PROTOCOL NUMBER CLS001-CO-PR-006

Title:
A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety of Omiganan Topical Gel in Subjects with Rosacea

Test Product: CLS001 Omiganan topical gel, [redacted]

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

Date: 07 March 2017

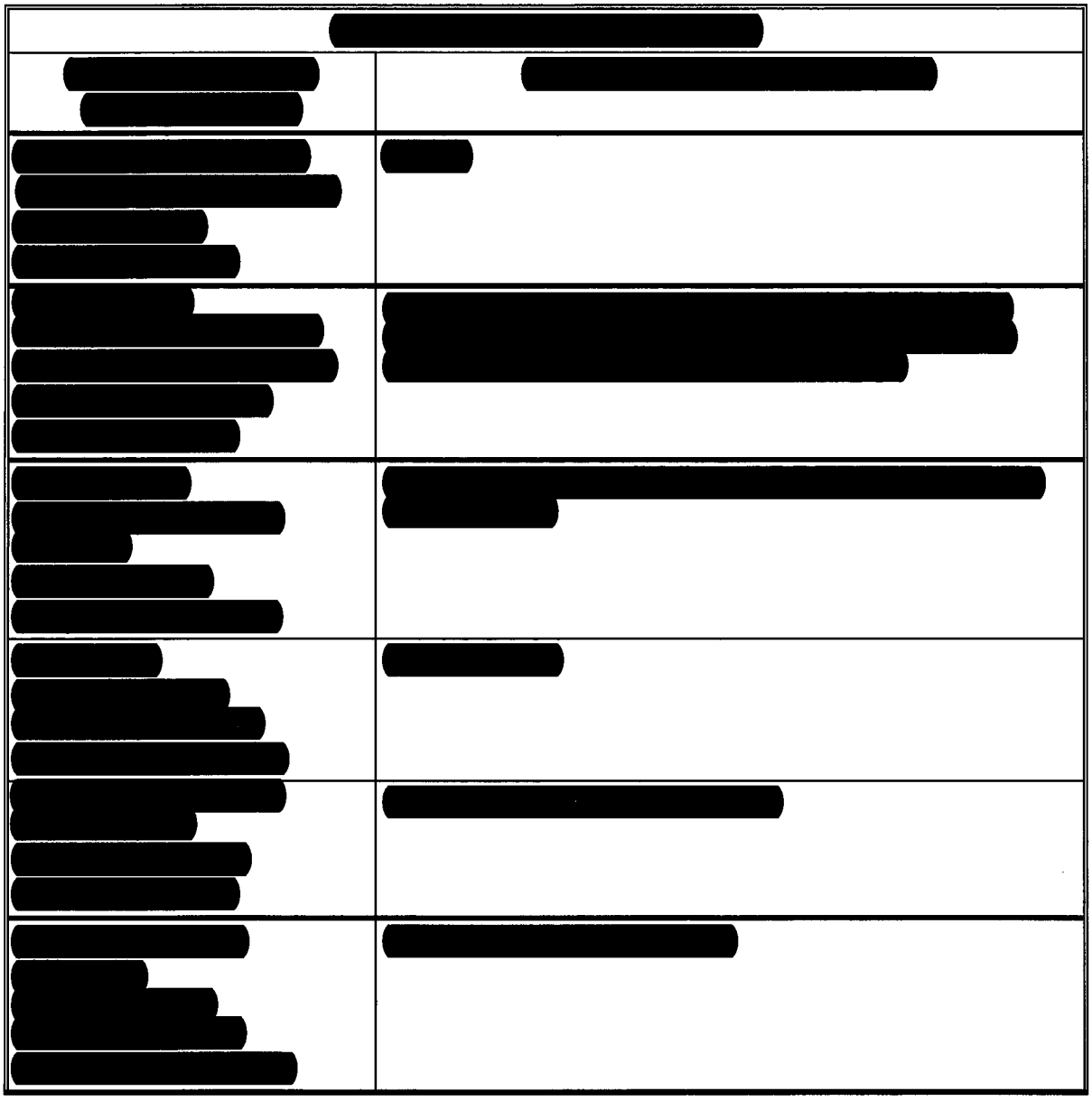
Confidentiality Statement

The confidential information in this document is provided to you, as an investigator or consultant, for review by you, your staff, and the applicable Institutional Review Board. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Cutanea Life Sciences, Inc.

