Statistical Analysis Plan

Lakewood Amedex

LAI2014-1

A Phase I/IIa, Randomized Double Blind, Placebo-Controlled, Dose Escalating Study to Evaluate the Safety and Tolerability of Topically Applied Bisphosphocin™ Nu-3 on Infected Diabetic Ulcers of Subjects With Type I or II Diabetes Mellitus

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Approvals:

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
CRF	Case Report Form
CSR	Clinical Study Report
DFI	Diabetic Foot Ulcer Wound Infection Score
DUSS	Diabetic Ulcer Severity Score
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PP	Per Protocol
SAE	Serious Adverse Event
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

DEFINITIONS

Intent-to-Treat (ITT) Population	Includes all randomized subjects.
Safety Population	Includes all subjects administered any amount of the study drug.
Per-Protocol (PP) Population	Includes all randomized subjects who received all doses of the of investigational product as required by the protocol and had no major protocol violations.
Treatment-emergent Adverse Events (TEAE)	AEs with an onset time after dosing and pre-existing AEs that worsen during the study.

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of clinical trial data collected within the scope of Lakewood Amedex protocol LAI2014-1 [A Phase I/IIa, Randomized Double Blind, Placebo-Controlled, Dose Escalating Study to Evaluate the Safety and Tolerability of Topically Applied Bisphosphocin™ Nu-3 on Infected Diabetic Ulcers of Subjects with Type I or II Diabetes Mellitus]. The purpose of this plan is to provide specific guidelines from which the analysis performed by [redacted] will proceed. Pharmacokinetics (PK) data was not collected for this study. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2. OBJECTIVES

The primary objective of the study is as follows:

- To assess the safety and tolerability of a twice daily, 7-day repeat topical doses of Nu-3 in adult male and female subjects with chronically infected diabetic ulcer.

The secondary objectives of the study are as follows:

- To assess the clinical and microbiological response to Bisphosphocin™ Nu-3.
- To support determination of the appropriate dose range of Nu-3 to be employed in future clinical studies.

3. STUDY OVERVIEW

This is a phase 1/2a prospective, multi-center, blinded, randomized, dose escalation study. This study will be conducted at four investigational sites. Subjects with diabetic chronic foot ulcer(s) and a Diabetic Ulcer Severity Score (DUSS) of 0 to 3, ulcerated area(s) of not more than two ulcers between 0.5 and 6 cm^2, and no underlying DUSS Probing to Bone='Yes' are eligible to be enrolled into the study.

Doses of Nu-3 will be escalated in three planned sequential cohorts with 10 subjects in each cohort. Randomization will be 4:1 active to placebo in each cohort. The dose levels in each cohort are:

- Cohort 1 – 0.1% solution of Nu-3 in 0.9% saline with vehicle
- Cohort 2 – 1% solution of Nu-3 in 0.9% saline with vehicle
- Cohort 3 – 2% solution of Nu-3 in 0.9% saline with vehicle

Each cohort has placebo defined as 0.9% saline with vehicle. Dosing will be twice daily for 7 consecutive days.

Subjects will have scheduled study visits as follows:

- Screening (Day -7 to -4 hours)
- Single dose visit (Day 1)

- Safety review and multiple dose visit (Day 2)
- Safety review visit (Day 9 ±1 day)
- Final Visit (Day 15 ±2 days)

At the conclusion of each cohort, a Safety Review Committee will review the safety data and determined if it is safe to proceed to the next cohort. The committee includes, but is not limited to the Sponsor's designated Medical Monitor, the Medical Director of the CRO, and the Medical Director of Lakewood Amedex. Additional members can be added as the sponsor deemed appropriate.

4. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables and data listings. For all efficacy parameters, a comparison will be made of each active treatment group versus placebo using the appropriate statistical test. Unless otherwise indicated, all statistical tests will be two-sided and differences will be considered statistically significant if the associated p-value is less than 0.05. Continuous variables will be summarized with means, standard deviations (SD), medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. All data will be summarized by dose group (cohort), with all placebo subjects combined into one placebo arm.

Individual subject data obtained from the electronic data capture system, study lab, and any derived data will be presented by cohort for each subject in data listings.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock for individual subjects. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory. Post-hoc analyses will be identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher on a Windows platform. Tables and listings will be presented in PDF format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

5. ANALYSIS POPULATIONS

5.1 Intent-to-Treat (ITT) Population

All randomized subjects will be included in the ITT Population.

5.2 Safety Population

All subjects administered any amount of investigational product will be included in the Safety Population.

5.3 Per-Protocol (PP) Population

The PP Population will include all randomized subjects who receive all doses of investigational product as required by the protocol and have no major protocol violations. Major protocol violations will be reviewed and the subjects in the PP population will be identified prior to unblinding the study.

6. SUBJECT DISPOSITION

Subject disposition information will be summarized for all subjects by dose group. Summaries will include: the number of screened and screen failure subjects, the number of subjects in the ITT, Safety and PP Populations, the number of subjects completing the study, and the primary reason for discontinuing the study.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic information (age, sex, race, and ethnicity) and baseline characteristics (height, weight and BMI) will be summarized by dose group. These demographic and baseline characteristics summaries will be analyzed for the Safety Population. Inferential testing is not planned on any demographic and baseline characteristic data.

