PROTOCOL NUMBER CLS001-CO-PR-005

Title:
A Phase 3, Randomized, Vehicle-Controlled, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of a Once-Daily CLS001 Topical Gel Versus Vehicle Administered for 12 Weeks to Subjects with Papulopustular Rosacea with a 4 Week Follow-up Period

Test Product: CLS001 topical gel [redacted] versus vehicle gel

[redacted]

GCP Statement: This study will be conducted in accordance with the United States Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) guidelines on current Good Clinical Practice (GCP).

Date: 10 July 2015

Confidentiality Statement

1 SYNOPSIS

Title of Study: A Phase 3, Randomized, Vehicle-Controlled, Double-Blind, Multicenter Study to Evaluate the Safety and Efficacy of Once-Daily CLS001 Topical Gel Versus Vehicle Administered for 12 Weeks to Subjects with Papulopustular Rosacea with a 4 Week Follow-up Period	
Study Period (Planned): Start –First subject enrolled: [redacted] End – Last subject last visit: [redacted]	**Phase of Development:** Phase 3
Objective: To evaluate the safety and efficacy of once daily application of omiganan topical gel compared to vehicle topical gel in subjects with papulopustular rosacea	
Methodology: Double-blind, multicenter, randomized, vehicle-controlled, parallel comparison.	
Number of Subjects (planned): 450 (225 per treatment group)	
Number of Sites: Approximately 50 sites in the United States, Canada, Germany, France, Netherlands, United Kingdom, Ireland, Sweden, Australia and New Zealand.	
Diagnosis and Main Criteria for Inclusion: Male or non-pregnant female subjects at least 18 years of age with papulopustular rosacea, including at least 30 inflammatory lesions, and an Investigators Global Assessment (IGA) grade of 4 (severe) at baseline.	
Investigational Product: Omiganan topical gel **Comparator Product:** Vehicle gel **Dose:** Apply once daily (Preferably in the morning), as a thin film, to the entire face (Approximately 0.4 grams) **Mode of Administration:** Topical application to the entire face avoiding contact with the mouth, eyes and inside the nose. **Duration of Treatment:** 12 weeks	
Criteria for Evaluation: **Efficacy:** Co-Primary endpoints: 1. Absolute change in inflammatory lesion count at week 12; 2. IGA: 2 grade reduction at Week 12; Clear or Almost Clear (IGA of 0 or 1) rating at Week 12. **Safety:** Adverse events (AE) throughout the study; vital signs at Screening, Week 6 and Week 12; Physical Exam and Safety labs at Screening and Week 12. Immunogenicity will be assessed using samples collected at Baseline, and at Weeks 3, 6, 12 and 16. **Statistical Methods:** **Efficacy:** Absolute change in inflammatory lesion count at Week 12 will be analyzed using an Analysis of Covariance, with treatment as a main effect, and center as a covariate. Investigator Global Assessment (IGA) 2 grade reduction at Week 12, and Clear or Almost Clear rating at Week 12 will be analyzed using a Cochran–Mantel–Haenszel (CMH) test, with center as the stratifications factor. An interim analysis for futility will be conducted by an independent statistician. Only absolute lesion reduction count and IGA data (2 grade reduction, and Clear or Almost Clear (0, 1)) will be analyzed in the interim analysis. **Safety:** AEs will be coded and tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) body system and preferred term, number and percentage of subjects with AEs will be presented. Immunogenicity parameters will be summarized.	

2 STUDY CONTACTS

Company representative(s) individual contact information will be provided on the clinical study team contact list

3 LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS	
AE	Adverse Experience/Event
AHA	Alpha hydroxyl acids
ALT	Alanine aminotransferase
ANCOVA	Analysis Of Covariance
AST	Aspartate aminotransferase
BID	Twice Daily
BOCF	Baseline Observation Carried Forward
BUN	Blood urea nitrogen
CBC	Complete blood count
CLS001	Omiganan topical gel (referred to as omiganan)
cm	Centimeter
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
E. coli	Escherichia coli
eDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
FSR	Final Study Report
gm	Gram
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HDL	High-density lipoproteins
IAE	Investigators Assessment of Erythema
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IGA	Investigators Global Assessment

LIST OF ABBREVIATIONS	
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LDH	Lactic dehydrogenase
LDL	Low-density lipoproteins
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple Imputation
MIC	Minimum Inhibitory Concentration
MITT	Modified Intent-To-Treat
mL	Milliliter
P. acnes	*Propionibacterium acnes*
PI	Principal investigator
PK	Pharmacokinetic
PP	Per Protocol
QD	Once Daily
QSAD	As much as needed
RBC	Red blood cell
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
S. aureus	Staphylococcus aureus
SAE	Serious Adverse Experience/Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SE	Standard error
SOC	System Organ Class
USP	United States Pharmacopeia
UV	Ultra violet
w/w	Weight for weight
WBC	White blood cell

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5 INTRODUCTION

5.1 BACKGROUND

Rosacea is a chronic dermatologic disorder that primarily affects the facial skin. An estimated 16 million Americans have rosacea.[1] The prevalence of rosacea in Europe is between 1% and 10% of the adult population.[2,3] 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.[4] 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.[5] The subtypes may share common symptoms and may clinically overlap.

The typical age of onset is from 30 to 50 years of age and it is more common in women than men. However, men are more prone to the phymatous skin changes associated with rosacea. Rosacea patients experience periods of relapses and remissions. There are trigger factors that can exacerbate the disease such as: sun exposure, stress, hot or cold weather, alcohol, spicy foods, exercise, wind, hot drinks and certain skin care products and medications.[6]

According to surveys conducted by the National Rosacea Society, nearly 76 percent of rosacea patients said this condition had lowered their self-confidence and self-esteem, and 38 percent reported it had caused them to avoid public contact or cancel social engagements. Among those with severe rosacea, nearly 88 percent said the disorder had adversely affected their professional interactions, and nearly 51 percent said they had even missed work because of their condition. Over 80 percent reported medical treatment had improved their emotional and social wellbeing.[7]

Currently, there is no cure for rosacea and the etiology is poorly understood.[8] Many theories regarding the cause of rosacea have been highlighted in the literature. The pathology of rosacea may be multifactorial and has several associations still not well understood: abnormal vascular and immune system responses; proliferation of commensal mites seen in hair follicles (Demodex folliculorum); bacterial proliferation in the human gut of Helicobacter pylori; prolonged topical steroid use and other aggravating trigger factors like sun and stress.[9,10] Gallo and his colleagues found an abnormally high level of the naturally occurring antimicrobial peptides known as cathelicidins upon histopathological staining of the skin of patients with rosacea.[11]

Therapeutic approaches for rosacea treatment may be categorized by the subtype (1-4).[5] For example, systemic treatments and ablative therapy are used for erythematotelangiectatic rosacea (Subtype 1).

Surgery or laser therapy may be indicated for phymatous rosacea (Subtype 3). Topical or systemic medications may be prescribed for papulopustular and ocular rosacea (Subtype 2 and 4, respectively). The inflammatory (papulopustular) lesions of rosacea affect both the sebaceous and hair follicles.[12] Inflammatory cells may be key pathophysiologic factors in the development of rosacea.[13] Intrafollicular neutrophils have been observed in inflammatory rosacea and the proteases released by these neutrophils may degrade extracellular matrix macromolecules.[14]

There is no cure for rosacea and treatment is aimed at alleviating the symptoms. Topical or oral medications are generally prescribed for mild to moderate papulopustular rosacea. These topical medications include: metronidazole, azelaic acid, ivermectin, sodium sulfacetamide and sulfur, erythromycin, and tretinoin. Oral medications prescribed for severe disease include doxycycline at microbial and subantimicrobial doses and, minocycline, [4, 15, 16, 17] Isotretinoin, although not FDA approved for the treatment of rosacea, has also been prescribed when other agents have failed. In particular, treatments for severe rosacea are inadequate, and isotretinoin use has been recommended with increasing frequency in this patient population. [18, 19, 20, 21, 22, 23] Hence, topical Omiganan has the potential to become an important addition to the dermatologist's armamentarium in treating severe 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.[9] 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.

In general, antimicrobial peptides are believed to act by disrupting the cytoplasmic membrane of bacteria resulting in depolarization and death.[24, 25, 26, 27] Omiganan, in *in vitro* assays, demonstrated a rapid bactericidal activity against not only *P. acnes*, but also against other microorganisms that colonize the skin and that may play a role in the pathogenesis of inflammatory lesions. Omiganan permeabilized the outer membrane of *E. coli* in a dose-dependent manner but did not permeabilize the inner membrane, at concentration up to 4X MIC. Omiganan induced a dose-dependent depolarization in the cytoplasmic membranes of *S. aureus.*[28] In addition, a dose-dependent inhibition of DNA, RNA and protein synthesis in *S. aureus* was produced by omiganan.

Omiganan pentahydrochloride topical gel has been evaluated in human clinical studies at concentrations of 0.5%, 1.0%, 2.5% and 3% in Phase 1 studies; at concentrations of 1.0%, 1.75% and 2.5% in Phase 2 studies; and at concentrations of 1.0% in a Phase 3 study. In these studies, including two Phase 2 studies of omiganan topical gel applied to the face of subjects with moderate to severe papulopustular rosacea, omiganan was found to be safe, and well tolerated. In the most recent Phase 2 study in which vehicle or omiganan pentahydrochloride topical gel 1.0%, 1.75% or 2.5% was applied once daily to the face of 240 moderate to severe rosacea subjects for 12 weeks, the most frequently reported adverse events were headache, sinusitis, and upper respiratory tract infections. Most treatment emergent adverse events were considered mild or moderate in severity.

Additionally, the systemic absorption of omiganan pentahydrochloride topical gel has been evaluated at concentrations of 0.5%, 1%, 2.5% and 3%. Omiganan was not systemically absorbed when applied to the skin of subjects at concentrations ranging from 0.5% to 3% topical. In the most recent maximum use PK study of omiganan pentahydrochloride topical gel 2.5% w/w, applied for 21 days to the face of 26 subjects with moderate to severe papulopustular rosacea, no systemic absorption was detected. The results of the clinical studies and the safety data collected during the clinical studies of omiganan are summarized in the Investigator's Brochure.