1 SYNOPSIS

Title of Study: A Phase 3 Open-Label Extension Study to Evaluate the Long-Term Safety of Omiganan Topical Gel in Subjects with Rosacea	
Study Period (Planned): Start –First subject enrolled: [redacted] End – Last subject last visit: [redacted]	**Phase of Development:** Phase 3
Objectives: To evaluate the long-term safety of omiganan topical gel applied once daily to the face of subjects with papulopustular rosacea	
Methodology: Open-label, multi-center, long-term safety study	
Number of Subjects (planned): Up to 300 enrolled, to achieve up to 300 evaluable at 6 months and up to 100 at 12 months	
Number of Sites: Approximately 35 sites in the United States, Canada, France, Netherlands, United Kingdom, Sweden, Australia and New Zealand.	
Diagnosis and Main Criteria for Inclusion: • Male or non-pregnant female subjects at least 18 years of age with severe papulopustular rosacea (IGA score of 4)	
Investigational Product: Omiganan topical gel **Comparator Product:** None **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: Up to 12 months (52 Weeks ± 14 Days)	
Criteria for Evaluation: **Safety:** Adverse events (AE) throughout the study at Month 1, 3, 6, 9, 12. Physical exam, vital signs, immunogenicity and safety labs will be collected at select time-points. **Statistical Methods:** ***Safety***: Adverse events will be categorized by SOC and Preferred Term from the current version of MedDRA. Changes or shifts in safety laboratory data and vital signs be summarized at all time-points when available. Summaries will include means, standard deviations, median, minimum and maximum values for continuous data, or frequency and percent for categorical data. Additionally, shift tables will be provided for abnormal safety labs.	

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
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CLS001	Omiganan topical gel (referred to as omiganan)
DNA	Deoxyribonucleic acid
E. coli	Escherichia coli
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
eDC	Electronic Data Capture
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
gm	Gram
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HDL	High-density lipoproteins
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IGA	Investigators Global Assessment

LIST OF ABBREVIATIONS	
IRB	Institutional Review Board
LDH	Lactic dehydrogenase
LDL	Low-density lipoproteins
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIC	Minimum Inhibitory Concentration
mm	Millimeter
P. acnes	*Propionibacterium acnes*
PI	Principal investigator
PK	Pharmacokinetic
QSAD	As much as needed
RBC	Red blood cell
RNA	Ribonucleic acid
S. aureus	Staphylococcus aureus
SAE	Serious Adverse Experience/Event
SAR	Serious Adverse Reaction
SOC	System Organ Class
USP	United States Pharmacopeia
w/w	Weight for weight
WBC	White blood cell

4 TABLE OF CONTENTS

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 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, more than 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 well-being.[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 the treatment of rosacea 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 occurred 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 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 over 2,500 people 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. Omiganan topical solution for acne has been evaluated at concentrations of 1.0% and 5% in Phase 1 studies, as well as 1.25%, 2.5% and 5% in Phase 2 studies. 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 was evaluated at concentrations of 0.5%, 1%, 2.5% and 3%. Omiganan was not systemically absorbed when applied to the skin at concentrations ranging from 0.5% to 3% topical gel. 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

To date, the safety of omiganan pentahydrochloride topical gel [redacted] has been evaluated in subjects exposed to treatment for 12 weeks. This study is being conducted to meet recommendations of ICH-E1a and FDA guidance that 300 subjects be exposed for 6 months and 100 subjects exposed for one year to evaluate the long term safety of drugs intended for long-term treatment (chronic or repeated intermittent use for longer than 6 months). This study is designed contribute up to 300 of the required 300 subjects exposed for 6 months and up to 100 subjects exposed for one year. The Phase 3 Pivotal study (CLS001-CO-PR-004) has an open label extension phase which is designed to also contribute subjects required to fulfill 300 subjects exposed to study drug for 6 months and 100 subjects exposed for one year. The enrollment and completion of the study participants will be monitored via the electronic data collection system to determine when sufficient numbers of subjects have completed the studies to meet the long term safety exposure requirements.

