B. Braun Medical Inc.
CLINICAL STUDY PROTOCOL

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

ClinicalTrials.gov Identifier: NCT05205486

Document Date: 31 August 2021

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SHARING EXPERTISE

B. Braun Medical Inc.

FINAL CLINICAL STUDY PROTOCOL

Protocol Number: US-G-H-2101

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

Name of Products:	Cefazolin, 3 gram
Phase of Development:	1
Study Indication:	Surgical Prophylaxis
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Protocol Version:	1.0, Final
Protocol Date:	31 August 2021

-CONFIDENTIAL-

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SPONSOR APPROVAL PAGE

Product name: Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX® Container

B. Braun Protocol Number: US-G-H-2101

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

Product name: Cefazolin for Injection USP and Dextrose Injection USP in DUPLEX® Container

B. Braun Protocol Number: US-G-H-2101

I agree:

To assume responsibility for the proper conduct of the study at this site.

To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by B. Braun Medical Inc.

Not to implement any changes to the protocol without written agreement from B. Braun Medical and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to patients.

That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by B. Braun Medical.

That I am aware of, and will comply with, good clinical practices (GCP) and all applicable regulatory requirements.

To ensure that all persons assisting me with the study are adequately informed about the study and of their study-related duties and functions as described in the protocol.

To not disclose information regarding this clinical investigation or publish results of the investigation without authorization from B. Braun Medical Inc.

Signature: _____ Date: _____

Name (print): _____
Principal Investigator

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Synopsis

Title of Study:	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
Phase of Development:	1
Number of Study Sites:	Up to 5 study sites in the United States
Rationale:	This study is designed to evaluate the pharmacokinetics (PK) of a single 3 g 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) infusion, per cefazolin Package Insert. Based on a population pharmacokinetic modelling analyses, 5 PK samples per subject obtained up to 8 hours after dosing will be sufficient to assess the PK of cefazolin in this population. These data will then be assessed by the validated Cefazolin PK Model to verify there are no significant PK changes within this study population.
Objectives:	**Primary Objective:** The primary objective of this study is to determine the PK of a single IV 3 g dose of cefazolin administered to adult subjects (weighing ≥ 120 kg) scheduled for surgery. Safety in this population will also be assessed.
Planned Sample Size:	Subjects will be enrolled in to the study in order to have at least 12 subjects complete the PK portion of the study.
Study Design:	This is a Phase 1, open-label, single-dose, multiple-center, study to determine the pharmacokinetics of a single 3 g dose of cefazolin administered as a 30-minute IV infusion prior to surgery in adult subjects weighing ≥ 120 kg. Adult subjects will be enrolled in order to ensure at least 12 subjects complete the study. Enrollment will be competitive across the study sites. All subjects will have Screening and baseline evaluations performed to ensure their eligibility for the study The Screening Period is up to 30 days before administration of study drug on Day 1. 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-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. 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 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.
Selection of Patients:	**Inclusion Criteria** Subjects must meet all of the following Inclusion Criteria: 1. Male or female aged ≥18 years; 2. Must weigh ≥ 120 kg 3. Able to understand and sign the Informed Consent Form (ICF); 4. Is scheduled for surgery that is expected to last less than 3 hours. 5. Is scheduled for any type of surgery where a single-dose perioperative cefazolin prophylaxis is appropriate. **Exclusion Criteria** Subjects must not meet any of the following Exclusion Criteria: 1. If female, is pregnant or lactating/breastfeeding. 2. If female that is of childbearing potential and sexually active, and is not using an effective method of birth control, e.g., oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy. 3. Has a history of renal impairment: a. Subjects has an eGFR of <80 mL/min/1.73m^2 performed at Screening as calculated by the following equation: 186 x (**Creatinine**/88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) 4. Has a known allergy or hypersensitivity to β-lactam/cephalosporin antibiotics, corn products, or dextrose-containing products or solutions, or any of the other ingredients of Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP in DUPLEX. 5. Has a result of any laboratory test (or repeat test, if done), obtained as standard of care, that is outside the normal limit of the site's laboratory reference range AND is considered by the investigator to be clinically significant. 6. Has had a recent (within 14 days prior to participation in the study) administration of cefazolin. 7. Has had administration of any medication (e.g., prescription, herbal, over-the-counter medication[s] or dietary supplements) known to interact with cefazolin within 5 days prior to the study treatment administration. 8. Has a known history of human immunodeficiency virus, hepatitis B, or hepatitis C infection. 9. Has a current history of medical condition(s), which in the opinion of the investigator, would interfere with the evaluation of the study treatment. 10. Has a known history of organ transplant. 11. Has a clinically relevant disease/dysfunction of or a history of severe cardiac, pulmonary or hepatic disease 12. Is undergoing any cardiovascular procedure including, but not limited to, major cardiac surgery, cardiac catheterizations (including electrophysiology studies), ablations, automatic implantable cardioverter-defibrillator (AICD), and pacemaker. 13. Has received any other investigational drug/device within 30 days prior to the study treatment administration. 14. Has any planned medical intervention or personal event that might interfere with ability to comply with the study requirements. 15. The subject has any condition that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.