Omiganan Topical gel [redacted] in this protocol, in previously conducted phase 1 and 2 clinical studies, and in other historical documentation is based on the concentration of omiganan pentahydrochloride. The product concentration based on the active moiety is omiganan topical gel [redacted] To be consistent with the naming convention in pre-existing documents, the nomenclature concentration of omiganan [redacted] will be referred to in this protocol and associated clinical and non-clinical documents.

[redacted]

Further, in order to comply with USP General Chapter <1121> Nomenclature to express the strength of the drug product based upon the active moiety, [redacted]

5.2 RATIONALE

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. Subjects were treated for 9 weeks. The primary objective of the study was to evaluate the safety and efficacy of omiganan pentahydrochloride topical gel 1% w/w and 2.5% w/w compared to vehicle gel in subjects with papulopustular rosacea. Eligible subjects were randomized to 5 treatment groups in a 2:2:2:1:1 ratio. The treatment arms were:

- Omiganan pentahydrochloride topical gel, 1% w/w QD
- Omiganan pentahydrochloride topical gel, 2.5% w/w QD
- Omiganan pentahydrochloride topical gel, 2.5% w/w BID
- Vehicle QD
- Vehicle BID

All efficacy variables improved compared with Baseline in all treatment groups in the modified intent to treat (MITT) analysis. 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.

Analyses of the per protocol (PP) population were supportive of the results for the MITT population. All efficacy variables improved relative to Baseline for all treatments. For the Week 9 analyses, there were statistically significant differences between active and vehicle treatment for change from Baseline in inflammatory lesion count (for omiganan 2.5% QD versus vehicle, in favor of omiganan) and for scaling/peeling (omiganan 2.5% BID versus vehicle, in favor of vehicle).

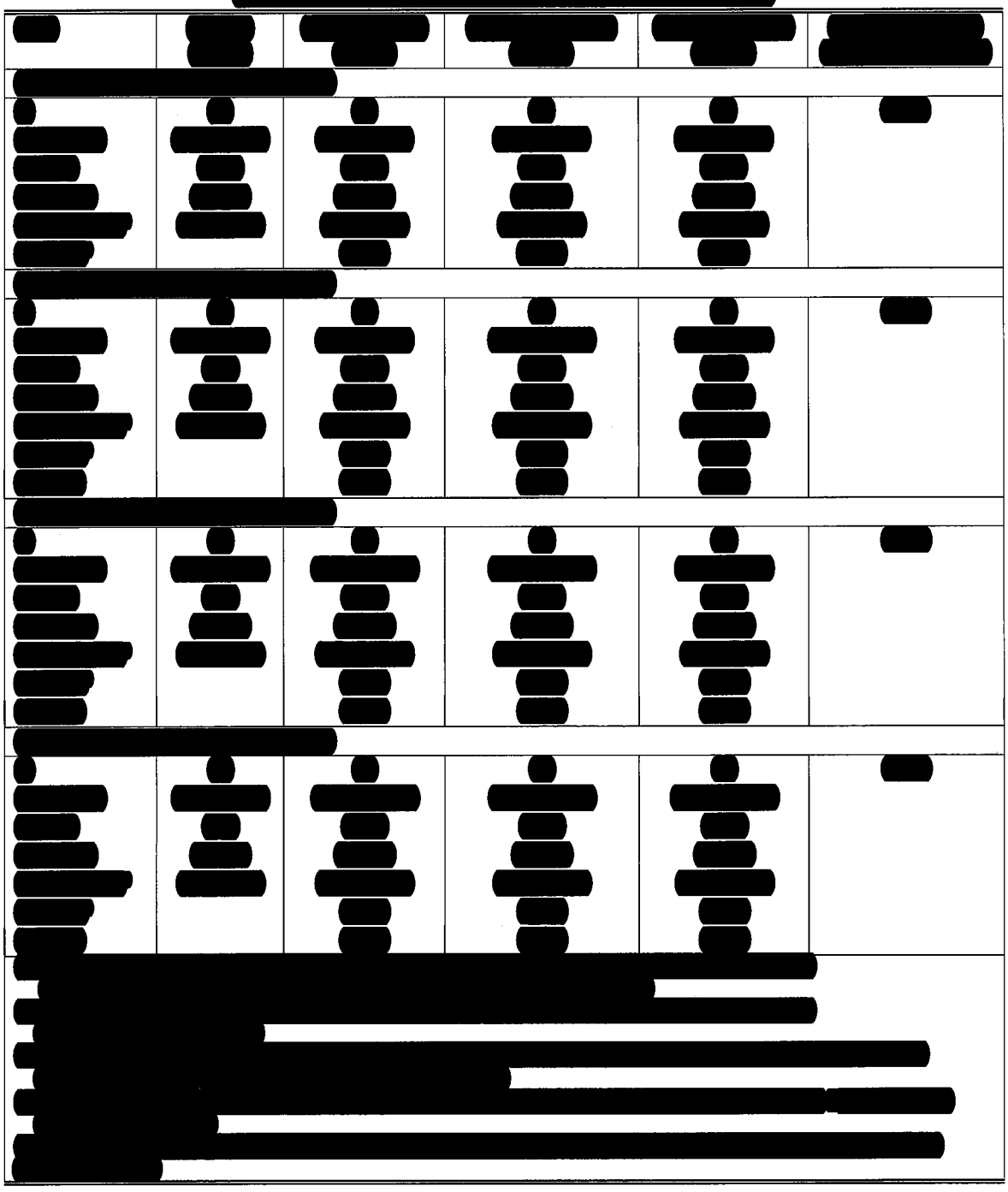
Further exploratory analyses with comparisons of the treatment groups, stratified by Baseline lesion count, demonstrated statistically significant difference in the mean change from baseline in inflammatory lesions counts for omiganan 2.5% QD versus vehicle QD in subgroups with more severe rosacea (> 14.5 lesions at baseline). Overall in the MITT population (all subjects), the mean change from Baseline in lesion count at Week 9 for omiganan 2.5% QD and vehicle QD was -5.93 versus -1.50, respectively (P=0.041). For subjects with a baseline lesion count >14.5, the mean change in lesion count was -7.58 and +0.63 for 2.5% QD and vehicle QD, respectively (P=0.013) at Week 9.

Treatment success rate was also explored by protocol specified and alternate definitions, stratified by baseline lesion count. The result of the exploration of success defined as clear or almost clear or a 2-grade reduction was suggestive of a dose response with omiganan 2.5% topical gel BID demonstrating the highest treatment success.

In addition, supplemental post-hoc analyses were performed as an alternative approach to evaluate the Treatment Success and baseline inflammatory lesions counts. A Receiver Operating Characteristic (ROC) analysis demonstrated that a cut-point of >15 baseline lesions could be utilized to optimize the study design.

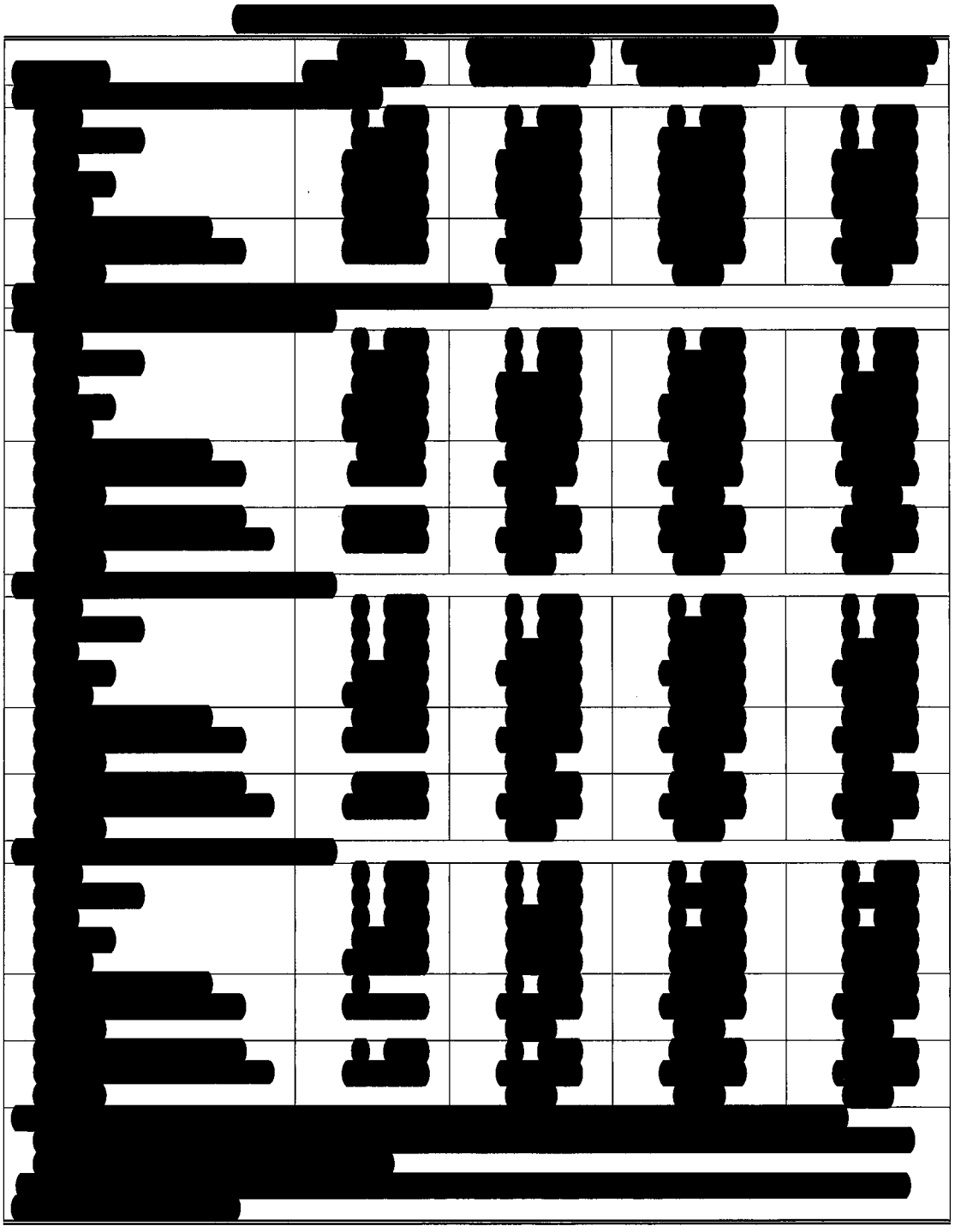
Based upon the results of this first Phase 2 study in rosacea, Cutanea determined that the dose-response relationship of omiganan warranted further exploration. An additional Phase 2B study CLS001-CO-PR-001 investigated the safety and efficacy of once-daily omiganan pentahydrochloride topical gel 1% w/w, 1.75% w/w and 2.5% w/w 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 overall results for the ITT population by these strata are included in **Table 1** below. [redacted]

[redacted]



The results of the Investigator's Global Assessment were also examined for the ITT population and various strata of baseline lesion counts. The results are presented in **Table 2** below.

