STATISTICAL ANALYSIS PLAN

PROTOCOL NO: ZX-ZP-0113

A Randomized, Controlled Clinical Trial Evaluating A Novel Perioperative Patient Skin Antiseptic Preparation

Protocol Version No.: 3 **Version Date:** 22Jun2021

Study Sponsor:
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1. ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
ChloraPrep®	ChloraPrep® Orange , 26-mL Applicator
cm	centimeter
eCRF	electronic case report form
EDMS	electronic data management system
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability Accountability Act
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
mL	milliliter
PP	per-protocol
preop	preoperative
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System, organ, class
SSI	surgical site infection
US	United States
WHO	World Health Organization
[redacted]	[redacted]

2 INTRODUCTION

This statistical analysis plan (SAP) for Protocol No. ZX-ZP-0113, "A Randomized, Controlled Clinical Trial Evaluating a Novel Perioperative Patient Skin Antiseptic Preparation" describes and expands upon the analytical plan presented in the protocol.

This document contains all planned analyses, reasons and justifications for these analyses for all study data. This plan also includes sample tables, figures, and listings that will be populated. The SAP will follow the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines as indicated in Topic E3 (Structure and Content of Clinical Study Reports), Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH.

The following sources were used in preparation of this SAP:

- Protocol # ZX-ZP-0113, Protocol Version No.: 3; Version Date: 22 June 2021
- ICH Guidance Topics E9, E3 and E8

3 PROTOCOL SUMMARY

3.1. Study Objectives

3.1.1. Primary Efficacy

The primary efficacy objective of this study is to determine the efficacy of two skin preparation products, [redacted] and a standard of care product, [redacted] on the rates of surgical site infections (SSI).

3.1.2. Primary Safety

The primary safety objectives are to determine the rates of skin irritation or allergic reactions attributed to each product and all other adverse events (AEs).

3.2. Study Design

This study is a 2-arm, randomized, parallel group, single-site study designed to determine the SSI rates within 30-days post-surgery of pre-surgical skin cleansing with [redacted] and [redacted] on patients who are planning to undergo clean (class I wound) or clean-contaminated (class II wounds) surgery based on medical chart review. After consenting to the study, screening will be conducted to determine patient eligibility. Eligibility will be determined from chart review and conducting any procedures for information not in the medical chart (e.g., signs of infection at the surgical site where an incision will be performed or patient reported allergies to components of the surgical scrubs). Pre-operative data to be collected on electronic case report forms (eCRFs) include patient's demographics, medical history, current antibiotics (last 4 days), adherence to [redacted] standard preop surgical instructions, and record of planned surgery. Eligible

patients will be randomized with stratification by type of surgery (clean versus clean-contaminated) in a 1:1 ratio to receive skin pretreatment with either [redacted] or [redacted] and will undergo surgery. The surgical site will be examined for signs of infection and local skin reactions at least once a day during hospitalization, and at discharge. The patient will be contacted by telephone approximately 3-to-5 days post hospital release and at 30-days post the day of surgery. During these telephone contacts, the patient will be asked about signs of local skin or systemic allergic reactions and a general question about how they are feeling to determine if any other AEs may have occurred. If during these queries, the patient reveals any events that may be indicative of an SSI, they will be asked to see a study doctor to determine if an SSI has occurred. If they have visited another doctor for an evaluation, the patient will be asked to provide any relevant medical records to include in the study files. At any time after discharge up to 30 days post-surgery, the patient will be encouraged to call a study nurse or doctor and arrange for a prompt clinical evaluation if an infection is suspected.

Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (**Table 1**).

Table 1: Schedule of Assessments

Study Day	**-21 to 1**	**2 – 30 if hospitalized (daily)**	**3 to 5 days post hospital release (telephone follow-up)**	**Outpatient follow-up visit – if conducted**	**Any time patient reports possible SSI or clinician reports SSI and visits a doctor's office or comes to the hospital or other clinic**	**30 (telephone follow-up)**
Informed Consent	X					
Locator Form	X					
Medical History / Surgical Plan	X					
Physical Exam Per Standard of Care[a]	X	X		X	X	
Prescribed antibiotics	X	X	X	X	X	X
Demographics	X					
Eligibility Checklist[b]	X					
Randomization, Treatment and Surgery	X					
Adherence to MCW standard preop surgical instructions	X					
AEs (open ended question) and elicited AE questions[c]	X	X	X	X	X	X
SSI Evaluation		X	X	X	X	X

Study Day	**-21 to 1**	**2 – 30 if hospitalized (daily)**	**3 to 5 days post hospital release (telephone follow-up)**	**Outpatient follow-up visit – if conducted**	**Any time patient reports possible SSI or clinician reports SSI and visits a doctor's office or comes to the hospital or other clinic**	**30 (telephone follow-up)**
Final Patient Disposition[d]						X

[redacted]

3.3. Study Endpoints

3.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the occurrence of any SSI within 30 days after surgery

3.3.2. Safety Endpoints

Safety endpoints will be analyzed over the entire treatment and follow-up period.