	16. Is unable or unwilling to adhere to the study-specified procedures and restrictions. 17. Is an employee of the Sponsor, Investigator or study center, has direct involvement in the study or other studies under the direction of that Investigator or study center, or is a family member of the employees or the Investigator.
Study Treatment, Dosage, and Route of Administration:	Cefazolin, single dose 3 g, 30-minute intravenous infusion Cefazolin for Injection USP and Dextrose Injection USP is a sterile, nonpyrogenic, 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 supplied in the drug chamber as a lyophilized form equivalent to 3 g of cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.
Study Duration:	The study consists of a Screening Period of up to 30 days prior to surgery, a Treatment Period on Day 1 (day of surgery), and a Follow-up visit on Day 8 (±1 day). The maximal study duration for an-individual subject will be approximately 38 days
Study Visits:	**Screening Visit:** The following assessments will be performed up to 30 days (Day-30 to Day -1) before the day of surgery (Day 1): sign study consent, pass all Inclusion and Exclusion criteria, obtain demographic information, medical history, medication history, full physical, vital signs (including height and weight), electrocardiograph, clinical laboratory tests, pregnancy test (if appropriate), and begin collection of concomitant medication and collection of adverse events. The Screening visit may occur on the day of surgery (Day 1), however, all Screening procedures must be completed before the study drug is administered. **Day 1 Pre surgery:** The following assessments will be performed before surgery on Day 1: review medical history, review medication history, physical exam, vital signs (including weight), clinical laboratory tests, pregnancy test (if appropriate), review of concomitant medication, and AE assessments. **Day 1 Surgery:** Study drug administration will be a 30-minute IV infusion beginning 30 to 60 minutes before surgery and following institutional guidelines. The following assessments will be performed upon the start of the surgery: vital signs, PK sample collection, review of concomitant medication, AE assessments and examination of the infusion site. **Day 2 Post-Surgery:** The following safely assessments will be performed approximately 24 hours after the completion of the surgery or at discharge from the hospital, whichever comes first: physical, vital signs, electrocardiograph, clinical laboratory tests, examination of the infusion site, review of concomitant medication, and AE assessments. **Day 8 (±1 day) Safety Follow-up:** The following safety assessments will be performed on Day 8 (±1 day). If this is an in-person visit: 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.
Clinical Laboratory Evaluation:	Laboratory tests (hematology and serum chemistry) will be performed by a local laboratory. Screening labs must be completed within 30 days prior to dosing. Laboratory results obtained presurgery on Day 1 will be used to determine baseline for the study. Aliquots of the screening plasma and serum samples will be sent to the Central laboratory (if a Central laboratory is used) for analysis. Results of the Day 1 pre-dose pregnancy test must be available before dosing.
Statistical Methods and Planned Analyses:	**Safety Analysis Set:** Safety will be determined by monitoring AEs, physical examination, vital signs, and clinical laboratory tests for all subjects receiving study drug. All AE's reported over the course of the study will be categorized based on

	MedDRA coding system and tabulated by system organ class, and preferred term within the system organ class. Descriptive statistics will be generated for all safety parameters. Continuous variables will be summarized by treatment group using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages Individual data will be listed in data listings. **Pharmacokinetic Analysis Set:** All subjects will have five (5) 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). PK samples cannot be collected from the same line/port as the study drug infusion nor from the same arm as the infusion. Exact time and date of each PK sample collection will be recorded. Descriptive statistics will be generated and summarized using mean, SD, median, minimum value, and maximum value from the plasma cefazolin concentrations. Details about the collection, storage and shipment of the PK samples will be provided in a separate document. Additional details on the statistical analyses will be describe in the separate Statistical Analysiss Plan (SAP). No inferential statistical analysis will be performed.

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1 Listing of Tables

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
OCT	Over-the-counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
US	United States

1 INTRODUCTION

1.1 Background information

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 g or 2 g of cefazolin (i.e., contains approximately 2 g dextrose [4.0% weight to volume ratio (w/v)] and 1.5 g dextrose [3.0% w/v] for the 1 g and 2 g dosages, respectively).

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

Microbiology

Cefazolin is an antibacterial agent that in in vitro testing has been shown to act by inhibition of bacterial cell wall synthesis.

Cefazolin has demonstrated activity against most strains of the following microorganisms, both in vitro and in clinical infections:

Gram-Positive Bacteria

- *Staphylococcus aureus* (*S aureus*)
- *Staphylococcus epidermidis*
- *Streptococcus pyogenes* (*S pyogenes*) and *Streptococcus agalactiae* (*S agalactiae*)
- *Streptococcus pneumonia (S pneumoniae*)

Methicillin-resistant staphylococci are uniformly resistant to cefazolin, as are many strains of enterococci resistant to cefazolin.

Gram-Negative Bacteria

- *Escherichia coli* (*E coli*)
- *Proteus mirabilis* (*P mirabilis*)

Most strains of indole-positive *Proteus* (*Proteus vulgaris*), *Enterobacter* spp, *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp, and *Pseudomonas* spp are resistant to cefazolin.

Indications and Usage

Cefazolin for Injection USP and Dextrose Injection USP is indicated for the treatment of the following infections when caused by susceptible bacteria:

Respiratory Tract Infections

- Respiratory tract infections due to *S pneumoniae*, *S aureus,* and *S pyogenes*

Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available.

Urinary Tract Infections

- Urinary tract infections due to *E coli* and *P mirabilis*

Skin and Skin Structure Infections

- Skin and skin structure infections due to *S aureus*, *S pyogenes*, and *S agalactiae*

Biliary Tract Infections

- Biliary infections due to *E coli*, various strains of streptococci, *P mirabilis*, and *S aureus*

Bone and Joint Infections

- Bone and joint infections due to *S aureus*

Genital Infections

- Genital infections due to *E coli* and *P mirabilis*

Septicemia

- Septicemia due to *S pneumoniae*, *S aureus*, *P mirabilis*, and *E coli*

Endocarditis

- Endocarditis due to *S aureus* and *S pyogenes*

Perioperative Prophylaxis

The prophylactic administration of cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy and cholecystectomy in high-risk patients such as those older than 70 years and those with acute cholecystitis, obstructive jaundice, or common bile duct stones).

The perioperative use of cefazolin may also be effective in surgical patients for whom infection at the surgical site would present a serious risk (e.g., during open-heart surgery or prosthetic arthroplasty).

Pharmacodynamics in Humans

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 for the bacterial pathogen is the relevant pharmacokinetic/pharmacodynamic (PK/PD) index for cefazolin (Leggett et al 1989).

Pharmacokinetics in Humans

Absorption

Cefazolin is only available as an intravenous (IV) formulation. Thus, no human bioavailability data are available for other routes of administration.