[redacted]



The current trial will evaluate the safety and efficacy of omiganan pentahydrochloride topical gel [redacted] versus vehicle gel administered once daily over a planned 12-week treatment period and assess relapse during a 4-week follow-up period.

6 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and efficacy of once-daily application of omiganan topical gel compared to vehicle gel in subjects with severe papulopustular rosacea (IGA grade 4 with baseline inflammatory lesion count ≥ 30).

7 INVESTIGATIONAL PLAN

7.1 OVERALL STUDY DESIGN

This study will be conducted in accordance with the FDA and ICH guidelines on current GCP, following the ethical principles originating from the Declaration of Helsinki. Additionally, the study will be conducted in accordance with any applicable laws or regulations of the country in which the clinical research is conducted.

The study will be a double-blind, multicenter, randomized, vehicle-controlled, parallel group study at approximately 50 sites, involving approximately 450 subjects with severe subtype 2, papulopustular rosacea. The study will be conducted in the United States, Canada, Germany, France, Netherlands, United Kingdom, Ireland, Sweden, Australia and New Zealand. After giving informed consent, each subject will be screened for study eligibility according to specific inclusion/exclusion criteria. Eligible subjects will be randomized to one of two treatment groups in a 1:1 ratio. The treatment arms are either: omiganan topical gel or vehicle applied once daily for 12 weeks followed by a 4 week follow-up period to assess relapse.

Omiganan topical gel or vehicle will be topically applied once daily to the entire facial area; cheeks, chin, forehead and nose, avoiding contact with the eyes, mouth, and inside the nose.

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 12 weeks. Following the 12 week treatment period, subjects will remain in the study for an additional 4 week follow-up period. No concurrent rosacea therapy of any kind, especially over the counter antimicrobial soaps, prescription topical (on the face) and/or systemic antibacterial agents, will be allowed during the course of the study. No changes in topical soaps should occur. Other concurrent therapies will be recorded throughout the study. A bland non-medicated soap or soapless cleanser should be used for the purposes of washing, showering, and bathing. Safety assessments will be done on all of the designated study visit days. The end of the study will be the date that the last study subject completes the last visit for the study.

7.2 SELECTION OF STUDY POPULATION

7.2.1 Inclusion Criteria

Subjects must meet each of the following criteria to be considered eligible for entry into the study:

1. Subjects who provided written informed consent to participate in the study.
2. Healthy, male and non-pregnant female subjects, 18 years of age or older.
3. A diagnosis of papulopustular rosacea with ≥30 inflammatory facial lesions (papules, pustules) at Baseline. Subjects must have no more than 2 nodular lesions, at Baseline.
4. Subjects with the presence of telangiectasia at Baseline.
5. Subjects with an erythema score of at least 2 on the Investigator Assessment of Erythema (IAE) scale at Baseline.
6. Subjects with a grade 4 (severe rosacea) on the 5-point Investigators Global Assessment (IGA) scale at Baseline.
7. Non-nursing, female subjects of child bearing potential, who are using a highly effective form of birth control or females not of childbearing potential due to menopause (must be postmenopausal for at least one year).
    - Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Forms of birth control include: Oral (birth control pills), Intravaginal: (e.g. NuvaRing®), Implantable (e.g. Norplant®), injectable (e.g. Depo-Provera®) or transdermal (e.g. Ortho Evra®) contraception; intrauterine device (IUD); double-barrier (diaphragm or condom with spermicidal gel or foam); for two months prior to study enrollment (see exclusion criteria #6) or a vasectomized partner or true abstinence (in line with preferred and usual lifestyle of subject) with an acceptable form of birth control should the subject become sexually active. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. All female subjects of child bearing potential must undergo an in-office, highly sensitive urine pregnancy test, with a negative result, prior to being randomized to receive study drug. In addition, women of childbearing potential must agree to have a highly sensitive urine pregnancy test at the end of the study.
8. Subjects who have used the same brand of soap, make-up, hair products, or shaving lotion/foam/cream/gel for a period of at least four weeks prior to the Baseline Visit and agree not to change these product brand/types during the study.
9. Male subjects who are willing to shave, if applicable, at approximately the same time every day.

10. Subjects who are willing and able to return to the study clinic for the designated study visits.

11. Subjects who are willing to refrain from sunbathing, using sun tanning booths/beds, or excessive exposure to the sun for the duration of the study.

12. Subjects who are willing to comply with the protocol and visit requirements.

7.2.2 Exclusion Criteria

Subjects are not eligible to participate in the study if any of the following are present:

1. Subjects with clinically significant abnormal findings at the Baseline/Day 1 Visit that would require a new intervention or treatment or a change in treatment that would in the opinion of the investigator supersede participation in the clinical trial.

2. Subjects with steroid rosacea or subtype 3 (phymatous rosacea).

3. Subjects with nodular rosacea (defined as more than 2 lesions greater than 5 mm).

4. Subjects with underlying diseases or other dermatological conditions, such as; atopic dermatitis, perioral dermatitis, or seborrheic dermatitis, which requires the use of interfering topical or systemic therapy or may interfere with the rosacea diagnosis or its assessment.

5. Subjects using concomitant treatments that may influence study end points within 2 weeks of the Baseline Visit (e.g., facial or chemical peels, dermal fillers, acne surgery, intralesional steroids, spironolactone, debridement, cryotherapy, dermabrasion, X-ray, laser therapy or UV therapy).

6. If using estrogens or progesteronal agents (e.g, Gynogen, Valergen, Depo-Testadiol, Depogen, birth control pills), for less than 2 months prior to the Baseline Visit. (Subjects using estrogens for 2 months or more need not be excluded unless the subject expects to change dose, drug, or discontinue estrogen use during the study. See Inclusion #7)

7. Subjects with known allergies to the active ingredient or any of the excipients. (See Section7.6.2)

8. Subjects who have not undergone the specified washout period(s) for the following topical preparations applied to the face or subjects who require the concomitant use of any of the following topical preparations/treatments applied to the face:

Product	Washout Period (Prior to Baseline/First Dose)
▪ Abradants, astringents, toners, facials, masks, or moisturizers containing retinols, AHA (alpha hydroxyl acids), salicylic acids,	1 week
▪ Tanning booths/beds	2 weeks
▪ Antibiotics (other than topical ocular application)	2 weeks
▪ Antimicrobial soaps	2 weeks
▪ Corticosteroids	2 weeks

▪ Other anti-inflammatories	2 weeks
▪ Other rosacea treatments (e.g., azelaic acid, metronidazole, ivermectin, sulfacetamide)	2 weeks
▪ Retinoids	4 weeks

9. Subjects who have not undergone the specified washout period(s) for the following systemic treatments or subjects who require the concomitant use of any of the following systemic treatments:

Product	Washout Period (Prior to Baseline/First Dose)
▪ Antibiotics	4 weeks
▪ Corticosteroids	4 weeks
▪ Retinoids	12 weeks

10. Female subjects who are pregnant, nursing, or planning a pregnancy within the study period.

11. Subjects who have a beard, or excessive facial hair. A moustache will be allowed, if in the investigator's judgment it does not impair the assessment of rosacea.

12. Subjects using an investigational drug within 30 days of the Baseline Visit or who are currently participating in an investigational study. Use of an investigational drug/device and/or participation in another investigational study is prohibited during this study.

13. Subjects who currently abuse alcohol or drugs or who have a history of chronic alcohol or drug abuse with in the past year.

14. Subjects who have a chronic medical condition that may require the use of a prohibited medication to treat new symptoms or exacerbations.

7.2.3 Withdrawal from Study Criteria

Reasons for discontinuation of study medication include, but are not limited to, the following:

- Adverse Event
- Pregnancy
- Withdrawal By Subject
- Lost To Follow-Up. The Investigator will try to reach the subject, twice by telephone (document telephone calls) and once by certified letter, before considering the subject lost-to-follow-up. The lost to follow-up discontinuation will be reported on the appropriate eCRF, and a copy of the follow-up letter will be maintained in the Investigator's file.
- Study Terminated By Sponsor
- Physician Decision
- Non-Compliance with Study
- Other

All premature discontinuations from the study must be documented by the Investigator on the eCRF, and if due to an adverse event, on the Adverse Event Case Report page of the eCRF. All subjects should attempt to complete all visits and evaluations.

Subjects not completing the entire study should be fully evaluated (i.e., final double-blind Week 12 visit procedures performed during the double-blind period and the Follow-up Week 16 visit procedures during the follow-up period). All subjects are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice to his or her medical care by a physician. Subjects who withdrawal from the study will not be replaced.