6 STUDY OBJECTIVES

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

7 INVESTIGATIONAL PLAN

7.1 OVERALL STUDY DESIGN

This study will be conducted in accordance with the FDA and ICH guidelines on current GCP, and 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 conducted as an open-label, multicenter study at approximately 35 sites in the United States, Canada, , France, Netherlands, United Kingdom, Sweden, Australia and New Zealand and involving approximately 300 subjects with severe papulopustular rosacea. After giving informed consent, each subject will be screened for study eligibility according to specific inclusion/exclusion criteria. Eligible subjects will be enrolled to evaluate the long-term safety of omiganan topical gel. Omiganan gel will be topically applied once daily to the entire facial area; cheeks, chin, forehead and nose, avoiding contact with the eyes, mouth, and inside the nose.

Following baseline testing and evaluation for acceptance into the study, eligible subjects will be supervised during the first test drug application on Day 1 to ensure that the study treatment is applied correctly. Thereafter, each subject will apply the study treatment at home (unsupervised) once daily for up to 12 months. Once 100 subjects have completed

one year and 300 subjects have completed 6 months of treatment with omiganan topical gel (in the CLS001-CO-PR -004 and -006 studies combined), the remaining subjects in this study will discontinue treatment and will have their final study visit performed and no additional subjects will be recruited.

Other concurrent therapies will be recorded throughout the study. A bland non-medicated soap or soap less cleanser should be used throughout the study for the purposes of washing the subject's face.

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 have provided written informed consent to participate in the study.

2. Healthy, male and nonpregnant female subjects, 18 years of age or older.

3. A diagnosis of severe papulopustular rosacea using the Investigator Global Assessment (IGA) grading scale (Grade 4; described as numerous (≥20) small and or large inflammatory papules/ pustules, and up to 2 nodules, (at baseline))

4. Subjects with the presence of telangiectasia at Baseline

5. Subjects with the presence of facial erythema associated with their rosacea at Baseline

6. 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 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 receiving study drug. In addition, women of childbearing potential must agree to have a highly sensitive urine pregnancy test at the end of the study.

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

8. 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.

9. 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 Screening or 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 with known allergies to the active ingredient or any of the excipients. (See Section 7.5.2)

6. 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

7. 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	4 weeks

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

9. 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.

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

11. Subjects who have a chronic medical condition that may require the use of a prohibited medication to treat new symptoms or exacerbations, for example, rheumatoid arthritis.

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 letter sent to the subject will be maintained in the Investigator's file.
- Study Terminated By Sponsor
- Physician Decision
- Non-Compliance with Study
- Other

All premature discontinuations of study medication 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 visit procedures performed). 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.

7.3 CONDUCT OF STUDY

7.3.1 Table of Study Procedures

Procedures	Screening (Within 30 days of Baseline)	Baseline (Day 1)	Interim Visits: Month 1, 3, 6, and 9 (Week 4, 12, 26 and 39 ± 14 days) or Unscheduled Visit	Final Visit: Month 12/EOT (Week 52 ± 14 days)
Informed Consent	X			
Demographics, Medical and Rosacea History	X	X		
Limited Physical Exam including weight	X (including height)			X
Vital signs	X		X (Month 6 only)	X
Blood collection for Clinical Laboratory Test (hematology, chemistry)	X			X
Blood collection for immunogenicity testing		X	X	X
Urine Pregnancy Test, if applicable	X			X
Investigator Global Assessment	X	X	X	X
Inclusion/Exclusion Criteria	X	X		
Weigh Tubes/Dispense Study Drug		X	X	
Dispense Diaries		X	X	
Collect Diaries			X	X
Instruct on Treatment Application		X	X	
Apply Study Drug		X	X	X
Collect drug/ Drug Accountability/ Compliance check			X	X
Previous/Concomitant Medication/Therapy Review	X	X	X	X
Adverse Event Assessment		X[1]	X	X

[1] Adverse event assessment during the Baseline visit will be performed following the first application of study drug.

7.3.2 Study Procedures by Visit

Visits following the Baseline Visit are to occur at Months 1, 3, 6, 9, and 12 at Week 4, 12, 26, 39 and 52 (Final Visit). Interim study visits and the Final Month 12 (Week 52) study visit may be conducted (on an individual subject basis) up to 14 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 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 7.5.9.1). 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
  - 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 7.4.2) 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. **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.