Distribution

Studies have shown that after IV administration of cefazolin to healthy volunteers, mean serum concentrations peaked at approximately 185 µg/mL and were approximately 4 µg/mL at 8 hours for a 1-g dose.

Bile concentrations in patients without obstructive biliary disease could reach or exceed serum concentrations by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin were considerably lower than serum concentrations (<1.0 µg/mL).

In synovial fluid, the cefazolin concentration became similar to that reached in serum at approximately 4 hours after drug administration.

Studies of cord blood showed prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Metabolism

Cefazolin is not a substrate, inducer, or inhibitor of hepatic cytochrome P450 isoenzymes. No significant amounts of metabolite have been observed in human plasma.

Excretion

Cefazolin is excreted unchanged in the urine. In the first 6 hours, approximately 60% of the drug is excreted in the urine, and this increases to 70% to 80% within 24 hours.

The mean serum half-life for cefazolin is approximately 1.8 hours after IV administration.

Adult Pharmacokinetic Studies

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 (Leggett et al 1989).

In a study (using healthy volunteers) of constant IV infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg for the next 2 hours (approximately 100 mg), cefazolin produced a steady serum concentration at the third hour of approximately 28 µg/mL.

Plasma PK parameters of cefazolin in healthy volunteers (n=12) after a single 15-minute IV infusion of 2 g of Cefazolin for Injection USP and Dextrose USP (the formulation being evaluated in the current proposed study) are summarized in **Table 1**

Table 1: Plasma Pharmacokinetic Parameters of Single-Dose Cefazolin of 2 g as a 15-Minute Intravenous Infusion in Healthy Volunteers

	N	C_{max} (µg/mL)	T_{max}[1] (h)	AUC_{0-inf} (µg·h/mL)	$t_{1/2}$ (h)	CL (L/h)	V_z (L)
Mean (SD)	12	280.9 (45.9)	0.25 (0.25-0.33)	509.9 (89.3)	2.01 (0.28)	4.03 (0.68)	11.50 (1.53)

Abbreviations: AUC_{0-inf}, area under the plasma concentration-time curve extrapolated to infinity; CL, total clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent plasma terminal elimination half-life; T_{max}, time to maximum plasma concentration; V_z, volume of distribution.

[1] T_{max} reported as median (range).

Studies in patients hospitalized with infections indicated that cefazolin produces mean peak serum concentrations approximately equivalent to those seen in healthy volunteers.

Safety and Efficacy

Surgical Prophylaxis

There are no reports of adequate and well-controlled randomized prospective studies of surgical prophylaxis in the literature. One prospective study in burn patients showed no benefit from cefazolin prophylaxis (Rodgers et al 1997). Two retrospective studies [one cardiac (Maher et al 2002), one orthopedic (Nahata et al 1985)] lacked non-cefazolin control arms; in one the use of fixed doses of cefazolin was associated with an overdose risk (Nahata et al 1985). One survey (Lee et al 1995) and 3 PK/PD studies (Haessler et al 2003); Nahata et al 1991; Koshida et al 1987) evaluated cefazolin intravenously in surgical prophylaxis. Dosing varied widely, but 25 mg/kg repeated 8 hourly for up to 48 hours represents a consensus position. The results of a retrospective analysis comparing the efficacy of two antimicrobial prophylaxis (AMP) protocols with cefazolin in preventing surgical site infection in adolescent idiopathic scoliosis suggest that two doses of AMP are as effective as continued antimicrobial use until drain removal and cefazolin appears to be effective and safe for prophylaxis (Kamath et al 2016).

Adverse Events (AE)

Cefazolin is well tolerated and there is little mention of AEs in the published literature. One study noted no AEs in a series of only 5 subjects (Ross et al 1977) and another noted no AEs in 52 subjects (Nahata et al 1985). Two other reports noted eosinophilia (Ross et al 1977, Khan 1973), and hepatic dysfunction and rash were also noted (Khan 1973). Drug rash, eosinophilia and systemic symptoms with severe interstitial nephritis were described in a single patient receiving cefazolin and gentamycin combination treatment (Yilmaz *et al*, 2016). One study noted a single case of hypotension as possibly related to the cefazolin treatment (Schmitz *et al*, 2015).

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis, indicated no clinically significant changes attributed to cefazolin.

Cefazolin was first approved for use in the United States in October 1973 (GLAXOSMITHKLINE). The B. Braun 1 g Cefazolin finished product currently approved by FDA has been marketed since 2001. From 1/1/2001 to 1/31/2021 83,481,470 1 g units have been shipped. The B. Braun 2 g Cefazolin finished product was approved in adult populations on January 13, 2012 and first sales to the US market were on February 13, 2012 with a total unit volume of 39,872,375 units through January 31 2021. Only 53 AEs have been reported with the use of cefazolin. Of these 53 AEs, 17 were serious/unexpected (13 of which were from literature and not confirmed to be the B. Braun Medical Inc. product). The remaining 36 AEs included 11 non-serious/expected and 25 serious/expected events. For a full description of the AEs please refer to the investigator's brochure (B. Braun Medical Inc. 2021).

1.2 Study rationale

Patients weighing ≥ 120 kg may not achieve a similar or therapeutic level of exposure to 2 grams of cefazolin as patients weighing ≤ 120kg. 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 gram 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-gram or 3-gram dose of cefazolin in 2 simulated populations of obese (≥ 120kg) 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 g 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 modeling analyses will be reported separately from the Clinical Study Report.

1.3 Risk-Benefit Assessment

Cefazolin is a first generation cephalosporin antibiotic with a well-established and favorable safety profile that has been in use for almost 50 years (originally approved in 1973). It is a standard of care for perioperative prophylaxis today and widely recommended for prophylaxis for a variety of surgical procedures for the prevention of infections by gram positive bacteria. Cefazolin has been shown to be active against some gram negative bacteria, such as E. coli and P. mirabilis. Subjects in this study will be adults weighing ≥ 120 kg, scheduled for surgery and will receive a single 3 g IV dose as a 30 minute infusion approximately 30 minutes before surgery.