7.3 CONDUCT OF STUDY

7.3.1 Table of Study Procedures

Procedures	Screening (Within 30 days of Baseline)	Baseline/Day 1 (prior to study drug application)	Interim Visits: Weeks 1, 3, 6 and 9 (± 3 days)	Final Double-Blind Visit: Week 12 (± 3 days)	Follow-Up Visit: Week 16 (± 3 days) [4]
Informed Consent	X				
Demographics, Medical and Rosacea History	X	X			
Previous Medications	X				
Concomitant Therapy/Medication Review	X	X	X	X	X
Limited Physical Exam	X			X	
Vital Signs	X		X (week 6 only)	X	X
Blood collection for clinical laboratory testing	X			X	
Blood collection for immunogenicity testing		X	X (week 3 &6)	X	X
Urine Pregnancy Test, if applicable	X			X	
Investigators Global Assessment (IGA)	X	X	X	X	X
Investigators Assessment of Erythema (IAE)	X	X	X	X	X
Other Signs and Symptom Assessment	X	X	X	X	X
Inflammatory Lesion Counts	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X			
Randomization		X			
Dispense Study Drug		X	X[1]		
Dispense Diary		X	X		
Drug Accountability / diary review, and Collection of Drug and diary			X	X	
Instruct on Treatment Application		X			
Apply Study Drug[2]		X[2]	X	X	
Adverse Event Assessment		X[3]	X	X	X

[1] Study drug will not be dispensed at the Week 1 visit. .
[2] The first application of study drug will be performed at the study center.
[3] Adverse event assessment during the Baseline visit will be performed following the first application of study drug.
[4] The end of the study will be the date that the last study subject completes the last visit for the study.

7.3.2 Study Procedures by Visit

Visits following the Baseline Visit are to occur at the end of Weeks 1, 3, 6, 9, and 12 (Final Treatment Visit) and a follow up visit at Week 16. However, all interim study visits and the follow up Week 16 study visit may be conducted (on an individual subject basis) up to 3 days before or after the regularly scheduled study visit. An unscheduled visit may occur in the event that the investigator determines that the subject should be seen for safety or any other reasons.

7.3.2.1 Screening Visit

The following procedures will be performed during the Screening visit:

- Obtain subject's written informed consent prior to initiating any study procedures, including instructing the subject to discontinue use of medication that requires a washout (see Section 7.6.11.1). Provide subject with a copy of signed and dated consent form. Document subject's informed consent in the subject's medical record.
- Screen the potential subject according to the study inclusion/exclusion criteria.
- Schedule the Baseline/Day 1 visit to occur after the results of the laboratory safety testing are received and any required washout period is completed.
- Record Demographic information including age, sex, race, ethnicity and Fitzpatrick skin type (Appendix B)
- Record medical history. Include information on subject's history of rosacea and any previous therapies, including:
    - The approximate date of physician's diagnosis of rosacea;
    - The subject reported signs and symptoms of rosacea,
    - How often they experience these symptoms?
    - Whether symptoms are continuous or occasional?
    - What, if anything, appears to trigger or worsen these symptoms?
        - Sunlight
        - Stress
        - Alcohol
        - Exercise
        - Hot and cold temperatures
        - Spicy food
- Previous rosacea therapies within the previous 5 years;
- Review and record concomitant medications/therapies used in the last 30 days
- Assess whether the subject will require a washout period
- Perform a limited Physical Exam (refer to Section 7.5.2) with vital signs, height and weight measurements.
- Obtain a blood sample for hematology and chemistry analysis
- Perform an in-office urine pregnancy test on all females of childbearing potential.
- Perform the Investigators Global Assessment (IGA) of rosacea, the Investigators Assessment of Erythema (IAE) and Other Signs and Symptoms Assessment before performing the lesion count (refer to Section 7.4.1, 7.4.2, and 7.4.3). **It is important that the same evaluator performs the evaluations for the same subject at each visit, however it may not be**

feasible in all instances. Every effort should be made to maintain consistency of the evaluator for each subject.

- Perform the inflammatory lesion count (papules and pustules) (refer to Section 7.4.4). **It is important that the same evaluator performs the lesion count for the same subject at each visit, however it may not be feasible in all instances. Every effort should be made to maintain consistency of the evaluator for each subject.**

7.3.2.2 Baseline Visit (to be scheduled within 30 days of Screening)

- Review the study inclusion/exclusion criteria to confirm eligibility, including review of the laboratory results for any clinically significant findings that would exclude the subject from eligibility for the study.
- Review any changes since the first visit in concomitant medications/therapies, and the subject's health.
- Perform the Investigators Global Assessment (IGA) of rosacea, the Investigators Assessment of Erythema (IAE) and Other Signs and Symptoms Assessment before performing the lesion count (refer to Section 7.4.1, 7.4.2, and 7.4.3). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- Perform the inflammatory lesion count (papules and pustules) (refer to Section 7.4.4). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- If the subject has fulfilled the eligibility requirements, as stated in the inclusion/exclusion criteria, randomize the subject to treatment according to the randomization instructions using the eDC system to access the Interactive Web Response System (IWRS). The eDC/IWRS system will generate the kit number assigned to the randomized subject for the duration of the study. The subject's assigned kit number should match the kit number on all drug treatment supplies dispensed to the subject. Record the subject number on the kit that is assigned to that subject.
- Record the assigned kit number and the subject number on the source document.
- Obtain the Pre-Dose blood sample for immunogenicity testing prior to the first application of study gel.

- First Treatment Application –
  - Weigh the tube that is designated to be dispensed to the subject prior to the subject applying their first dose of study medication. The tube should be weighed with the cap on as outlined in Section 7.6.9.
  - Give the subject a copy of the treatment application instructions (see Appendix A) and allow the subject to take time to read them. Provide instruction to the subject on the daily application of study drug and confirm the subjects understanding of the instructions.
  - Record the Subject # and date of dispensing on the tube label and dispense the tube to the subject.
    - The subject should be instructed to apply the treatment once daily, preferably each morning (with the exception of the first dose at the site which may be later in the day), at approximately the same time for the duration of the study. A thin layer of the assigned study drug (approximately 0.4 g) should be applied to the subject's face, including the non-affected areas (as described in Appendix A).

- Under the supervision of the study coordinator or designee, the subject should apply the first dose of study drug at the study site and the observer should observe that the subject applies a thin film to the entire face.

- Instruct the subject on the use of the daily diary and dispense the diary.
  - Have the subject record the first application of study drug in the diary during the site visit and confirm their understanding of the use of the diary.

After the first application of study drug at this visit -

- Observe the subject for any immediate adverse events.
- Remind the subject about restricted therapies (see Section 7.6.11.1).
- Remind subject to contact the investigator if he/she experiences any adverse events.
- Remind subject that the study drug tube is not to be discarded and that the drug tube must be returned to the site at the next study visit. Subjects should be instructed to immediately report a lost tube to the site.
- Remind the subject to apply the study drug once daily, as directed, preferably in the morning.
- Remind the subject to record their study drug application in the diary each day during the study and to return the diary to the site at the next study visit.
- Remind subjects to follow the treatment instructions.

7.3.2.3 Interim Visits Week 1, 3, 6, and 9 (± 3 days)

- Question the subject about any new or changes in adverse events
- Question the subject about any new or changes in concomitant medications/therapies.
- Obtain vital signs at Week 6 visit ONLY.
- Obtain a blood sample for immunogenicity testing at Week 3 and Week 6.
- Perform the Investigators Global Assessment (IGA) of rosacea, the Investigators Assessment of Erythema (IAE), and Other Signs and Symptoms Assessment before performing the lesion count (refer to Section 7.4.1, 7.4.2, and 7.4.3). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- Perform the inflammatory lesion count (papules and pustules) (refer to Section 7.4.4). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- The subject should apply the study drug at the study site under supervision of the study coordinator or designee
- Treatment Compliance Check - Collect the diary to perform a treatment application compliance review. Check compliance by reviewing the number of treatment applications in the diary to determine if there are missed doses. The subject should be re-instructed on study drug application, if compliance is an issue.
- Collect the previous diary and dispense a new diary to the subject at the Week 3, 6, and 9 Visits. The diary reviewed at the Week 1 Visit should be returned to the subject for use until the Week 3 Visit. The Week 9 Visit diary should be collected at the Week 12 Visit.
- Dispensing and Return of Study Treatment - No new study drug supply will be dispensed at the Week 1 visit; the drug tube which was dispensed to the subject at Baseline should be returned to them at Visit 1 after completing the treatment application compliance check. Collect the old study medication tube and dispense a new tube of study medication after weighing it at the Week

3, 6, and 9 Visit. Record the date of dispensing on the tube label. Weigh returned tubes. The dispensing and return information should be recorded on the source document.
- Remind the subject about restricted therapies (see Section 7.6.11.1).
- Remind the subject to apply the study drug once daily, as directed, preferably in the morning and record their daily treatment application in their dairy.
- Remind the subject to contact the investigator if he/she experiences any adverse events.
- Remind subject that the study medication tubes are not to be discarded and all must be returned to the site at the next study visit. Remind them to notify the site immediately if they have lost a tube.
- Remind the subject to return the diary to the site at the next study visit.
- Remind the subject to follow the treatment instructions.

7.3.2.4 Final Double-Blind Treatment Visit (Week 12) (± 3 days)

- Question the subject about any new or changes in adverse events.
- Question the subject about any new or changes in concomitant medications/therapies.
- Perform the Investigators Global Assessment (IGA) of rosacea, the Investigators Assessment of Erythema (IAE) and Other Signs and Symptoms Assessment before performing the lesion count (refer to Section 7.4.1, 7.4.2, and 7.4.3). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- Perform the inflammatory lesion count (papules and pustules) (refer to Section 7.4.4). **Every effort should be made to maintain consistency of the evaluator for each subject.**
- Perform a limited Physical Exam with vital signs and weight measurement.
- Obtain a blood sample for hematology and chemistry analysis.
- Obtain a blood sample for immunogenicity testing.
- Perform an in-office urine pregnancy test on all females of child-bearing potential.
- The subject should apply the study drug at the study site under supervision of the study coordinator or designee
- Treatment Compliance Check - Collect the diary to perform a treatment application compliance review. Check compliance by reviewing the number of treatment applications in the diary to determine if there are any missed doses.
- Drug Return -All double-blind study drug tubes should be collected by the Week 12 treatment visit. The weight of the tubes at dispensing and return should be documented. Any missing tubes must be documented.
- Remind the subject to contact the investigator if he/she experiences any adverse events.
- Remind the subject about restricted therapies (see Section 7.6.11.1).