8. EFFICACY ANALYSIS

8.1 Definition of Efficacy Endpoints

All efficacy endpoints will be summarized by visit and evaluated statistically at the end of the MAD portion of the study. Efficacy endpoints include:

- The proportion of subjects with a normal culture
- The change from baseline in the DUSS score
- The change from baseline in the DFI score
- The absence of each of the following as reported by the investigator on the CRF:
    - Purulent discharge
    - Nonpurulant drainage
    - Erythema
    - Induration
    - Tenderness
    - PainLocal warmth (no change)
- Data captured on the total wound size for each subject using the Aranz Medical Silhouette™ System:
    - Wound area (cm2)

- Percentage of area reduction
- Perimeter (mm)
- Maximum depth (mm)
- Mean depth (mm)
- Volume (cm3)
- Length (mm)
- Width (mm)

8.2 Analysis of Efficacy Endpoints

For each dose group, the proportion of subjects with a normal culture at the end of the MAD portion of the study will be compared to the proportion of subjects with a normal culture at the end of the MAD portion of the study for the combined placebo group using a Fisher's exact test. A subject with a normal culture at this time will be considered a success. Any subject with a missing value at the end of the MAD portion of the study will not be included in the analysis. A p-value less than 0.05 will be considered statistically significant and a p-value less than 0.0167, employing a Bonferroni correction for multiple comparisons, will be considered highly conclusive.

For continuous efficacy endpoints, data will be summarized descriptively at and a comparison using the Wilcoxon Rank Sum test between each of dose groups and the combined placebo group will be performed at each visit. For these endpoints, no imputation for missing values will be performed.

For categorical endpoints, a Fisher's exact test will be performed in a similar manner. Subjects missing a value for a secondary endpoint will be considered a failure (counted in the denominator) for that endpoint.

For all tests, a p-value less than 0.05 will be considered statistically significant and a p-value less than 0.0167, employing a Bonferroni correction for multiple comparisons, will be considered highly conclusive. Analysis for each secondary endpoint will be performed on the ITT population and the PP population.

Ulcer measurements and percentage of area reduction will be summarized descriptively by visit and statistical testing using a Wilcoxon Rank Sum test between each dose group and the combined placebo group. For all tests, a p-value less than 0.05 will be considered statistically significant. Analysis for each additional endpoint will be performed on the ITT population and the PP population.

9. SAFETY ANALYSES

For all safety analyses, the safety population will be used.

9.1 Adverse Events

All AE summaries will be restricted to Treatment-Emergent Adverse Events (TEAE), which are

defined as those AEs that occurred after dosing and those pre-existing AEs that worsened during the study. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary (version 14.1).

Each AE summary will be displayed by dose group. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. An event with missing severity will not be imputed.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Not Related, Unlikely, Possibly, Probable, Definite). At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered definite related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.

9.2 Vital Signs

Vital sign assessments will be analyzed by dose group at baseline and each scheduled post-baseline visit. Mean observed measurements and mean changes from baseline will be summarized. Baseline is defined as the last non-missing value obtained prior to receiving study drug.

An outlier analysis will be performed to provide counts and percentage of subjects above or below certain cutoffs for specific vital sign parameters. The following cutoffs will be used in the outlier analysis for the vital signs data:

Heart Rate
- Any post-baseline value > 120 bpm or > 130 bpm
- Any increase from baseline of ≥ 20 bpm or ≥ 30 bpm

Systolic Blood Pressure
- Any post-baseline value > 150 mmHg or < 90 mmHg
- Any increase from baseline of ≥ 20 mmHg or ≥ 30 mmHg
- Any decrease from baseline of ≥ 20 mmHg or ≥ 30 mmHg

Diastolic Blood Pressure

- Any post-baseline value > 100 mmHg or < 50 mmHg
- Any increase from baseline of ≥ 20 mmHg or ≥ 30 mmHg
- Any decrease from baseline of ≥ 20 mmHg or ≥ 30 mmHg

The above outlier analysis will be conducted for post-baseline vital sign assessments collected throughout the entire study period.

9.3 Physical Examinations

Physical examination results will be provided in a listing.

9.4 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) Level 4 categories and Drug Reference Names using the World Health Organization (WHO) dictionary (WHODDE B2 format, March 1, 2011 release).

Prior medications are those medications taken within the last 14 days prior to the dose of study drug, and will be provided in a by-subject listing. Ongoing prior medications taken during the study will be considered concomitant medications.

Concomitant medications are those medications taken after the dose of study drug. Concomitant medications will be summarized by WHO ATC class and medication name for each dose group. The summary will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC category and medication. At each level of subject summarization, a subject is counted once if s/he reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and generic drug name within each ATC class.

10. SAMPLE SIZE AND POWER

This is a pilot dose-ranging study. No sample size calculations were conducted.

11. APPENDICES

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