The safety monitoring practices employed in this study are adequate to protect the subjects' safety and detect all expected treatment-emergent AEs.

Table 2 shows the volume of blood planned for collection from each subject over the course of the entire study (Screening to Follow-up, but not including repeat or additional tests ordered by the investigator) follows the standard of local laboratory practices and presents no undue risk to the subjects. The planned blood volume collected in this study is approximately 52 mL (32 mL for Clinical and 20 mL for PK) and is well within the guidelines presented in "NIH M95-9, Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center".

Table 2: Blood Volume

Sample Type	Total Blood Volume (Planned)
Clinical Laboratory	32 mL (8 mL × 4 collections)
Pharmacokinetic	20 mL (4 mL × 5 collections)
Combined Clinical and Pharmacokinetic	52 mL

The available information suggests that the present clinical study has an acceptable risk benefit ratio.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

3 Study Design

This is a Phase 1, open-label, single-dose, multiple-center, study to determine the pharmacokinetics of a single 3 g 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 acministrated 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-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. 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 labcratory 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.

3.1 Rational of Study Design

Cefazolin is widely used for perioperative infection prophylaxis in adult patients. Cefazolin will be administered as a 30-minute intravenous (IV) infusion, per cefazolin Package Insert for surgical prophylaxis. Current clinical practice and overall experience with cefazolin administration for perioperative infection prophylaxis will be followed.

This study is designed to evaluate the pharmacokinetics (PK) of a single 3 g dose of cefazolin from a DUPLEX container, in adult subjects (weighing ≥120 kg) scheduled for surgery.

Based on a population pharmacokinetic modelling analyses, 5 PK samples per subjects obtained up to 8 hours after dosing will be sufficient to assess the PK of cefazolin in this population. These data will then be assessed by a validated Cefazolin PK Model to verify there are no significant PK changes within this study population.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Informed Consent

A written informed consent in compliance with 21 CFR 50 shall be obtained from each subject before entering the study or performing any unusual or non-routine procedure that involves risk to the subject.

The Investigator shall explain the nature, purpose and risks of the study and provide the subject with a copy of the informed consent. The subject will be given sufficient time to consider the study before deciding whether to participate. The Investigator is at his/her option to provide the subjects with an additional information sheet containing any details required by local legal requirements. Additional signatures may be required by the Institutional Review Board (IRB) or according to current FDA Guidance.

An informed consent template may be provided by the sponsor or its designee to study sites. If any institution-specific modifications to study-related procedures are proposed to be made by the study site, the consent must be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed and approved, the consent will be submitted by the investigator to his or her IRB for review and approval before the start of the study. If the Informed Consent Form (ICF) is revised during the course of the study, all active participating subjects must sign the revised form.

The investigator shall retain the signed original ICF(s).

Should there be any amendments to the Final Protocol that would directly affect the subject's participation in the study, such as a change in study procedures, the Informed Consent Form must be amended to incorporate this amendment and the subject's informed consent to the amendment must be obtained.

4.2 Subject Inclusion Criteria

Subjects will be enrolled across 1 or more study sites in the United States to ensure at least 12 subjects complete the study. Subjects will be assigned to study drug administration only if they meet all of the inclusion criteria and none of the exclusion criteria to be considered for the study. Enrolment will be competitive across the study sites.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects must meet all of the following Inclusion Criteria:

1. Male or female aged ≥18 years;
2. Must weigh ≥ 120 kg
3. Able to understand and sign the Informed Consent Form(s) (ICF);
4. Is scheduled for surgery that is expected to last less than 3 hours;
5. Is scheduled for any type of surgery where a single-dose perioperative cefazolin prophylaxis is appropriate.

4.3 Subject Exclusion Criteria

Subjects must not meet any of the following Exclusion Criteria:

1. If female, is pregnant or lactating/breastfeeding.
2. If female that is of childbearing potential and sexually active, and is not using an effective method of birth control, e.g., oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy.
3. Has a history of renal impairment:
    a. Subjects has an eGFR of <80 mL/min/1.73m^2 performed at Screening as calculated by the following equation: 186 x (**Creatinine**/88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) (FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function)
4. Has a known allergy or hypersensitivity to β lactam/cephalosporin antibiotics, corn products, or dextrose-containing products or solutions, or any of the other ingredients of Cefazolin for Injection United States Pharmacopeia (USP) and Dextrose Injection USP in DUPLEX.
5. Has a result of any laboratory test (or repeat test, if done), obtained as standard of care, that is outside the normal limit of the site's laboratory reference range AND is considered by the investigator to be clinically significant.
6. Has had a recent (within 14 days prior to the planned surgery) administration of cefazolin.
7. Has had administration of any medication (e.g., prescription, herbal, over-the-counter medication[s] or dietary supplements) known to interact with cefazolin within 5 days prior to the study treatment administration.
8. Has a known history of human immunodeficiency virus, hepatitis B, or hepatitis C infection.
9. Has a current history of medical condition(s), which in the opinion of the investigator, would interfere with the evaluation of the study treatment.
10. Has a known history of organ transplant.
11. Has a clinically relevant disease/dysfunction of or a history of severe cardiac, pulmonary or hepatic disease
12. Is undergoing any cardiovascular procedure including, but not limited to, major cardiac surgery, cardiac catheterizations (including electrophysiology studies), ablations, automatic implantable cardioverter-defibrillator (AICD), and pacemaker.
13. Has received any other investigational drug/device within 30 days prior to the study treatment administration.

14. Has any planned medical intervention or personal event that might interfere with ability to comply with the study requirements.
15. The subject has any condition that, in the opinion of the investigator, would compromise the safety of the subject or the quality of the data.
16. Is unable or unwilling to adhere to the study-specified procedures and restrictions.
17. Is an employee of the Sponsor, Investigator or study-center, has direct involvement in the study or other studies under the direction of that Investigator or study-center, or is a family member of the employees or the Investigator.