7.3.2.5 Follow-Up Visit (Week 16) (± 3 days)

- Question the subject about any new or changes in adverse events.
- Question the subject about any new or changes in concomitant medications/therapies.
- Obtain vital signs.
- Obtain a blood sample for immunogenicity testing.
- Perform the Investigators Global Assessment (IGA) of rosacea, the Investigators Assessment of Erythema (IAE) and Other Signs and Symptoms Assessment before performing the lesion count

(refer to Section 7.4.1, 7.4.2, and 7.4.3). **Every effort should be made to maintain consistency of the evaluator for each subject.**

- Perform the inflammatory lesion count (papules and pustules) (refer to Section 7.4.4). **Every effort should be made to maintain consistency of the evaluator for each subject.**

7.4 EFFICACY VARIABLES

The efficacy evaluations should be performed by the Principal Investigator or appropriately qualified Sub-Investigator. The same evaluator should perform the Investigators Global Assessments (IGA), the Investigators Assessment of Erythema (IAEs), Other Signs and Symptoms Assessment and the lesion counts, (see Sections 7.4.1, 7.4.2, 7.4.3, and 7.4.4) for the same subject at each visit. **It is important that the same evaluator performs the Investigator assessments and lesion count for the same subject at each visit, however it may not be feasible in all instances. Every effort should be made to maintain consistency of the evaluator for each subject.**

7.4.1 Investigators Global Assessment (IGA)

The IGA should be performed at screening and each study visit (Baseline, Weeks 1, 3, 6, 9, 12, and 16) prior to performing the lesion count. The IGA is intended for the global evaluation of papulopustular rosacea. Background nontransient erythema and telangiectasias should not be assessed as part of the IGA. The IGA score represents the subject's condition at the time of the evaluation.

The following categories will be used from the IGA scale to perform the global evaluation of papulopustular rosacea:

Investigators Global Assessment (IGA) Scale

Grade	Grading Scale Score	Description of Papulopustular Rosacea Disease Status
Clear	0	No inflammatory papules or pustules.
Almost clear	1	Very few with 1 or 2 inflammatory papules/pustules.
Mild	2	Several (3-10) small inflammatory papules/pustules.
Moderate	3	11 to 19 small or large inflammatory papules/pustules and no nodules.
Severe	4	Numerous (≥20) small and or large inflammatory papules/ pustules, and up to 2 nodules, (at baseline).

7.4.2 Investigators Assessment of Erythema (IAE)

The IAE should be performed at screening and each visit (Baseline, Weeks 1, 3, 6, 9, 12, and 16) prior to performing the lesion count using the scale below. The IAE is intended for the global evaluation of erythema of rosacea. This is an assessment of nontransient erythema, or background erythema. Telangiectasias are assessed separately as described under section 7.4.3.

Investigators Assessment of Erythema (IAE) Scale

Grade	Grading Scale Score	Description of Background Erythema
Clear	0	No redness present. Background erythema is consistent with non-involved areas.
Almost Clear	1	Slight and localized background erythema in involved areas of the face, usually limited to the malar prominence of the cheeks. Gives the impression of a healthy glow to the cheeks.
Mild	2	Slight to mild background erythema NOT limited just to the cheeks, but extends to the lateral cheeks, chin, or forehead.
Moderate	3	Definite background redness, easily recognized, and extending to lateral cheeks, chin, or forehead.
Severe	4	Severe background erythema over the entire face.

The IAE rating of erythema is considered as part of the baseline assessment. If a worsening of erythema from Baseline is believed by the investigator to be related to the study drug and not the disease, then it should be recorded as an AE.

7.4.3 Other Signs and Symptoms Assessment

At screening and each study visit (Baseline, Weeks 1, 3, 6, 9, 12, and 16), the investigator must evaluate the severity of the other signs and symptoms of Rosacea. This should be done after evaluating the IGA and IAE, but before performing the lesion count. The areas that will be evaluated are as follows:

- Telangiectasia
- Scaling/peeling
- Pruritus

The score represents that subject's condition at the time of the evaluation. These signs and symptoms will be assessed using the following scales:

Telangiectasia Scale

Grade	Grading Scale Score	Description: Telangiectasia; fine superficial blood vessels that are visible near the surface of the skin.
None	0	No telangiectasias present on the face.
Mild	1	Some to a few telangiectasias are present on the face.
Moderate	2	Many telangiectasias, easily recognized, and extending to lateral cheeks, chin, or forehead.
Severe	3	Many to numerous telangiectasias over the entire face that blends in or matches with the erythema caused by inflammatory lesions. Few matted and dense cluster of vessels present.

Scaling/Peeling Scale

Grade	Grading Scale Score	Description: Scaling/ Peeling
None	0	No evidence of scaling.
Mild	1	Cracks easily evident.
Moderate	2	Marked cracks, wide and deep; scales large and lifting.
Severe	3	Large lifting scales, barely attached or shedding.

Pruritus Scale

Grade	Grading Scale Score	Description: Pruritus
None	0	No itching.
Mild	1	Occasional, slight itching; not really bothersome.
Moderate	2	Constant or intermittent itching that is somewhat bothersome.
Severe	3	Bothersome itching; excoriations of the skin from scratching may be present.

These clinical signs and symptoms of Rosacea: telangiectasia, scaling/peeling and pruritus are considered as part of the baseline and ongoing efficacy evaluation. If a new Rosacea sign or symptom or worsening of a Rosacea sign or symptom is believed by the investigator to be related to the study drug and not the disease, then it should also be recorded as an AE.

7.4.4 Inflammatory Lesion Counts

The area of lesion count assessment is defined as the face from the jaw line to the hairline. The lesion counts will be performed at screening and each study visit (Baseline, Week 1, 3, 6, 9, 12, and 16). The Investigator Global Assessment (IGA), Investigator Assessment of Erythema (IAE) and Other Signs and Symptoms Assessment should be performed prior to performing the lesion count at all visits.

The lesion counts will be performed as follows:

Instructions On Performing Inflammatory Lesion Counts

1. Subjects should have washed their face and removed all makeup at least 15 minutes prior. Male subjects should have already shaved before the study visit.

2. Subjects should be seated at arm's length (or slightly closer) from the evaluator performing the lesion counts and at the same height as the assessor. Subjects should not be seated in direct sunlight.

3. The room should have a balanced and consistent artificial light source or natural light source.

4. The **Principal Investigator or appropriately qualified Sub-Investigators** participating in this study will perform **all** lesion counts. It is essential that the same assessor perform all lesion counts for a given subject for the duration of that subject's participation in the study.

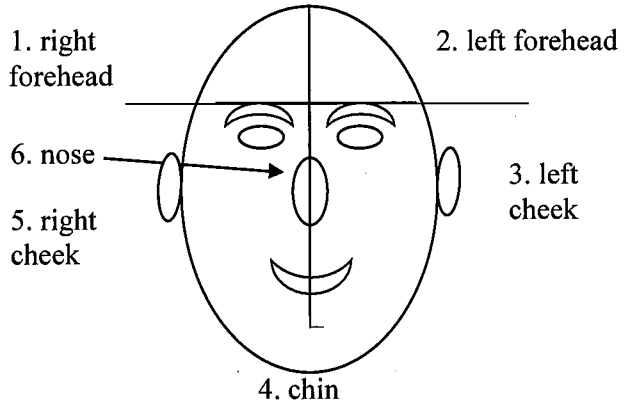
5. Lesions on each area of the face should be considered separately according to the diagram below. Lesions should be counted just to the hairline and no lower than the mandibular line (jaw line). Scan each section of the face systematically from left to right and count only one lesion type at a time. Record each count on the source documents and initial your counts.

6. ALL LESIONS COUNTED SHOULD BE PALPABLE. If a lesion is not palpable it should be considered non-active (emerging or resolving). Post-inflammatory lesion pigment changes should not be counted. The inflammatory lesion count includes the total count of papules and pustules, which are defined as follows:

PAPULE – A type of inflammatory lesion; a small erythematous, palpable lesion, usually solid ≤ 0.5 cm in diameter.
PUSTULE – A type of inflammatory lesion; a small palpable lesion with an erythematous base approximately 0.5 cm in size and containing pus or yellow-white liquid.
NODULE – A type of inflammatory lesion; a large palpable erythematous papule or plaque that is greater than 0.5 cm in diameter.

Papules should be counted separately from pustules (inflammatory lesions). All lesion types should be counted separately for each quadrant on the face.

Figure 1: Lesion Count Facial Diagram



7.5 SAFETY VARIABLES

7.5.1 Medical/Medication History and Demographics

A medical history including rosacea history, a medication history (including known rosacea treatments used in the last 5 years) will be performed, as well as collection of demographic information at the Screening visit. Medical and medication history will be updated at the Baseline visit. Demographic information will include the subject's age, sex, race, ethnicity and Fitzpatrick skin type (Appendix B). Skin type will be collected based on the subject reported skin type.

7.5.2 Limited Physical Exam and Vital Signs

A limited physical exam will be performed at the Screening Visit (including height and weight) and at the final Week 12 Visit (End of Treatment Visit or Early Termination Visit), including weight will be performed. The limited Physical Exam should include an assessment of the following:

- General Appearance
- Head
- Eyes
- Ears
- Nose
- Throat
- Lungs
- Heart
- Skin

Vital signs (blood pressure, respirations, heart rate) will be measured at the Screening Visit, Week 6, Week 12 (Final or Early Termination) Visit and at the Week 16 (Follow up) Visit.

7.5.3 Clinical Laboratory Testing

Blood samples (approximately 11 mL)) will be collected at Screening and the Week 12 Visit (Early Termination, or Final Visit), for hematology and chemistry laboratory analysis (total expected volume of approximately 22 ml). A central laboratory will perform the sample analysis for all study sites. Instructions for sample collection, preparation, labeling, and shipping will be provided by the laboratory.
All laboratory values that are considered clinically significant will be reported as an adverse event and followed as such. The laboratory tests will include the following parameters:

- Hematology: Complete blood count (CBC), including hemoglobin, hematocrit, red blood cell (RBC), white blood cell (WBC), count with differential, and platelet count.