- Schedule the next visit.

7.3.2.2 Baseline Visit (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 and record any changes since the first visit in medications/therapies, and the subject's health.
- Obtain a blood sample for immunogenicity testing
- Perform the Investigators Global Assessment (IGA) of rosacea. **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, provide the subject four tubes of omiganan topical gel. Record the subject number and dispensing date on the tubes that are assigned to that subject. Record the dispense date and the subject number on the source document.

- First Treatment Application –
  - Weigh the tubes that are designated to be dispensed to the subject prior to the subject applying their first dose of study medication. The tubes should be weighed with the cap on as outlines in section 7.5.7.
  - Give the subject a copy of the treatment application instructions (see Appendix A) and allow the subject 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 labels and dispense the tubes to the subject.
    - The subject should be instructed to apply the treatment once daily, preferably each morning, at approximately the same time for the duration of the study. A thin layer of the assigned study drug (approximately 0.4 gm) should be applied to the subject's face, including the non-affected areas (as described in Appendix A). The subject should be reminded to use all of the contents of one tube before they start using a new tube from their dispensed supply
    - 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 layer to the entire face as per the treatment application instructions (see Appendix A).

- 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 7.5.9.1).
- Remind the subject to contact the investigator if he/she experiences any adverse events.
- Remind the subject that the study drug tubes are not to be discarded and that the drug tubes must be returned to the site at the next study visit. Subjects should be instructed to immediately report lost tubes 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 use the gel from one tube before opening a new tube.
- Remind the subject to return the diary to the site at the next study visit.
- Remind the subject to follow the treatment application instructions.
- Schedule the next visit.

7.3.2.3 Interim Visits at Months 1, 3, 6, and 9 (Weeks 4, 12, 26 and 39 ± 14 days)

- Question the subject and record any new or changes in adverse events.
- Question the subject about any new or changes in concomitant medications/therapies.
- Obtain a blood sample for immunogenicity testing
- Perform the Investigators Global Assessment (IGA) of rosacea. **Every effort should be made to maintain consistency of the evaluator for each subject.**
- Vital signs will be measured (Month 6 Visit ONLY)
- The subject should apply the study drug at the study site under supervision of appropriate site personnel
- Treatment Compliance Check - Collect the study 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.
- Dispensing and Return of Study Treatment - No new study drug supply will be dispensed at the Month 1 visit; the drug tubes which were dispensed to the subject at Baseline should be returned to them at the Month 1 Visit after completing the treatment application check (unless the tube is empty; then it should be retained at the site and weighed). Record the date of dispensing and subject number on each tube label. Weigh returned tubes. The dispensing and return information should be recorded on the source document. Collect the previous diary and dispense a new diary to the subject at the Month 1, 3, 6, and 9 Visits. The diary should be collected at each visit.
- Remind the subject about restricted therapies (see Section 7.5.9.1).

- Remind the subject to apply the study drug once daily, as directed, and record their daily treatment application in their diary.
- 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 application instructions.
- Schedule the next visit

7.3.2.4 Final Treatment Visit at Month 12/End of Treatment Visit (Week 52 ± 14 days/EOT Visit)

- Question the subject and record any new or changes in adverse events.
- Question the subject and record any changes or additions to concomitant medications/therapies.
- Perform the Investigators Global Assessment (IGA) of rosacea. **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 immunogenicity testing
- Obtain a blood sample for hematology and chemistry analysis
- 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 appropriate site personnel
- Treatment Compliance Check - Collect the study drug tubes and diary to perform a treatment application compliance review. Check compliance by reviewing the number of treatment applications in the diary to determine if there were any missed doses. All study drug tubes should be collected by the last study visit. The weight of the tubes at dispensing and return should be documented. Any missing tubes must be documented.

7.3.3 Investigator Assessment

7.3.3.1 Investigators Global Assessment (IGA)

This is not an efficacy study, and therefore the Investigators Global Assessment is done for informational purposes. The evaluations should be performed by the Principal Investigator or appropriately qualified Sub-Investigator at each visit. **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.**

The IGA is intended for the global evaluation of papulopustular rosacea. Background non-transient 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 SAFETY VARIABLES

7.4.1 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.