4.4 Stopping and Discontinuation Criteria

The duration of the study is defined for each subject as the date signed written informed consent is provided through the completion of all study related procedures performed approximately 24 hours after the completion of the surgery (Day 2) or at discharge from the hospital, whichever comes first. It is highly preferred that the subjects also participate in the Day 8 (±1 day) Safety Follow-up. For those subjects who withdraw prematurely, subject completion is defined as the time of the subject's last data collection.

When an individual patient's participation in the study is stopped or discontinued, the nature of termination must be documented (scheduled end or premature termination or discontinuation). In the event of premature termination or discontinuation, the basis for such termination or discontinuation should be documented.

If the study as a whole is prematurely terminated or suspended, the concerned IRB/ Independent Ethics Committee (IEC) and the regulatory authorities will be informed promptly and provided with the reasons for the termination or suspension by the sponsor.

4.4.1 Reasons for Discontinuation From the Study

Any subject may withdraw from the study at any time and for any reason without prejudice to the subject's future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. If the subject is unreachable by at least 2 telephone calls, a registered letter, at the minimum, should be sent to the subject requesting that he or she contacts the investigator. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria
2. Noncompliance with the protocol
3. A serious or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study
4. Lost to follow-up
5. Pregnancy
6. Request to withdraw informed consent or HIPAA authorization by subject
7. Any other reason warranting withdrawal at the discretion of the investigator with approval of B. Braun Medical Inc.

Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed up to satisfactory resolution. Any subject may withdraw their consent at any time. The investigator will also withdraw a subject if B. Braun Medical Inc. terminates the study.

4.4.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study drug at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study prematurely, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page in the electronic case report form (eCRF). Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all safety assessments scheduled for Day 8 (±1 day). The following safely assessments will be performed: physical, vital signs, clinical laboratory tests, examination of the infusion site, review of concomitant medication, and AE assessments.

For the subjects who are unable to attend the in-person final safety assessments, a phone call to the subject is acceptable. In this scenario, the following safety assessments will be performed: review of concomitant medication, and AE assessments.

It is vital to obtain follow-up data on any subject withdrawn a serious or intolerable AE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

Female subjects who are known to be pregnant should not be enrolled in the study. All female subjects will have a pregnancy test at Screening and presurgery on Day 1. If a pregnant subject is administered study drug in error, the subject will be followed though completion or termination of the pregnancy. Please refer to Section 6.3 for specified reporting and follow-up processes.

4.5 Randomization, Blinding and Unblinding

This is an open-label, non-randomized pharmacokinetic study. All subjects will be receiving the same study treatment, thus blinding is unnecessary.

5 Study Products

The Study Product will be made available to the study site (*e. g. pharmacist*) by the Sponsor or designee. If defects in the Study Product are observed, the Investigator or the medical monitor must be informed immediately.

5.1 Name and Description of the Study Product(s)

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 g or 2 g of cefazolin. The diluent chamber contains approximately 50 mL of Dextrose Injection USP.

For the Investigational 3g 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.

B. Braun Medical Inc. or its designee will provide to the study sites directly adequate supplies of the study drug.

5.2 Study Drug Administration

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 hour 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.

5.3 Packaging and Labelling

Cefazolin for Injection USP and Dextrose Injection USP will be manufactured in the DUPLEX container and shipped by the sponsor or its designee. Each DUPLEX container will contain 1 dosage for 1 subject.

A label will be attached to each subject's study drug. Each label will bear the following information:

- Study drug name (Cefazolin)
- Dosage (3g)
- Lot number
- Expiration date
- Storage requirements
- Investigational new drug statement in accordance with US Title 21 Code of Federal Regulations (CFR) Subpart A 312.6: [Caution: New Drug - Limited by Federal (or United States) law to investigational use]
- Name and address of the sponsor
- Study number

Further details and written instructions may be provided by the study site monitor prior to or at study initiation. Labels may have additional information or modifications as required to meet local regulations.

5.4 Storage

Study drug must be stored in a secure area (e.g., a locked cabinet), protected from moisture, and kept at controlled room temperature according to the storage conditions on the label (20°C to 25°C [68°F to 77°F]) and in the investigator's brochure. After reconstitution (activation), study drug must be used within 24 hours if stored at room temperature or within 7 days if stored under refrigeration.

5.5 Study Product Accountability

In accordance with regulations, the Investigator or a pharmacist or other appropriate individual designated by the Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt and storage conditions. In addition, accurate records will be

kept regarding when and how much study drug is dispensed and used by each subject in the study. Treatment compliance will be determined based on the amount of study drug used by each subject. It is expected that the entire dose will be administered.

5.6 Retrieval and/or Destruction of Unused Study Product

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.7 Other Supplies

Instructions and materials for collection, processing, storage, and shipping of clinical and PK laboratory samples to be analysed at the laboratory(ies) will be provided to the study sites in a separate document(s).

Other supplies provided to the study sites include eCRF completion guidelines, pharmacy manual, and SAE and pregnancy report forms.

5.8 Overdose Management

An overdose is any dose of study drug given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the sponsor or its designee. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported in relevant AE/Serious Adverse Events (SAE) sections in the eCRF.

5.9 Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

6 TREATMENT COMPLIANCE

Study drug will be administered by trained, qualified personnel designated by the investigator. Study drug will be administered over 30 minutes as an infusion starting approximately 0.5 hour before surgery begins and following institutional guidelines. The date and time of study drug administration will be documented. It is expected that the entire dose will be administered. The amount dosed as well as the start and stop time of the infusion must be recorded.

The date and time of anaesthesia induction will also be documented. Comments will be recorded if there are any deviations from the planned administration procedures. All study assessments will be performed by qualified study personnel and recorded in subject eCRFs. Compliance may also be ensured by sponsor audit of the source documents, including study subject eCRFs.

7 PRIOR AND CONCOMITANT THERAPY

Concomitant use of or treatment with any medication (e.g., prescription, herbal, over-the-counter (OTC) medication[s] or dietary supplements) known to interact with cefazolin is prohibited within 5 days prior to the study drug administration until completion of the follow-up visit. Concomitant use of probenecid is also prohibited for this period.