- Blood Chemistry/Lipids: sodium, potassium chloride, bicarbonate or carbon dioxide, glucose, blood urea nitrogen (BUN), creatinine, calcium, uric acid, total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT), total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides, and lactic dehydrogenase (LDH).

7.5.4 Immunogenicity Testing

Blood samples (approximately 6 mL) will be collected at Day 1 (Pre-dose), Week 3, 6, 12 (End of Treatment) and the Post treatment follow-up visit (Week 16) for immunogenicity testing. Samples from all sites will be shipped to a central laboratory and stored prior to sample analysis (total expected volume of approximately 30 mL). Instructions for sample collection, preparation, labeling, and shipping will be provided by the laboratory. It is necessary that the central laboratory has knowledge of the randomization as only samples from subjects who have been randomized to receive omiganan pentahydrochloride topical gel will undergo immunogenicity testing. Sample testing will occur periodically dependent upon an adequate number of samples having been received at the laboratory. Any positive anti-drug antibody test result will be made available following the subject's completion of treatment. It is intended to follow any subjects with positive anti-drug antibody results for up to 1 year from the last study medication use to allow for antibody levels to return to baseline.

7.5.5 Urine Pregnancy Test

An in-office, highly sensitive urine pregnancy test must be performed for all female subjects of child-bearing potential at Screening and the Week 12 Visit (Early Termination, or Final Visit). All female subjects of childbearing potential must have a negative urine pregnancy test prior to randomization. Urine pregnancy testing should also be conducted at an unscheduled visit for any female who is suspected of being pregnant. Any female who becomes pregnant should be withdrawn from the study and followed to term. The CRO/Sponsor must be notified of any pregnancy that occurs while on

therapy. In the event of pregnancy, the site will complete a pregnancy report form to capture the pregnancy outcome.

7.5.6 Adverse Event

7.5.6.1 Definition of Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Clinical signs and symptoms of rosacea: erythema, telangiectasia, burning, dryness, scaling/peeling and pruritus are considered as part of the baseline dermatological history. If a new rosacea sign or symptom or worsening of a rosacea sign or symptom is believed by the investigator to be related to the study drug and not the disease, then it should also be recorded as an AE.

At each visit, the study site personnel will question the subject about adverse events using an open question taking care not to influence the subject's answers, e.g., "Have you had any problems since your last visit?"

Any adverse event, whether or not it is related to the test products, will be reported on the source document and eCRF along with the date of onset, the severity, the relationship to the test product and the outcome. Under certain circumstances, additional information may be requested.

When an adverse event persists at the end of the study, the Investigator will ensure a follow-up of the subject until the Investigator/CRO/Sponsor agree that the event is satisfactorily resolved or that no further follow-up is required.

7.5.6.2 Severity and Relationship of Adverse Event to Study Drug

The severity of an adverse event is to be scored according to the following scale:

1	Mild	Awareness of sign or symptom, but easily tolerated
2	Moderate	Moderate Discomfort enough to cause interference with usual activity
3	Severe	Severe Incapacitation with inability to work or perform usual activity

The relationship of an adverse event to study drug is to be assessed according to the following definitions:

- Not related – no temporal association or the cause of the event has been identified, or the drug cannot be implicated based upon available information.
- Possibly Related – temporal association, but other etiologies are likely to be the cause. However, involvement of the drug cannot be excluded, based upon available information.

- Definitely Related – established temporal or other association (e.g., re-challenge) and event is not reasonably explained by the subject's known clinical state or any other factor, based on available information.

7.5.7 Serious Adverse Event:

A serious adverse drug event (SAE) is any adverse event (AE) or suspected adverse reaction (SAR) that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- death;
- a life-threatening adverse event or life-threatening suspected adverse reaction, (the term "life-threatening" in the definition of "serious" refers to an event or suspected adverse reaction in which in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death);
- inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant incapacity; or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the serious definition above. 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.
The Investigator or designee must report any SAE occurring in a subject receiving study medication to the Medical Monitor immediately (within 24 hours (1 business day) of becoming aware of the event), even if the SAE does not appear to be drug-related. This should be done by telephone and by sending a copy of the Serious Adverse Event form (via fax or email pdf copy) plus other supporting documentation, as required.

All additional follow-up evaluations must also be reported as soon as possible. All SAEs will be followed until the CRO/Sponsor agrees that the event is satisfactorily resolved or that no further follow-up is required.

The CRO/Sponsor will be responsible for notifying the relevant authorities of any SAE according to applicable regulations. The CRO/Sponsor will also ensure that any central IRB/IEC and any other participating Investigators are notified of the SAE. The PI is responsible for ensuring that their local IRB/IEC, if applicable, is notified of the SAE, as per the IRB/IEC standard operating procedures.

Serious Adverse Events must be reported immediately to the appropriate medical monitor as listed below:

Medical Monitors:

[redacted]

7.6 TEST MATERIALS

7.6.1 Administration

Study drug will be applied by the subject to the entire area of the face, once daily, in the morning, for a period of 12 weeks after performing the first application of study drug at the study site, under the supervision of the study coordinator or designee to ensure the subject understands the treatment application instructions (see Appendix A, Instructions on Application of Study Drug). The subject will be provided a copy of the Instructions on Application of Study Drug. Once the subject has read the instructions and demonstrated proficiency in application at the study site, subjects will continue daily treatment application, each morning, during the treatment period, in an outpatient setting.

Subjects will be instructed to wash their face with a non-medicated soap or soapless cleanser at least 15 minutes prior to application of the study drug. The study drug is packaged in a tube. The cap of the tube should be removed and a thin film coating of the gel should be applied to the entire face, avoiding contact with the eyes, mouth and inside the nose. The dose applied will be applied as a thin film, approximately 0.4 gram each day preferably in the morning.

At the Baseline visit and Week 3, 6 and 9 visits only subjects will be dispensed one tube of study gel. Each tube contains enough gel for 4 weeks of treatment. When the tube is dispensed and prior to application of study drug, the tube will be dated and weighed and the weight will be recorded in the source documents and eCRF. When the used tubes are returned at the next visit, the tube will be weighed again, and the weight will be recorded in the source documents and the eCRF. At each visit, the subject's diary should be reviewed to determine if they missed any applications since the last visit. Reported missed applications should be recorded in the eCRF. In addition, the date of the last application should be collected. At each visit the returned tube will be weighed to assess product use. If necessary, the subject will be reinstructed on study drug application if compliance is an issue. All tube weighing will be done with the cap in place.

7.6.2 Products Identity

Omiganan Topical gel [redacted] in this protocol, in previously conducted phase 1 and 2 clinical studies, and in other historical documentation is based on the concentration of omiganan pentahydrochloride. The product concentration based on the active moiety is omiganan topical gel [redacted] To be consistent with the naming convention in pre-existing documents, the nomenclature concentration of omiganan [redacted] will be referred to in this protocol and associated clinical and non-clinical documents.

[redacted]

Further, in order to comply with USP General Chapter <1121> Nomenclature to express the strength of the drug product based upon the active moiety, the strength of the omiganan product will be recorded on the clinical supplies documentation for phase 3 studies as Omiganan topical gel, [redacted]

[redacted]

7.6.3 Method of Treatment Assignment

Prior to the start of the study, a randomization list assigning kit numbers to one of two treatment groups in a 1:1 ratio for each study center will be generated by the CRO responsible for biostatistics in the trial. This list will be used by the manufacturer to package study drug into treatment kits. Each treatment kit will be labeled with a unique number, which will also match the number on each tube of

study drug inside the kit. Treatment kits will be shipped to the study sites when IRB/IEC approval has been obtained and all required study documents are submitted to the sponsor.

Once it has been established that subjects are eligible to participate in this study, each eligible subject will be assigned a treatment kit from those available at the site, which is labeled with the assigned kit number. Treatment kits must be assigned to subjects using the Interactive Web Response System (IWRS).

7.6.4 Unblinding a Subject

This is a double-blind, multicenter study. Subjects will be randomized to once daily treatment with either omiganan topical gel or vehicle. Study drug supplies will be packaged in a manner supporting the blinding of the study.

Unblinding a subject, if needed, will be done through the IWRS. Unblinding a subject's treatment assignment should ONLY be performed in an emergency, when knowing the identity of a subject's assigned treatment is essential to their continuing medical care. If at all possible, every attempt should be made to contact the Medical Monitor to discuss this before opening the blinded panel to determine the subject's treatment assignment. The contact information for the Medical Monitor's is provided on the front page of the protocol In the event of unblinding, the Medical Monitor and Project Manager must be notified immediately (within 24 hours(1 business day)), and the circumstances under which the code for a given subject was broken must be documented in the subject's eCRF.

7.6.5 Packaging

Study drug will be provided in 20-gram tubes. Drug supplies will be packaged to provide one treatment kit that contains 5 tubes of study drug per subject. Four tubes will be provided in order to dispense a tube at Baseline, Weeks 3, 6 and 9; 1 extra tube will be in the kit in case tubes are lost or damaged. Each tube will be printed with the treatment kit number that will correlate through the randomization list to the contents of the tube.

7.6.6 Labeling

The requirements for drug product labeling will comply with the Regulations of the country where the clinical trial will be conducted.

Subjects will be provided a leaflet or card to keep with them at all times during the study that will provide the investigational site with the address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding.

Each treatment kit (consisting of 5 tubes of study drug) will be labeled with language that adheres to the applicable regulatory requirements in each country.

Each tube within the treatment kit will be labeled with labeling that corresponds to the treatment kit number. The study site personnel will write in the subject number and date of dispensing on the label

when dispensing a tube. Tube labeling will contain language that adheres to the applicable regulatory requirements in each country.

7.6.7 Subject Dosing and Use Instructions

Under the supervision of the study coordinator or designee, the first dose of study drug will be applied by the subject, as a means of educating subjects in the proper technique for applying the study drug (see Appendix A for instruction on applying the drug). Once the subject has shown proficiency in application, subjects will then apply the dose each day in the morning, in an outpatient setting.