7.4.2 Limited Physical Exam

A limited physical exam, will be performed at the Screening Visit (including height and weight) and at the final Month 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

7.4.3 Vital Signs

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

7.4.4 Clinical Laboratory Testing

Blood samples (approximately 11 mL) will be collected at Screening and the Month 12 Visit (Early Termination, or Final/EOT 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 following parameters will be determined:

- 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).

7.4.5 Immunogenicity Testing

Blood samples (approximately 6 mL) will be collected at Day 1 (Pre-dose), Month 1, 3, 6, 9 and 12 for immunogenicity testing (total expected volume of approximately 40 mL). Samples from all sites will be shipped to a central laboratory and stored for sample analysis. Instructions for sample collection, preparation, labeling, and shipping will be provided by the laboratory. Sample testing will occur periodically dependent upon assay development and when an adequate number of samples have been received at the laboratory. The assay configuration provides for a screening and confirmatory assay. Any positive anti-drug antibody assay results from confirmatory testing will be made available once known. It is intended to follow any subjects with positive confirmatory anti-drug antibody assay results for up to 1 year from discovery to allow for reactive

antibody results to return to baseline. Any subjects with positive confirmatory anti-drug antibody assay results who have completed the study or discontinued from the study for any reason, will be contacted and requested to return to the clinical study site for additional immunogenicity testing as noted previously.

7.4.6 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 Month 12 Visit (Early Termination, or Final Visit). All female subjects of child bearing potential must have a negative urine pregnancy test prior to receiving study drug. Urine pregnancy testing should also be conducted 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.

7.4.7 Adverse Event

7.4.7.1 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.

7.4.7.2 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.

7.4.8 Serious Adverse Event

A serious adverse event (SAE) is an 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 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 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/or by sending a copy of the Serious Adverse Event form (via fax or email pdf copy) plus other supporting documentation, as required. SAE forms should be sent to:

[redacted]

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, as required. 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]

7.5 TEST MATERIALS

7.5.1 Administration

Study drug will be applied by the subject to the entire area of the face, once daily, preferably in the morning, for a period of up to 12 months (52 Weeks ± 14 days) 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 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 layer 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 layer, each day, preferably in the morning

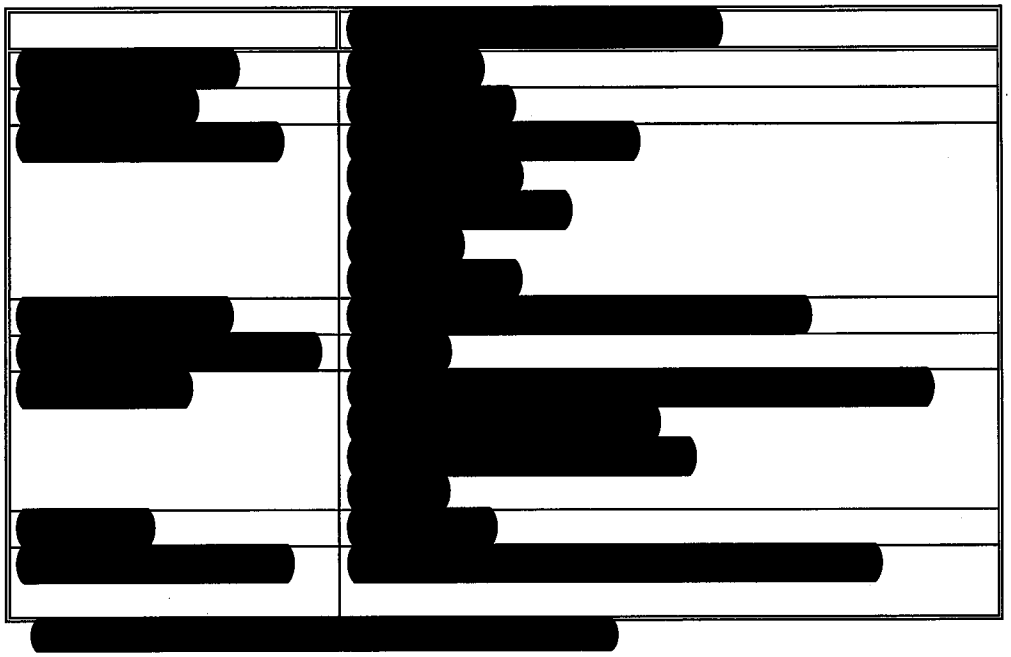
At the Baseline visit and Months 3, 6 and 9 visits, subjects will be dispensed three or four tubes of study drug. Each tube contains enough study drug for 4 weeks of treatment. Prior to application of study drug, the subject number and date of dispensing should be recorded on the tube and the tube weighed. The tube weights will be recorded on the appropriate source document. When the used tubes are returned at the next visit, the tubes will be weighed again, and the weight will be recorded. 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 tubes will be weighed to confirm product use. All tube weighing will be done with the cap in place.