If a subject has an infusion-related reaction due to study drug, the study drug will be discontinued and the subject will not be rechallenged with the study drug. The choice of an alternate antibiotic for surgical prophylaxis will be made by the investigator or designee under the direction of the investigator.

Any acute medication necessary during conduct of the study will be recorded in the eCRF.

Use of all concomitant medications from Screening through completion of the study will be recorded in the subject's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications also will be recorded in the subject's eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Subjects will be enrolled in order to complete at least 12 subjects. Enrollment will be competitive across the study sites. Before performing any study procedures, all potential subjects must sign an ICF. Specified requirements for potential subjects on the informed consent process are detailed in Section 4.1. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign the ICF.

Subjects will undergo the study procedures at the time points specified in the schedule of events (**Table 3**).

8.1 Screening (up to 30 days before study drug administration)

The Screening Visit will take place within the 30 days before study drug administration (Day -30 to Day –1). The Screening Visit can occur on Day 1 (day of surgery) as long as all Screening Visit assessments are properly completed.

During the Screening Period, subjects will be evaluated by the investigator according to the inclusion (Section 4.2) and exclusion criteria (Section 4.3) to determine eligibility.

Screening Visit:

- Sign study Informed consent (Section 4.1)
- Inclusion and Exclusion Criteria
- Assigned a Subject Identification Number (SIN), if appropriate
- Demographics: (race, ethnicity, gender, date of birth)
- Height (without shoes)
- Weight (with indoor clothing and without shoes)
- Medical history
- Medication history
- Electrocardiograph (Section 10.3)
- Complete physical examination (Section 10.1)
- Vital signs (Section 10.2)
- Clinical laboratory tests (Section 10.5)
- Pregnancy test (Section 10.6)
- Begin concomitant medication documentation
- Begin AE assessments

8.2 Pre-surgery Visit Day 1:

The following assessments and procedures will be performed at the pre-surgery visit:

- Weight (with indoor clothing and without shoes)
- Review medical history
- Review medication history

- Full physical examination (Section 10.1)
- Vital signs (Section 10.2)
- Clinical laboratory tests (Section 10.5)
- Pregnancy test (Section 10.6)
- Review of concomitant medications and AE assessments

8.3 Surgery Visit Day 1:

- Vital signs (Section 10.2)
- Study drug administration as a single 30-minute infusion
- Study drug infusion site assessments (Section 10.4)
- Pharmacokinetic blood sample collections (Section 11.1)
- Review of concomitant medications and AE assessments

8.4 Post-surgery Visit Day 2:

Postsurgery assessments will be performed at 24 hours after surgery or discharge from the study site, whichever comes first.

The following assessments and procedures will be performed at the postsurgery visit:

- Physical examination (Section 10.1)
- Vital signs (Section 10.2)
- Electrocardiograph (Section 10.3)
- Clinical laboratory tests (Section 10.5)
- Study drug infusion site assessment (Section 10.4)
- Review of concomitant medications and AE assessments

8.5 Safety Follow-up Visit Day 8 (±1 day):

If this is an in-person visit:

- Vital signs (Section 10.2)
- Clinical laboratory tests (Section 10.5)
- Study drug infusion site assessment (Section 10.4)
- Review of concomitant medications and AE assessments

If an in person follow-up visit is not possible, a phone call to the subject is acceptable. In this scenario:

- Review of concomitant medications and AE assessments

8.6 Schedule of Events

Table 3 shows the schedule of study events.

Table 3: Schedule of Study 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] Screeing Visit may occur on Day 1 (Dey 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 terminaiton, 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 approximatley 30 minutes before study drug administration.

[6] Screening Clinical labs must be competed 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 test will be performed for all females of childbearing potential. If positive, a serum pregnancy test will be performed to confirm 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.

9 ASSESSING AND REPORTING OF ADVERSE EVENTS

The investigator is responsible for reporting all treatment-emergent AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

9.1 Definitions

9.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after beginning study participation if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

Note: This definition does not imply that there is a causal relationship between the adverse event and the device under investigation (ISO 14155-1).

9.1.2 Serious Adverse Event

An 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 appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.1.3 Adverse Event Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

- Mild: An event usually transient in nature and generally not interfering with normal activities. Minimal or no treatment is indicated.
- Moderate: An AE that is sufficiently discomforting to interfere with normal activities. Treatment may be necessary.
- Severe: An AE that is incapacitating and prevents normal activities. Systemic drug therapy or other treatment may be necessary.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

9.1.4 Adverse Event Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drug in causing or contributing to the AE will be characterized using the following classification and criteria:

- **Unrelated:** This relationship suggests that there is no association between the study drug and the reported event.
- **Possible:** This relationship suggests that study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known

response pattern to the study drug, but could also have been produced by other factors.

- **Probable:** This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.
- **Definite:** This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

9.2 Recording and Reporting of Adverse Events and Serious Adverse Events

9.2.1 Recording of Adverse Events

Adverse events will be assessed from the time the subject signs the ICF until exit from the study.

Serious AEs, brought to the investigator's attention after the subject has completed the study, need NOT be reported unless the investigator considers them related to study drug.

At every study visit, subjects will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, vital sign changes) or identified from review of other documents that are relevant to subject safety will be documented on the AE page in the eCRF.

9.2.2 Reporting of Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes study drug administered, dose, event term, date of onset and resolution, exact time of onset only for events occurring on day of surgery, investigator specified assessment of severity and relationship to study drug, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed up to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 9) must be reported to the sponsor or their designee immediately (i.e., within 24 hours) after the time that study site personnel first learn about the event. Contact information to be used for SAE reporting will be inserted and or supplied to the study site when available:

CRO name Pharmacovigilance:

24 Hour Safety Hotline phone number: +XXXXX

24 Hour Safety Hotline fax number: +XXXXX

9.3 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the relevant page in the eCRF and followed up to satisfactory resolution. For the purposes of this study, satisfactory resolution means that the investigator deems the event to be chronic or not clinically significant, or considers the subject to be stable.