7.6.8 Treatment Compliance

Subjects should not miss ANY visits to the study site for status assessments. Study drug treatment compliance will be assessed by reviewing the diary for any missed applications since the last visit or based on subject reported information on missed applications in the event of a lost diary. Subjects should be applying the topical gel each day during the study treatment period.

7.6.9 Dispensing and Return of Study Product

For use in the outpatient setting, 1 tube of study drug will be dispensed to each subject from their assigned study drug supply kit at Baseline, and again at their Week 3, 6 and 9 visits. The first dose of study drug will be applied at the study site. Subjects will be instructed on the proper procedure for study drug application for subsequent doses.

When a new tube of study drug is dispensed, study personnel must record the date dispensed and subject number on the label. The dispensing information must be recorded in the source documents.

The tube should be weighed prior to dispensing to the subject and again after the subject returns the tube to the clinical study site. The weight of the tube should be recorded to the nearest tenth of a gram. Tubes should be weighed with the cap on.

The subject will be instructed to return the tube of study drug at each study visit (Weeks 1, 3, 6, 9, and 12) to check compliance. At the Week 3, 6 and 9 Visit, the used tube will be exchanged for a new tube of study drug. One extra tube is available in each kit for dispensing in the event that tubes are lost or damaged.

7.6.10 Accountability

In accordance with local country regulations, the Investigator must agree to keep all clinical supplies in a secure location with restricted access.

Upon receipt of the clinical supplies, the Investigator or designee will conduct a complete inventory of all test materials and assume responsibility for storage and dispensing. Dispensation and return of test material must be appropriately documented. Under no circumstance should any of the clinical supplies sent to the Investigator be used in any unauthorized manner.

All used and unused clinical supplies will be appropriately inventoried and returned to the designated facility as specified by the Sponsor.

7.6.11 Prior and Concomitant Medication/Therapy

Therapies used within one month prior to the Baseline visit should be recorded on the Previous/Concomitant Medication/Therapy Form of the CRF. Washout medications should be listed on the Previous/Concomitant Medication/Therapy Form, when applicable. Rosacea treatments used in the last 5 years should be recorded.

Any therapy used by the subject either at or following the Baseline visit through study completion will be considered concomitant therapy; e.g., aspirin, Tylenol, birth control pills, vitamins, etc. Every attempt should be made to keep concomitant therapy dosing constant during the study. Any change to concomitant therapy should be noted on the Previous/Concomitant Therapy page in the eCRF.

An Adverse Event should be recorded for any subject starting a concomitant therapy (except therapies used as prophylaxis) to treat any health condition/event not identified in the subject's medical history.

Subjects should wash their face 15 minutes prior to study drug applications. Subjects must adhere to the following restrictions during the treatment period starting in the morning of Day 1:

- Showering/bathing (when subject showers/bathes, he or she should wait at least 15 minutes prior to applying study drug).
- Males should shave at the same time every day, at least 15 minutes before study drug application.
- Wait until the gel dries before applying makeup.
- Refrain from sunbathing, using sun tanning booths/beds, or excessive exposure to the sun No new lotions, gels, powders, moisturizers, etc., are to be used on the skin in the treatment areas. A bland moisturizer) may be used throughout the study. All makeup, approved lotions, moisturizers, etc. and sunscreen should be applied after the study gel is dry.

7.6.11.1 Excluded Concomitant Therapy

No other rosacea treatment, other than the study drug, will be permitted. Receiving interfering rosacea therapy during the study will be deemed a major protocol violation and may exclude the subject from the per protocol population for efficacy analyses. The medical monitor should be notified of deviations related to concomitant therapy. Interfering concomitant therapies include those listed below:

Interfering Topical Therapies (on the face)

- Abradants, astringents, toners, facials, masks, washes, or medicated facial cleansers
- Tanning booths/sunbathing, excessive exposure to the sun (tanning is not permitted)
- Antibiotics other than topical ocular application
- Antimicrobial soaps
- Corticosteroids

- Other anti-inflammatory drugs
- Retinoids
- Other acne or rosacea treatments (e.g., benzoyl peroxide, alphahydroxy acids, salicylic acid, azelaic acid, or metronidazole)

Interfering Systemic Therapies

- Antibiotics
- Corticosteroids other than inhaled/nasal corticosteroids
- Other acne or rosacea treatments (including oral retinoids or therapeutic vitamin A supplements)
- Change in dose, initiation and/or discontinuation of estrogen therapy (e.g., Gynogen, Valergen, Depo-Testadiol, Depogen, birth control pills)

7.7 STATISTICAL METHODS PLANNED

7.7.1 General Considerations

Unless otherwise specified, all statistical tests will be two-sided with a significance level of 0.05.

7.7.2 Sample Size Determination

The primary objective of the study is to show superiority of Omiganan over vehicle for the treatment of rosacea in patients with severe papulopustular rosacea (IGA grade 4 with baseline inflammatory lesion count of $\geq$ 30). A sample size calculation was made for two co-primary endpoints. For change from baseline in inflammatory lesions, it is assumed that in the omiganan treatment arm, subjects will have an average reduction of 13.5 inflammatory lesions, compared to 4 in the vehicle arm. The standard deviation is assumed to be 12. For 95% power, a sample size of 86 subjects (43 per group) is needed. For Investigator Global Assessment (IGA), it is assumed that Clear or Almost clear (IGA of 0 or 1) at Week 12 has a lesser power than a 2 grade (point) reduction. It is also assumed that 17% of the subjects in the Omiganan treatment arm versus 6% in the vehicle arm will have an IGA of Clear or Almost Clear at Week 12. For 95% power and using a Fisher's Exact test, 450 subjects (225 in each arm) are needed. Therefore, the number of subjects needed to ensure at least 95% power for both endpoints is 450.

The sample sizes were calculated using 95% power in order to ensure 90% power across two Phase 3 studies.

7.7.3 Randomization

Subjects providing written informed consent and having met all inclusion and exclusion criteria will be randomized to 1 of 2 treatment groups in a 1:1 ratio, according to a predetermined computer-generated randomization code.

Subjects will be randomized to treatment using an Interactive Web Response System (IWRS). The randomization scheme will include investigative site. The randomization will be performed using permuted blocks.

7.7.4 Analysis Populations

The 'Intent-to-treat' (ITT) analysis population will include all randomized subjects. The ITT population will be the primary population for all efficacy analyses.

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.

The Per-Protocol (PP) population will include all subjects in the ITT population who provide Baseline and Week 12 efficacy data for all primary endpoints and complete the 12-week treatment period without any major deviations from the protocol.

The subjects to be included in the PP analysis population will be determined by the Sponsor/CRO prior to the unblinding of the study. The PP population will be secondary for the co-primary endpoints only.

7.7.5 Handling of Missing Data

The primary method of dealing with missing data is multiple imputation (MI) technique. All co-primary and secondary endpoints will be analyzed using MI for missing data. As a sensitivity analysis, Observed case and Baseline Observation Carried Forward (BOCF) will be utilized for the co-primary endpoints only.

In general, data will not be imputed for safety analysis.

7.7.6 Efficacy Endpoints

7.7.6.1 Co-primary Endpoints

- The absolute change from Baseline to Week 12 in inflammatory lesions.
- IGA at Week 12: 2 grade reduction; Clear or almost Clear (IGA 0, or 1)

7.7.6.2 Secondary Endpoints

- The absolute change from baseline to Week 9 in inflammatory lesions (papules and pustules).
- The absolute change from baseline to Week 6 in inflammatory lesions (papules and pustules).
- IGA at Week 9: 2 point reduction; Clear or Almost Clear (IGA 0, 1).
- IGA at Week 6: 2 point reduction; Clear or Almost Clear (IGA 0, 1).

7.7.6.3 Exploratory Endpoints

- The absolute change from baseline to Weeks 1 and 3 in inflammatory lesions (papules and pustules).
- Percentage of subjects with an IGA of clear or almost clear (0 or 1) at Weeks 1 and 3.
- Percentage of subjects with a 2 point IGA reduction at Weeks 1 and 3.
- Percentage of subjects with an Investigator's Assessment of Erythema (IAE) of clear or almost clear (0 or 1) at each visit.
- Percentage of subjects with telangiectasia score of none or mild (0 or 1) at each visit.
- Percentage of subjects with scaling/peeling score of none or mild (0 or 1) at each visit.
- Percentage of subjects with pruritus score of none or mild (0 or 1) at each visit.

7.7.7 Demographic and Baseline Characteristics

Continuous demographic and baseline parameters will be summarized by the number of non-missing observations, mean, standard deviation, median, minimum, and maximum. Categorical parameters will be summarized by frequencies and percentages.

7.7.8 Subject Disposition

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

7.7.9 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.

7.7.10 Efficacy Analysis

The co-primary endpoint of absolute change from baseline in inflammatory lesions will be analyzed using an Analysis of Covariance (ANCOVA) model, with treatment as a main effect, and center as a covariate. To investigate consistency of efficacy results across study centers, treatment by study center interaction will be tested at 0.10 level of significance, and if significant, it will be further explored.

The co-primary endpoint of IGA will be tested in the following manner: the 2 grade reduction, and the Clear or Almost Clear (0, 1) will be tested using the Hochberg procedure as follows: Statistical significance will be concluded if both endpoints are significant at a two-sided 0.05 level, or either endpoint is significant at a two-sided 0.025 level. Both IGA endpoints will be analyzed using a Cochran–Mantel–Haenszel (CMH) test, with center as the stratification factor. If the overall IGA response rates are less than 10%, a Fisher's Exact test may be used to corroborate the CMH test. All tests of the co-primary endpoints will be analyzed.

If the co-primary endpoints of absolute lesion reduction and the two IGA endpoints (2 grade reduction, and Clear or Almost Clear (0, 1)) are both significant, the secondary endpoints will be analyzed sequentially in the order listed as follows:

- Test first secondary endpoint at 0.05. If not significant, stop; otherwise,
- Test second secondary endpoint at 0.05. If not significant, stop; otherwise,
- Test third secondary endpoint at 0.05 using Hochberg (similar to the primary method). If not both IGA (0,1) and IGA 2 point reduction are significant, stop; otherwise,
- Test fourth secondary endpoint at 0.05 using the Hochberg method.