7.5.2 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]



7.5.3 Packaging

Study drug will be provided in 20-gram tubes. Drug supplies will be packaged as bulk supplies.

7.5.4 Labeling

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

7.5.5 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). After the initial onsite instruction and treatment application, subjects will apply the dose each day, preferably in the morning, in an outpatient setting.

7.5.6 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 subject's 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.

7.5.7 Dispensing and Return of Study Product

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. For use in the outpatient setting, three or four tubes of study drug will be dispensed to each subject at the study visits at Baseline (4 tubes), Month 3 (3 tubes), 6 (4 tubes) and 9 (3 tubes) visits.

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

The subject will be instructed to return the tubes of study drug at each study visit (Months 1, 3, 6, 9 and 12) to check compliance. At the Month 3, 6 and 9 Visit, the used tubes will be exchanged for three or four new tubes of study drug. Additional tubes are available for dispensing in the event that tubes are lost or damaged.

Tubes 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.

7.5.8 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.

7.5.9 Prior and Concomitant Therapy

Therapies used within one month prior to the Baseline visit should be recorded on the Previous/Concomitant Therapy Form of the CRF. Washout medications should be listed on the Previous/Concomitant 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 study instructions during the treatment period starting in the morning of Day 1. The instructions include the following:

- Wait until study gel is dry before applying makeup.
- 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 study gel is dry.

7.5.9.1 Excluded Concomitant Therapy

No other rosacea treatment, other than the study drug, will be permitted. 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/beds, 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 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)

7.6 STATISTICAL METHODS PLANNED

7.6.1 General Considerations

The statistical methods for this study are descriptive only. No hypothesis testing will be performed.

7.6.2 Sample Size Determination

The sample size for this study is based upon ICH E1a.

7.6.3 Randomization

This study is not randomized. Subjects providing written informed consent and having met all inclusion and exclusion criteria will be enrolled in the study.

7.6.4 Analysis Population

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

7.6.5 Handling of Missing Data

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

7.6.6 Safety Endpoints

Summaries will be presented to determine long-term safety in place of conducting statistical testing.

7.6.6.1 IGA Summary

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

7.6.7 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.

7.6.8 Subject Disposition

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

7.6.9 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.

7.6.10 Safety Summaries

Adverse events will be categorized by SOC and Preferred Term from the current version of MedDRA. The focus of the adverse event summaries will be on treatment-emergent adverse events. Treatment-emergent adverse events will be summarized overall, by severity, and by relationship to study product.
Changes or shifts in safety laboratory data andvital signs will be summarized at all time-points when available. Summaries will include means, standard deviations, median, minimum and maximum values for continuous data, or frequency and percent for categorical data. Additionally, shift tables will be provided for abnormal safety labs.

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, and 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, and the IRB/IEC. 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 protocol, 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 data.

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 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-006 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 monitor the conduct of the study. In addition, inspections or on-site audits may be carried out by the FDA, 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 should apply study drug once daily, preferably in the morning.

Before applying the study drug:

1. Wash your hands and face before applying study medication.
2. For the first dose, the study staff will review treatment application with you before you apply the study drug. 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 your entire face, including cheeks, chin, forehead and nose, avoiding the corners of the eyes, mouth and inside your 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 layer 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 off of the treated areas until the gel is dry.

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).
- 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 are to be used on the skin in the treatment areas.

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

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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