10 Safety Evaluations

10.1 Physical Examination

Complete physical examination will be performed at Screening by the investigator or a delegate.

The complete physical examination includes an assessment of 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).

A physical examination will be performed by the investigator or a delegate as described in the Schedule of Events (Table 3).

It is preferred that the same clinician conduct all physical exams on any single subject.

All treatment-emergent findings that were not present at Screening or described in medical history will be reported in the eCRF.

10.2 Vital Signs

Vital signs (including blood pressure [systolic and diastolic], pulse, body temperature, and respiratory rate) should be taken with subjects in supine position after resting for 5 minutes.

The vital signs will be measured and assessed at Screening, Day 1, discharge from the facility and at the follow-up visit on Day 8 (±1 day)

Pre-surgery vital sign measurements should be obtained within approximately 30 minutes before the start of study drug administration.

Time points for vital sign measurements on Day 1 are: 30 minutes [±10 minutes] end of infusion, 2.0 hour [±15minutes], 4.0 hours [±15minutes] and 8.0 [±15minutes] hours after the start of the study drug infusion, and after surgery as specified in Table 3 will be measured and assessed at:

10.3 Electrocardiograph

Electrocardiographs will be performed at as specified in the Schedule of Events (Table 3). Subjects should be resting quietly in fully supine position for 5 minutes before the ECG recording. Clinical review and assessment of cardiac rhythm, conduction, waveform morphology and ECG interval duration will be performed at the study site, as close as possible to the time an ECG was obtained, by the investigator or his/her designee.

10.4 Infusion Site Assessments

The site of study drug infusion will be evaluated for signs of infusion-related reactions on Day 1 at 0.5h (end of infusion), 1.0 h, 2.0 h, 4.0 h and 8.0 h after the start of the study drug infusion, as listed in the Schedule of Events (Table 3). The infusion site will also be evaluated at the follow-up visit on Day 8 (±1 day), if this is an in-person visit.

10.5 Clinical Laboratory Assessments

All Clinical Laboratory tests procedures will be performed by the local or central laboratory. Screening laboratory tests should be performed within 30 days of Day 1 and can be the same tests as assessed for surgical clearance. Screening laboratory tests will be performed at local laboratories. If appropriate, aliquots of the serum and plasma collected at Screening will be sent to the central laboratory for replicate analysis. Blood samples for clinical laboratory assessments and urine samples for pregnancy testing will be collected at the time points specified in Table 3.

The following laboratory analyses will be performed:

Hematology	Clinical Chemistry
• Hemoglobin	• Alanine aminotransferase
• Hematocrit	• Albumin
• Mean corpuscular volume	• Alkaline phosphatase
• Mean corpuscular hemoglobin	• Aspartate aminotransferase
• Mean corpuscular hemoglobin concentration	• Blood urea nitrogen
• Platelets	• Serum creatinine[1]
• Red blood cell	• Total bilirubin
• White blood cell with differential count	• 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.

Urine pregnancy tests will be performed for all females of childbearing potential at Screening and be repeated on Day 1. If positive, pregnancy will be confirmed with serum test (Table 3). If pregnancy is confirmed, the subject will not be enrolled, or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

Any abnormal laboratory test results (haematology and clinical chemistry) or other safety assessments (e.g., physical examination and vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

Sample Collections

The blood samples and urine pregnancy samples collected at Screening will be analysed by a local laboratory. If appropriate, aliquots of the serum and plasma collected at Screening will be sent to the central laboratory for replicate analysis. The amount of blood to be drawn for these clinical laboratory samples will be approximately 32 mL per subject (8 mL × 4 samples). The planned blood volume collected in this study is well within the guidelines presented in "NIH M95-9 "Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center". Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

The blood samples collected at Treatment and Follow-up Periods (Days 1 to 8) may be analysed by the central laboratory, if a central laboratory is utilized. Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

10.6 Pregnancy

Female subjects who are known to be pregnant should not be enrolled in the study. All female subjects of childbearing potential will have a urine pregnancy test at Screening and on Day 1 (pre-surgery). If positive, pregnancy will be confirmed with a serum test. If pregnancy is confirmed, the subject will not be enrolled, or if already enrolled and not yet dosed the subject will be dropped. If a pregnant subject is administered study drug in error, the subject will be followed through the completion or termination of the pregnancy. All pregnancy tests will be performed at local laboratories.

Pregnancy is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to B. Braun Medical Inc. or its designee within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study drug must be promptly reported to B. Braun Medical Inc. or its designee.

Females of childbearing potential will be required to use an effective method of birth control as determined by the investigator from Screening period until exit from the study. Effective methods of birth control may include oral contraceptives, double barrier methods, hormonal injectable or implanted contraceptives, tubal ligation, or have a partner with a vasectomy.

11 PHARMACOKINETIC EVALUATIONS

PK blood samples will be obtained to determine the PK of cefazolin. Plasma samples will be analysed at a sponsor-approved bioanalytical facility using validated and specific methods.

11.1 Pharmacokinetic Sample Collection

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 subjects for the PK samples will be approximately 20 mL. The planned blood volume collected in this well within the guidelines presented in "NIH M95-9 "Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center". Instructions for collection, processing, storage, and shipping of these samples will be provided to the study sites as a separate document.

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.

A separate venous catheter for PK sample collection be placed contralateral to the catheter used for study drug infusion. It is important to note that PK blood samples can NOT be collected from the study drug infusion line nor from the same arm as the study drug infusion.

12 STATISTICS

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.

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

There will be no interim analyses.

12.1 Statistical methods

Statistical analysis of the safety and PK analyses sets will be performed using SAS® software Version 9.2 or later (SAS Institute Inc, Cary, North Carolina). Descriptive statistics will be presented for all safety parameters. Continuous variables will be summarized by treatment group using the mean, SD, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the statistical analysis plan.

