https://doi.org/10.1002/jcph.1785.

12. Appendices

12.1. Schedule of Events

Study Phase	Screening	Treatment								Follow-up[2]
Visit	Screening[1]	Day 1 Pre- Dose	Day 1						Day 2 (Or at Discharge)	Day 8
Procedure	Up to 30 Days before Study Drug Administration	Pre dose	0 h (±10min)	0.5 h (±15min)	1 h (±15min)	2 h (±15min)	4 h (±15min)	8 h (±15min)		
Admission to the Study Site										
Sign Study Consent	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Height and Weight[3]	X	X[4]								
Medical History	X									
Review Medical History		X								
Medication History	X									
Review Medication History		X								
Full Physical	X	X							X	
Vital Signs	X	X[5]		X		X	X	X	X	X
Electrocardiogram	X								X	
Clinical Laboratory Tests[6]	X	X[5]							X[2]	X
Pregnancy Test[7]	X	X[5]								
Study Drug Administration[8]			X							
Assess Study Drug Infusion Site				X	X	X	X	X	X[2]	X
Pharmacokinetic Samples[9]				X	X	X	X	X		
Concomitant Medication	continuous									
Collection of Adverse Events	continuous									

[1] Screening Visit may occur on Day 1 (Day of Surgery). All Screening procedures must be completed before study drug administration on Day 1.

[2] Assessments will be performed for subjects who received study medication and were an early termination, if possible. For Day 8, this will either be an in-person visit or a phone call.

[3] To be measured with indoor clothing and without shoes.

[4] Weight only

[5] To be completed approximately 30 minutes before study drug administration.

[6] Screening Clinical labs must be completed by the local laboratory. Study clinical labs need to be performed by the Central lab if a Central lab is used, otherwise a local lab is acceptable.

[7] Urine pregnancy tests will be performed for all females of childbearing potential. If positive, a serum pregnancy test will be performed to confrim the results. Pregnancy tests will be performed by the local laboratory.

[8] Study drug administration will be a 30-minute infusion and following institutional guidelines.

[9] Pharmacokinetic blood samples (4 mL) will be collected at selected timepoints after the start of study drug administration. NOTE: Pharmacokinetic samples cannot be collected from the same line/port as the infusion nor from the same arm as the infusion.

12.2. Table of Contents of Tables, Listings and Figures

List of Tables

Table 14.3.8.2 Summary of Infusion Site Reaction by Timepoints Safety Analysis Set

List of Listings

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