For all efficacy analyses, small centers may be pooled in order to ensure sufficient cell counts for statistical testing.

Subgroup analyses (e.g. Gender, Age, Race, and Center) of the co-primary endpoints will be performed.

7.7.11 Interim Analysis

An interim analysis for futility will be conducted by an independent statistician. The sole purpose of the interim analysis is to help make a decision whether to continue the trial to the planned sample size, or to stop the trial for futility. No increase or decrease to the sample size will be performed, except to stop the trial for futility, therefore no adjustment to type-1 error is indicated. The interim analysis will be based on conditional power analysis when approximately 60 subjects (per group) have completed the double blind portion of the study. Only absolute lesion reduction count and IGA data (2 grade reduction, and Clear or Almost Clear (0, 1)) will be analyzed. The process for conducting the interim analysis and disseminating the recommendation to the sponsor will be described in the Statistical Analysis Plan. A charter will be written to describe in detail the process and roles related to this interim analysis. This charter will name the independent statistician to conduct the interim analysis, and the sponsor's designated personnel that will make final decisions.

7.7.12 Safety Analysis

Treatment emergent adverse events, and serious adverse events will be categorized by system organ class and Preferred Term from the current version of MedDRA. Treatment-emergent adverse events will be summarized overall, by severity, and by relationship to treatment. Changes from baseline in vital signs, laboratory parameters, immunogenicity parameters, and shifts from baseline laboratory parameters and in physical examinations will be summarized by treatment. All safety endpoints will be displayed for all treated subjects.

7.7.13 Week 16 (4 week follow-up) summary

Summary statistics for Week 16 study period will include baseline demographics, disposition, exposure, safety, and efficacy variables.

Efficacy summaries will include:

- The absolute change from baseline to Week 16 in inflammatory lesions (papules and pustules).
- IGA at Weeks 16: 2 point reduction; Clear or Almost Clear (IGA 0, 1).
- Percentage of subjects with an Investigator Assessment of Erythema (IAE) of clear or almost clear (0 or 1) at Week 16.
- Percentage of subjects with telangiectasia score of none or mild (0 or 1) at Week 16.
- Percentage of subjects with scaling/peeling score of none or mild (0 or 1) at Week 16.
- Percentage of subjects with pruritus score of none or mild (0 or 1) at Week 16.

Safety summaries will include:

- Concomitant medications
- Adverse events
- Vital signs and laboratory tests.

All efficacy and summaries will be performed by original double-blind randomized treatment group, and overall

7.7.14 Multicenter Analysis

Approximately 50 centers are planned in this study; whenever possible, approximately 16 subjects will be enrolled per center. In the event a center has a low (< 16) number of subjects enrolled or no subject that meets either of the IGA co-primary endpoints, pooling of centers may be performed based on geographical center location until the pooled center has at least 16 subjects and at least one subject with an IGA of clear or almost clear and at least one subject with a 2 point reduction in IGA.

Centers that do not meet above criteria will be pooled according to the following priorities:

1. Within a state/territory/country;
2. Across states/territory/country.

The exact pools will be determined prior to unblinding according to the above methodology.

Descriptive summary statistics will be generated including center and pooled-center (when appropriate) by co-primary and secondary efficacy endpoints.

8 ETHICS AND GENERAL STUDY CONDUCT CONSIDERATIONS

8.1 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with the FDA and ICH guidelines on current GCP following the ethical principles originating from Declaration of Helsinki. Additionally, the study will be conducted in accordance with any applicable laws or regulations of the country in which the clinical research is conducted.

8.2 CHANGES IN STUDY CONDUCT/STATISTICAL ANALYSES/AMENDMENTS

No change in the conduct of the study should be instituted without written approval from the CRO/Sponsor. Substantial Amendments to the protocol require written approval from the Sponsor, Institutional Review Board, ethics committee and the regulatory authority, as applicable.

8.3 INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC)

This study, all appropriate amendments, all advertising, and written materials given to the subjects will be reviewed and approved by an Institutional Review Board/Independent Ethics Committee, prior to use.

8.4 SUBJECT INFORMATION AND CONSENT

The study personnel will inform all subjects in this study, in accordance with GCPs, about the study. The study personnel will review the informed consent form (ICF) with each subject and give the subject an opportunity to read the consent and have all questions answered before proceeding. A current written consent form, approved by an IRB/IEC, is to be supplied by the Investigator and willingly signed by each subject, prior to initiating any study procedures, including instructing the subject to discontinue the use of medications requiring wash-out. The Investigator is responsible for maintaining each subject's consent form in the study file and providing each subject with a copy of the signed form(s).

8.5 PROTOCOL ADHERENCE

The Investigator must read the protocol thoroughly and must follow the instructions exactly. Any change should be agreed upon by prior discussion between the CRO/Sponsor and the Investigator, with appropriate written protocol amendments made prior to implementation of the agreed-upon changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented.

8.6 CONTRACTUAL REQUIREMENTS

A contractual agreement will be signed between the Sponsor/CRO and the Investigator/clinical site. This document will contain complementary information, i.e. financial agreement, confidentiality, study schedule, and publication of study results.

8.6.1 Publication Policy

All data generated from this study are the property of the Cutanea Life Sciences, Inc. Publication of data will be done in accordance with the contractual agreement between the Sponsor/CRO and Investigator/clinical site.

8.7 RECORD KEEPING

8.7.1 Data Collection

The Investigator must maintain detailed records on all study subjects. Data for this study will be recorded in the subject's chart and entered into eCRFs through the electronic data capture (eDC) system provided by the Sponsor's designated data management group. Applicable data from the subject's chart should be recorded in the eCRFs completely, promptly, and taking time to correct any mistakes as prompted by the eCRF system. Upon study completion or at any other time specified by the CRO/Sponsor, a monitor will review the appropriate eCRF pages.

Completed eCRFs should be ready for review by the CRO/Sponsor's Monitor, within one (1) week of each study visit for a given subject.

8.7.2 Data Corrections

Corrections of data entered into the eCRF must be made in the system for electronic case report forms, as appropriate.

- The CRO/Sponsor's Monitor will review the eCRFs, evaluate them for completeness and accuracy, and ensure that all appropriate information is entered.
- No changes will be made to the data on the eCRF pages after the data are determined to be final by the CRO/Sponsor's Monitor and data management group. Queries and comments may still be generated and answered on eCRFs as outlined in the eDC system.

8.7.3 Source Documentation

Investigators must keep accurate separate records (other than the eCRF) of all subjects' visits, which include all pertinent study-related information including the original signed/dated informed consent forms, and drug accountability records. As a minimum, a statement should be made in the subject's record indicating that the subjects have been enrolled in Protocol CLS001-CO-PR-005 and that they signed an informed consent form. Any adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the subjects and/or the CRO/Sponsor concerning the study must also be recorded.

8.7.4 Monitoring/Auditing

Representatives of the CRO/Sponsor, following GCP guidelines, will closely monitor the conduct of the study. In addition, inspections or on-site audits may be carried out by the local regulatory authority or by the CRO/Sponsor's independent Quality Assurance Department. The Investigator will allow the CRO/Sponsor's representatives and any regulatory agency to examine all study records, eCRFs, corresponding subject medical records, clinical drug dispensing records, drug storage area, and any other documents considered source documentation.

8.7.5 Archives

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of subjects, source documents, eCRFs and study drug inventory must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in the an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during the study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The CRO/Sponsor must be notified in writing of the name and address of the new custodian.

[redacted]

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11 APPENDICES

APPENDIX A

Instructions On Application Of Study Drug

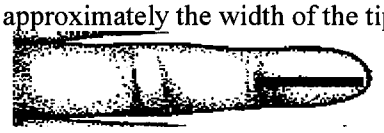
You will apply study drug once daily, preferably in the morning.

Before applying the study drug:

1. Using a non-medicated soap or soapless cleanser, wash your hands and face at least 15 minutes before study drug is to be applied.
2. For the first dose, the study staff will review treatment application with you before you apply the study medication. The amount of product that you will apply each day should be a sufficient amount to cover your face with a thin layer of gel.

Application of the study gel:

1. Remove the cap from the study medication tube and squeeze a small line of product from the crease of your last knuckle to the tip of your finger (see picture below). The line should be approximately the width of the tip of the tube.



2. Next, apply the product in a thin layer by gently dabbing and blending it evenly over the entire face, including cheeks, chin, forehead and nose. Avoid contact with the corners of the eyes, mouth and inside the nose.
3. If additional product is needed to cover your face, then squeeze very small amounts of product from the tube and blend it evenly on the untreated areas of your face until your entire face has a thin film of product applied to it. If you notice dried or flaking product on your face, you may be applying too much product.
4. Return the cap to the study medication tube and store the tube of study medication at room temperature.
5. Record your treatment application on your diary
6. Keep clothing from contacting the treated areas until the gel dries.

You must not apply more than the recommended dose at any application.

- Showering/bathing (when you shower or bathe, use a non-medicated soap or soapless cleanser and wait at least 15 minutes prior to applying study drug).
- Males should shave at the same time every day, at least 15 minutes before study drug application.
- Wait until the gel is dry before applying makeup.
- Excessive exposure to the sun and tanning booths/beds should be avoided Wait until the gel has dried before applying sun screen to your face. No new lotions, gels, powders, moisturizers, etc. and no topical medications should be used on the skin in the treatment areas.

Remember to bring your tube and diary back to the clinic at EVERY visit. Please call the clinic immediately if you have lost your tube.

Clinic Phone number: _____ Your next appointment is: _____

APPENDIX B

Fitzpatrick skin type classification:

-**I**: Always burn, never tan
-**II**: Usually burn, tan less than average (with difficulty)
-**III**: Sometimes mild burn, tan about average
-**IV**: Rarely burn, tan more than average (with ease)
-**V**: Rarely burns, tans profusely
-**VI**: Never burns, tans profusely

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