No inferential statistical analysis will be performed.

Baseline will be defined as the values obtained presurgery on Day 1.

Baseline demographic and background variables will be summarized by arm and overall for all subjects. The number of subjects who enrol in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

12.1.1 Safety Analysis

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. Adverse events will be listed. The number and percentage of subjects experiencing an event will be tabulated by treatment and overall for each system organ class and preferred term. Adverse events will also be tabulated according to severity and causality.

Serious AEs and AEs leading to discontinuation will be listed separately.

Individual data listings of laboratory results will be presented for each subject. Flags will be attached to values outside of the laboratory's reference limits along with the investigator's assessment on clinical significance. Clinically significant laboratory test abnormalities that were considered AEs by the investigator will be presented in the AE listings.

Clinical laboratory tests (observed and change from baseline) will be summarized descriptively in tabular format.

Individual data listings of vital signs (observed and change from baseline) will be presented for each subject. Individual clinically significant vital sign findings that were considered AEs by the investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized descriptively in tabular format for individual vital sign measurements.

Individual data listings of ECG results (observed and change from baseline) will be presented for each subject. Individual clinically significant ECG findings that were considered AEs by the investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized by treatment descriptively in tabular format for individual ECG results.

Abnormal physical examination findings will be listed.

Summary statistical analyses will be provided for demographics and baseline characteristics.

12.1.2 Pharmacokinetic Analysis

Cefazolin plasma concentrations will used to estimate the PK parameters of a 3 g dose of cefazolin utilizing the population PK model. The details of the refined population PK model analysis will be contained in a separate report.

Plasma samples will be analysed at a sponsor-approved bioanalytical facility using validated and specific methods.

12.2 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.

13 DATA MANAGMENT

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include demographic and medical information for the subject and should be as complete as possible.

Study site personnel will enter subject data in the eCRFs. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA, an internal validated medication dictionary.

After database lock, each study site will receive a compact disk read-only memory (CDROM) containing all of their site-specific eCRF data as entered in the eCRF for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study sites' data from the study will be created and sent to the sponsor for storage.

13.1 Access to Study Records

The Investigator will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections and provide access to primary patient data (i.e. source data) which supports the data on the eCRFs for the study, e.g. general practice charts, hospital notes, appointment books, original laboratory records) to Sponsor, authorised representatives of the Sponsor such as study monitors and auditors, and appropriate regulatory authorities.

Any party with access to study records shall take all reasonable precautions consistent with applicable regulatory requirements to maintain the confidentiality of patient identifying information and Sponsor's confidential and/or proprietary information.

The investigator should promptly notify the sponsor and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor or its designee.

13.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current Good Clinical Practice (GCP) and current standard operating procedures.

14 ETHICAL CONSIDERATIONS

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) GCP, and all applicable regulations.

14.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6(R1): GCP will be maintained by the study site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, protocol version and/or date, and the date approval or a favourable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The investigator must promptly supply the sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

14.2 Amendments to Protocol

All amendments to the clinical study protocol should be agreed between the Sponsor and the Investigator and be recorded with a justification for the amendment. The Investigator or the Sponsor should not implement any deviation from, or changes of, the protocol without mutual agreement and review/approval from the IRB/IEC, and other agencies as required, of a proposed amendment. The only exceptions are where necessary to eliminate an immediate safety hazard to study subjects, or when the changes involve only administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)).

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the Sponsor and the Principal Investigator. Protocol amendments will be submitted to the appropriate IRB/IEC and competent authorities in line with pertinent regulatory requirements.

14.3 Protocol Violations and Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

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 (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

14.4 Financial Agreement

The financial agreement between Sponsor and an Investigator shall be documented in a written clinical trial agreement (CTA) which will be signed by the Investigator and the Sponsor prior to the commencement of the study.

14.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor its designee is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor its designee is financially responsible for further treatment of the subject's disease.

14.6 Conduct of Study

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be registered at www.clinicaltrials.gov according to the requirement from the FDA before enrolment of subjects begins.

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

14.7 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- IRB-approved informed consent, samples of study site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject
- Laboratory certifications and normal ranges for any local laboratories used by the study site, in accordance with 42 CFR 493

14.8 Investigator's Brochure

The Investigator shall be informed by means of *specify, e.g.: the Investigator's Brochure* about the preclinical and clinical state of knowledge concerning the Study Product. This document should serve as the basis for the assessment of probability of occurrence / expectedness of an adverse effect / reaction.

14.9 Personal Data, Data Protection and Confidentiality

All data obtained in the context of the clinical trial are subject to appropriate standards for data protection.

The Investigator must ensure that case report forms or other documents transmitted to the Sponsor contain no names, but only the subjects' study identification (patient number, and / or a random number).

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject except as necessary for monitoring and auditing by the sponsor, its designee, the FDA, or the IRB.

The investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.10 DATA HANDLING AND RECORD KEEPING

14.10.1 Completion of Case Report Forms

Any data to be recorded directly on the eCRFs (to be considered as source data) will be defined at the start of the study.

The investigator must ensure the accuracy, completeness, legibility and timeliness of data reported in the eCRF and all required reports. Any change or correction to an eCRF must be dated, initialled and explained (if necessary) and must not obscure the original entry, this applies to both written and electronic changes.

Data reported on the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Within two weeks after completion of each patient, the Investigator should have completed and signed eCRFs available for full inspection by the clinical monitor.

14.10.2 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

15 PUBLICATIONS

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and may work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, which shall be in the sponsor's sole discretion.

16 STUDY TERMINATION

Although B. Braun Medical Inc. has every intention of completing the study, B. Braun Medical Inc. reserves the right to discontinue the study at any time for clinical, administrative, or any other reasons.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study

Should the study be terminated and/or the study site closed for any reason, all documentation pertaining to the study must be returned to the sponsor.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

17 FINAL REPORT

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

The study results will be posted on the clinical trial registry: www.clinicaltrials.gov.

18 List of References

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