CUTANEA LIFE SCIENCES, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product:	Omiganan topical gel[redacted]
Protocol No.:	CLS001-CO-PR-006
Protocol Title:	*A Phase 3 Open-Label Extension Study to Evaluated the Long-Term Safety of Omiganan[redacted]Topical Gel in Subjects with Rosacea*
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A Phase 3 Open-Label Extension Study to Evaluated the Long-Term Safety of Omiganan [redacted] Topical Gel in Subjects with Rosacea

Signature Page

This Statistical Analysis Plan has been reviewed and approved by the following personnel:

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1.0 Introduction

Rosacea is a chronic dermatologic disorder that primarily affects the facial skin. An estimated 16 million Americans have rosacea. The clinical signs and symptoms of rosacea are: facial flushing, telangiectasia, facial erythema, central facial inflammatory papules and pustules, hypertrophy of the sebaceous glands of the nose and ocular changes. Rosacea has been classified into four different subtypes; Subtype 1: erythematotelangiectatic, Subtype 2: papulopustular, Subtype 3: phymatous and Subtype 4: ocular. Each subtype has severity grades ranging from mild to severe.

Currently, there is no cure for rosacea and the etiology is poorly understood. Many theories regarding the cause of rosacea have been highlighted in the literature. The pathology of rosacea may be multifactorial: abnormal vascular and immune system responses; hair follicle mite Demodex folliculorum; bacteria such as Helicobacter pylori; prolonged steroid use and other aggravating trigger factors like sun and stress. Gallo and his colleagues found an abnormally high level of the naturally occurring antimicrobial peptide cathelicidins upon histopathological staining in the skin of patients with rosacea.

Cutanea Life Sciences is developing omiganan topical gel for the treatment of papulopustular rosacea. The exact cause of rosacea is unknown and may be in due in part to an inflammatory process. Recent research has shown that cationic peptides such as omiganan may have anti-inflammatory properties and may play a role in inhibiting the inflammatory response. Omiganan may also prevent the inflammatory cascade that is theorized to lead to the signs and symptoms of rosacea. A possible anti-inflammatory activity of omiganan is suggested by the observation of a reduction in inflammatory acne lesion counts with omiganan in two Phase 2 clinical trials. However, the exact mechanism of action is undetermined.

Two previous clinical studies of omiganan in rosacea were conducted. CLS001-R-001 was a double-blind, multicenter, randomized, vehicle-controlled, parallel group study in 240 adult subjects with subtype 2 papulopustular rosacea. Eligible subjects were randomized to 5 treatment groups in a 2:2:2:1:1 ratio. The treatment arms were Omiganan topical gel at 1% QD, 2.5% QD, 2.5% BID, and Vehicle QD and Vehicle BID. Subjects were treated for 9 weeks. In the MITT analysis, all efficacy variables improved compared with Baseline in all treatment groups. The reductions from Baseline tended to be greatest in the omiganan 2.5% QD group; however, there were no statistically significant differences between the active treatment groups and the combined vehicle group for any efficacy variable at the Week 9/end of treatment endpoint for the MITT population.

Based upon the results of the first Phase 2 study in rosacea, Cutanea determined that the dose-response relationship of omiganan warranted further exploration. An additional Phase 2B study CLS001-CO-PR-001 investigated the safety and efficacy of once-daily omiganan 1%, 1.75% and 2.5% compared to vehicle gel. Again this was a double-blind, multicenter, randomized, vehicle-controlled, parallel group study in 240 adult subjects with subtype 2 papulopustular rosacea. Subjects were randomized into 4 test groups at a 1:1:1:1 ratio and observed over the course of 12 weeks. In addition to the primary analysis of the change from baseline in inflammatory lesion counts for the ITT population, several strata based on baseline lesion counts were also evaluated

in post hoc analyses. The efficacy signal was improved with increasing baseline lesion count, and was best for the [redacted] omiganan treatment group.

2.0 Study Design

This study will be conducted in accordance with FDA guidelines on current Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

The study will be conducted as an open-label, multicenter study at approximately 30 sites and involving 300 subjects with subtype 2, papulopustular rosacea. After giving informed consent, each subject will be screened for study eligibility according to specific inclusion/exclusion criteria. Eligible subjects will be enrolled to evaluate the long-term safety of omiganan [redacted] topical gel.

Omiganan gel will be topically applied once daily to the entire facial area; cheeks, chin, forehead and nose, avoiding contact with the eyes, mouth, and other mucous membranes.

Following baseline testing and evaluation for acceptance into the study, the subjects will be supervised during the first test drug application on Day 1 to ensure that the study treatment is applied correctly. Thereafter, each subject will apply the study treatment at home (unsupervised) once daily for up to 12 months. Once 100 subjects have completed a year of treatment, the remaining subjects will discontinue treatment after a minimum of six months. Other concurrent therapies will be recorded throughout the study. A bland unmedicated soap or soapless cleanser should be used for the purposes of washing the subject's face.

Safety assessments will be done on all of the designated study visit days.

3.0 Study Objectives

The primary objective of this study is to evaluate the long-term safety of Omiganan [redacted] topical gel applied once daily to the face of subjects with severe papulopustular rosacea.

4.0 Statistical Methodology

No statistical testing will be performed. Continuous parameters will be summarized by N (number of non-missing observations), mean, standard deviation, median, minimum, and maximum. Categorical parameters will be summarized by count and percent.

4.1 Sample Size

The sample size for this study is based upon ICH E1.

4.2 Study Populations

The "All-treated" analysis population will consist of all subjects receiving at least one application of study medication. All safety analyses will be performed on the all-treated population.

4.3 Statistical Analysis

4.3.1 Subject Accounting, Demographic, and Baseline Characteristics

Demographic, baseline characteristics (including physical examinations, and subject reported signs and symptoms of rosacea), and prior and concomitant medications will be summarized. Study completion status and reasons for discontinuation will also be displayed by treatment.

Medical history and previous rosacea therapies taken within the last five years will only be presented in the listings.

4.3.2 Safety Summaries

The IGA will be summarized across the study duration in order to evaluate safety as it pertains to the underlying condition of papulopustular rosacea.

Adverse events will be categorized by SOC and Preferred Term from the current version of MedDRA. The focus of the adverse event summaries will be on treatment-emergent adverse events. Treatment-emergent adverse events will be summarized overall, by severity, and by relationship to study product.

Changes in safety laboratory data, vital signs, and physical exam will be summarized at all time-points when available. Summaries will include means, standard deviations, median, minimum and maximum values for continuous data, or frequency and percent for categorical data. Additionally, shift tables will be provided for abnormal safety labs.

4.3.3 Subject Disposition

Study completion status and reasons for discontinuation will be summarized by frequencies and percentages.

4.3.4 Study Product Exposure

The number of days of exposure will be summarized by the number of non-missing observations, mean, standard deviation, median, minimum, and maximum.

5.0 Data Handling Conventions

This section contains the data handling conventions that will be used to carry out the statistical analyses.

5.1 Baseline and Follow-Up Visits

Visits and timepoints for all analyses will be as record on the eCRFs. Baseline will be the later of the non-missing values from the Screening and Baseline/Day 1 visits scheduled to occur prior to receiving study medication.

5.2 Missing Data

Data will be handled on an observed case basis with no imputation..

5.3 Unscheduled Data

Unscheduled data will not be used in the summaries, but will be presented in the listings.