- AEs (including specifically local application site reactions and allergic reactions)

4. DEFINITION OF ANALYSIS SETS

The study analysis populations will consist of the following:

Full Analysis Set [modified intention-to-treat (mITT) analysis set: The mITT analysis set includes all patients who were randomized to study treatment, received the study treatment, and underwent surgery. Subjects will be analyzed by treatment received, not treatment randomized.

Safety Analysis Set: This is all patients that received study treatment. Patients are assigned to the treatment given, not randomized. If this set is different from mITT then it will be used in analysis and listings for adverse events

Per Protocol Analysis Set: The per-protocol (PP) subset includes all full analysis set patients who had final follow-up at 30 days post-surgery.

5. HYPOTHESES TO BE TESTED

This is a descriptive study. No hypothesis testing will be performed.

6. SAMPLE SIZE CONSIDERATIONS

The sample size is a convenience sample of 200 subjects (100 subjects per treatment group).

7. DATA QUALITY ASSURANCE

Data quality assurance will start with training of clinical investigative staff on data collection and assessment procedures including a Manual of Operations that describes what data to collect and procedures for completion of eCRFs. Completed eCRFs will be reviewed by [redacted] clinical monitors on a regular basis throughout the trial by comparison against the source documents.

All study data will come from the eCRFs and no other source data. eCRFs for this study were created using an electronic data management system (EDMS) [redacted]). eCRFs were created using an established data dictionary for each variable including the field name, field type, field attributes, and coding for variables. Range checks, alpha-numeric requirements, and null/not null parameters were programmed as applicable. Data entered into the EDMS system will be reviewed by [redacted] clinical monitors and data managers. If

incomplete or inaccurate data are found, the data will be queried in the system for site staff to address. The site will resolve data inconsistencies and errors using the EDMS with full audit trail of corrections being maintained within the system. Corrections and changes to the data will be reviewed by [redacted] clinical monitors and data managers.

Additional edit checks will be written to detect anomalies in the database. These checks will address inconsistencies (within visits, across visits), invalid/unusual values, missing values, and protocol violations. Edit checking will be validated on test data or actual clinical trial data. In addition to programmed edit checks, quality control examination of data will also be performed on reviews of data listings.

8. STATISTICAL CONSIDERATIONS

8.1. General Considerations

For descriptive purposes, dichotomous variables will be presented as number of observations and percentages; continuous variables will be given as means, standard deviations (SD), median, and range. All data will be presented in listings.

8.2. Participant Accountability and Protocol Deviations

A summary will be prepared to show the reason for early termination. Protocol deviations will be presented as summaries by type of deviation.

8.3. Demographics and Surgical Characteristics

Summaries of the characteristics of the subjects in each of the study groups at baseline will be prepared for the full and per protocol analysis sets. Demographic characteristics (e.g., age, gender, race, and ethnicity), antibiotic use prior to surgery, wound classification, and surgery category and type will be presented in tables and subject listings.

8.4. Efficacy Analysis

8.4.1. SSI Rates

The number and percentage of patients who were diagnosed with an SSI at any time post surgery will be presented to the full analysis set and the PP analysis set. The rates by type of SSI, superficial incisional, deep incisional, and organ space will also be summarized. A listing will be provided by patient that includes these endpoints as well as the medical findings that contributed to each diagnosis.

8.4.2. Antibiotic Use

The number and percentage of patients who were prescribed prophylactic antibiotics and antibiotics to treat an infection will be summarized by treatment group for each analysis set.

8.4.3. Preoperative Surgical Skin Prep Instructions

The number of patients prepped following the [redacted] standard pre-operative skin prep procedures using a topical antiseptic agent will be summarized.

8.5. Handling of Missing Data

Missing Data will not be imputed.

8.5.1. Missing Data within Dates

Missing dates are handled as follows:

- Missing day: The first day of the month will be used.
- Missing Month: The first month of the year will be used.

Completely missing dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

8.6. Safety Analysis

8.6.1. Adverse Events

AEs will be coded using the most recent version of the MedDRA and will be grouped by SOC and preferred terms designation. The severity, frequency, and relationship of AEs to investigational product will be presented by SOC and preferred term groupings. Elicited AEs will be separately tabulated by treatment group. Listings of each individual AE including start date, stop date, severity, relationship, outcome, and duration will be provided. Each AE (based on preferred terminology) will be counted once only for a given study subject. If the same AE occurred on multiple occasions, the highest severity will be assumed. Thus, study subjects are not counted multiple times in a given numerator in the calculation of frequencies for a specific AE.

9. VALIDATION OF PROGRAMMING CODE

All SAS codes used to generate tables and listings will be validated and reviewed before being finalized. The validation process will be used to determine that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Qualified personnel who have not previously been involved in the production of the original programming codes will perform the validation procedures. Methods of validation include independent programming and comparison to data listings. Tables will be reviewed for accuracy, consistency with this plan, consistency within tables, and consistency with corresponding output. Once validation is complete, a quality control reviewer will perform a final review of the documents for accuracy and consistency. Upon completion of validation and quality review procedures, all documentation will be collected and filed in the study documentation files [redacted].

10. TABLE, LISTING, AND FIGURE SHELLS

[redacted]

Listings

[redacted]